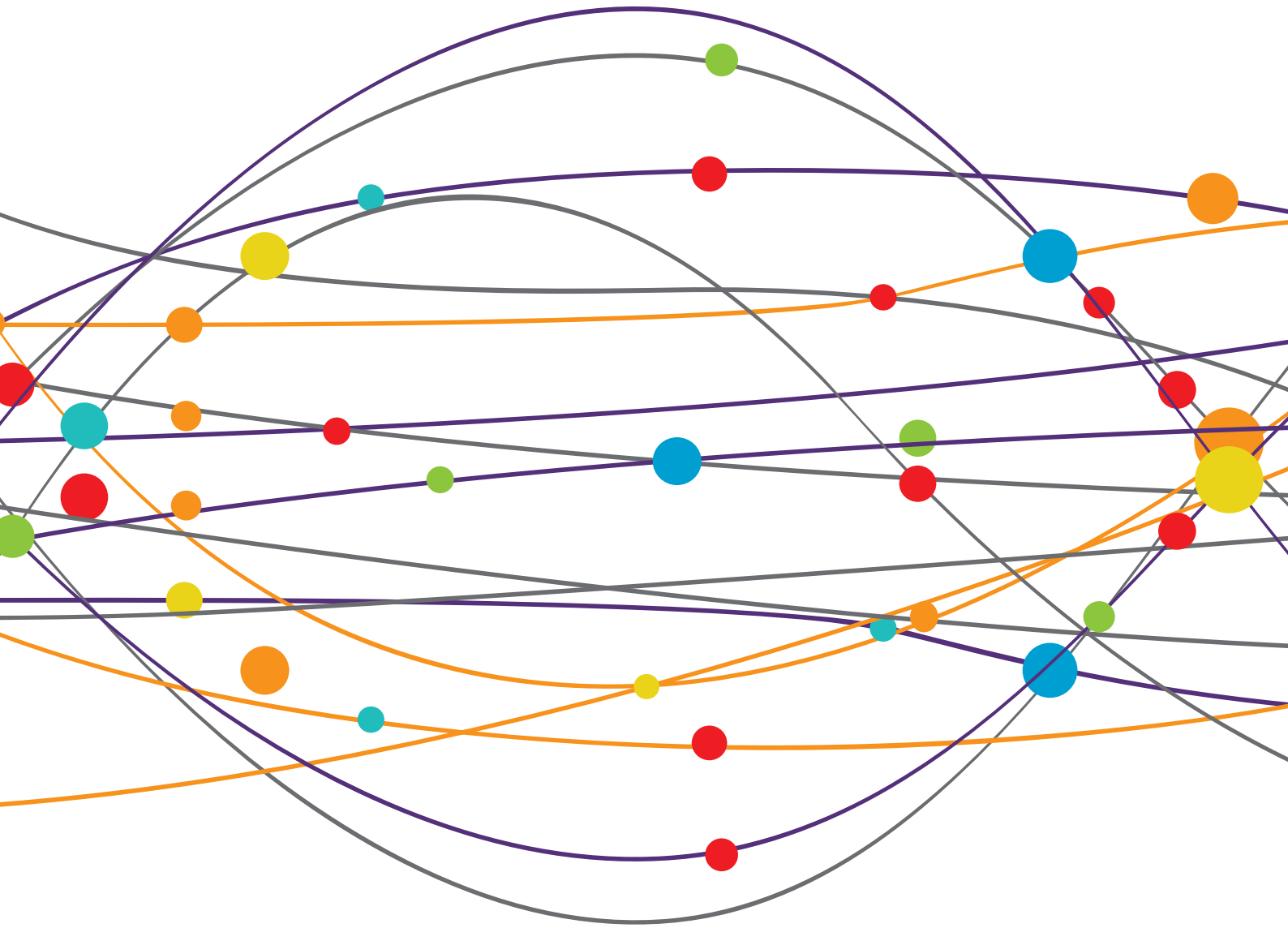
CURRENT STATE OF POSTURAL RESEARCH - BEYOND AUTOMATIC BEHAVIOR

EDITED BY: Emily Keshner and Joyce Fung
PUBLISHED IN: Frontiers in Neurology



frontiers Research Topics

frontiers

ISSN 1664-8714
ISBN 978-2-88963-295-4
DOI 10.3389/978-2-88963-295-4

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: researchtopics@frontiersin.org

CURRENT STATE OF POSTURAL RESEARCH - BEYOND AUTOMATIC BEHAVIOR

Topic Editors:
Emily Keshner, Temple University, United States
Joyce Fung, McGill University, Canada

Citation: Keshner, E., Fung, J., eds. (2019). Current State of Postural Research - Beyond Automatic Behavior. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88963-295-4

Table of Contents

frontiers in Neurology

EDITORIAL
published: 31 October 2019
doi: 10.3389/fneur.2019.01160

Editorial: Current State of Postural Research - Beyond Automatic Behavior

Emily A. Keshner[1]* *and Joyce Fung*[2]

[1] Department of Health and Rehabilitation Sciences, Temple University, Philadelphia, PA, United States, [2] School of Physical and Occupational Therapy, McGill University, Montreal, QC, Canada

Keywords: cognition, attention, technology, Parkinson's Disease, sensorimotor integration

Editorial on the Research Topic

Current State of Postural Research - Beyond Automatic Behavior

Postural control requires regulating the neural circuitry of musculoskeletal mechanics to maintain and change body spatial orientation to fulfill changing demands specific to the task and the environment. Knowledge progression has closely followed our understanding of the dynamic interplay between organism, task, and environment. Initially, Magnus (1) focused on the reflexes elicited when decerebrate and decorticate animals righted themselves in space. As the science of posturography progressed, minimization of movement reflected through a small center of pressure footprint during quiet stance became the criterion value. A major theoretical shift occurred in the 1970's with development of the dynamic force platform; reactive postural behaviors could be quantified and were found to be adaptive and modifiable. Thus, research began targeting sensory pathways triggering the postural reactions. Simplified mechanics were used to model the multisegmental body as an inverted pendulum with principal motion around the ankle. But recent studies implicate cognitive processing in the organization of postural behaviors. Thus, basic assumptions need to be challenged if posture control research is to continue to evolve. The papers presented in this special issue are evidence of the progress that has been made toward explaining and assessing effective postural control.

OPEN ACCESS

Edited and reviewed by:
Martina Mancini,
Oregon Health and Science University, United States

***Correspondence:**
Emily A. Keshner
ekeshner@temple.edu

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *05 September 2019*
Accepted: *15 October 2019*
Published: *31 October 2019*

Citation:
Keshner EA and Fung J (2019) Editorial: Current State of Postural Research - Beyond Automatic Behavior. Front. Neurol. 10:1160. doi: 10.3389/fneur.2019.01160

SENSORY INFORMATION AND POSTURAL CONTROL

To discern when multimodal sensory information impacts recovery of upright balance, Le Goic et al. examine subject-specific geometry and inertial parameters. Intrinsic properties of the lower limb, stiffness and damping, were the earliest influences; however, early muscle activity was insufficient to counteract the external forces. The head was the last segment to move; thus, active correction for a fall could not be initiated by vestibular and visual inputs. The authors conclude that proprioception serves as the sole source of information for up to 300 ms following onset of unexpected falls. Rather than improved anticipation with experience, they argue for improved efficiency of reactive behaviors.

Rasman et al. agree that active maintenance of the upright position requires sensorimotor control. Since the relative contribution of each sensory system is determined by its sensor dynamics and the coordinate system to which it links, they argue that active control is required to maintain balance. Thus, sensory contributions to postural control can only be fully interpreted by combining two common protocols: external perturbations and manipulating the balance control loop. Results from a multisegmental robotic balance system that responds to manipulation of sensor dynamics

are presented as basic principles underlying standing balance. Alternatively, Peterka et al. provide detailed methods for use and interpretation of a commercially available device to assess central sensorimotor integration. They argue that applying an external balance perturbation clarifies the cause and effect relationships between sensory processing, motor action, and body sway. Data from 40 subjects and prior results from individuals with vestibular deficit are presented to support this conclusion.

Lhomond et al. explore whether re-calibration of sensorimotor mechanisms in the postural control loop occurs during both movement preparation and execution. Facilitating transmission of cutaneous inputs during the planning phase of gait initiation produced increased somatosensory evoked potentials in primary sensorimotor areas; the neural response decreased when standing still. Premotor cortex, specifically supplementary motor area and superior parietal lobe, was concluded to be the putative source of efferent signals that update current body representation by increasing tactile sensitivity. In a review paper, Sienko et al. argue that long-term training with sensory augmentation devices allow time for the nervous system to develop optimal combinations and weights of sensory cues. They report that individuals with vestibular deficit as well as healthy older adults use real-time sensory augmented cues to reduce sway when the initial stance position, support surface, or visual inputs are modified during a static balance task.

HIGHER ORDER PROCESSES AND POSTURAL CONTROL

Neuroimaging advances have provided new tools to decipher higher order cortical processing relevant to postural adaptability underlying motor learning and rehabilitation. Using functional magnetic resonance imaging (fMRI) and mental imagery, Patel et al. identified increased activation in dorsolateral prefrontal cortex, superior parietal lobule, inferior occipital gyrus, and lingual gyrus following slip-perturbation training while walking. Imagined slipping increased activity compared to resting state in supplementary motor area, parietal regions, parahippocampal gyrus, and cingulate gyrus. Thus, higher-level processing is required for the timing and sequencing of an effective balance response.

The importance of cortical contributions to postural control is highlighted in the perspective paper by Adkin and Carpenter who have studied the emotional effects of height-induced threat on human postural control. They argue that threat-related postural changes promote a greater physical safety margin while maintaining upright stance. Their critical review of the static balance research literature highlights the need to recognize the potential contributions of psychological and physiological factors on balance deficits associated with age or pathology.

Dakin and Bolton provide a critical review of research methods and progress in the understanding of anticipatory postural behaviors to expose the role of prediction in postural control. Anticipatory behaviors can be facilitated by changes in the state, or set, of the nervous system. They argue that cortical expansion has improved prediction, termed "foresight," for preparing to interact with the changing environment. Internal models allow for the fine tuning and priming associated with motor affordances, while learning can be implemented in the cortical, basal ganglia, and cerebellar networks.

COGNITION AND ATTENTION AND POSTURAL CONTROL

Recent research has targeted cognitive and postural interactions to inform about functional behavior in a complex environment. Dual task paradigms are used extensively to reveal the contributions of cognition and attention to postural control, particularly in the aging population. The focused review by Li et al. distinguishes the neural circuits involved in cognitive or motor performance, and asserts that dual task interference should be greatest when the cognitive and motor tasks engage the same neural circuits in keeping with the principle of neural overlap. The literature reveals age-related differences in neural substrates underlying cognition and the degree to which the age-related decline of sensory systems (e.g., vision, hearing) contribute to cognitive load. Findings support focused cognitive training, exercise, and multimodal training of older adults to improve postural and gait outcomes.

Stins and Roerdink assert that maintaining quiet upright stance shifts between postural reflexes and higher (cortical) centers in accordance with the theory of "intermittent control." This involves a rapid succession of brief periods of postural stability, during which the body dwells relatively motionless in a particular posture, and postural instability, during which the body rapidly transitions to a new stable point. They hypothesize that exerting ballistic control consumes more attention than stiffness control, using variations in reaction time as the index of attention load. Evidence of attentional fluctuations in the control of quiet upright standing is provided by mapping stimulus-response intervals to local COP parameters.

The original research of Chow et al. corroborates the detrimental effect of directing too much conscious attention toward postural control in young but not old subjects. Using an electroencephalography (EEG) method previously identified as an objective indicator of conscious movement control, they assess neural coherence between T3 (verbal-analytical) and Fz (motor-planning) regions of the brain during a challenging balance task with and without directing attention internally to movement production. Increased EEG T3-Fz coherence in conjunction with increased sway path during the internal focus condition is only observed in young subjects. They caution that the observations may not readily translate between populations and are not robust to age-related changes.

By comparing healthy subjects to patients with Radiation-Induced Leukoencephalopathy (RIL), Bargiotas et al. demonstrates that alterations in executive function and attention can lead to postural deficits. Their RIL patients presented isolated dysexecutive syndrome without clinically detectable gait or posture impairment. Postural and visual measurements were made during the ecological task of reading a recipe while cooking. The main finding is that horizontal and vertical eye

movements, as well as the average duration of the saccades and fixations, can predict postural deficits in RIL patients. They conclude that increased balance impairment is coupled with a reduced focusing capacity in ecological tasks.

IMPACT OF PARKINSON'S DISEASE ON POSTURAL CONTROL

Parkinson's Disease (PD) has often been used as a model for understanding control mechanisms of posture because of the role of basal ganglia in motor planning and intention. Pantall et al. investigated the relationship between cognitive decline and postural dysfunction in individuals with PD. Longitudinal assessments of cognition and postural dynamics were performed. Postural measures were positively correlated with lower cognitive function and increased geriatric depression scores and negatively associated with a qualitative measure of balance confidence. The positive association between motor and non-motor features of PD reflects the potential for shared neural correlates, potentially the subcortical nuclei, between posture and depression.

If the sub-cortical nuclei and pre-supplementary motor areas are complicit in the motor dysfunction observed with PD, then we might expect impairments in motor planning and learning rather than motor production. The ability of individuals with PD to adapt to new task demands was reviewed by Olson et al. Individuals with PD can learn to execute a new motor plan, but have difficulty with rapidly and flexibly switching between plans; thus, their motor plans do not become implicit. It was concluded that individuals with PD may continuously require explicit information and augmented sensory information to create new motor plans. Wright examined motor adaptation in individuals with PD by manipulating somatosensory input. Support surface incline was changed during prolonged periods of quiet stance. Young healthy controls and aged-matched older adults exhibited long-term aftereffects of this incline, but those with PD did not. These results suggest that the basal ganglia play a role in tonic postural adaptation.

Cortical control for postural demands during walking is particularly challenging for people with PD. Fino et al. examine cognitive-locomotor interference using dual-task paradigms during the gait cycle. Dual tasking interfered with the duration of late swing and from foot contact to weight transference, both of which require higher-order cortical processing for planning and postural adjustments. Fling et al. measured spatial and temporal gait asymmetry in age-matched healthy and individuals with PD while in the levodopa off state. Individuals with PD exhibited significantly more temporal and spatial gait asymmetry than healthy controls, and changes in transcallosal fiber tract integrity of the pre-supplementary motor area (pre-SMA) and S1 was associated with their greater step length asymmetry.

Jacobs et al. propose that the mechanisms underlying low back pain are similar to those of PD. Evidence suggests that both low back pain and PD are associated with impaired proprioceptive function, sensory orientation during standing balance, anticipatory postural adjustments, automatic postural responses, and striatal-cortical function. A review of the data, however, indicated that although both health conditions can be associated with altered striatal-cortical function, the nature of the altered structure or function was different for PD and low back pain.

We learn from this special issue that the human organism is a dynamic system where all components, be they sensory, motor, mechanical, or cognitive, are operating in an interactive and continuous fashion within environmental and task constraints. Although it functions most efficiently as an automatic process, postural control is a motor task that needs to be learned and practiced throughout the lifespan to best serve the motor and cognitive demands presented to the individual performer.

AUTHOR CONTRIBUTIONS

EK and JF were co-editors of the special issue and shared all editorial responsibilities and contributions to the writing of this editorial.

REFERENCES

1. Magnus, R. Animal posture. *Proc R Soc Lond Ser B.* (1925) 98:339–53.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 04 April 2018
doi: 10.3389/fneur.2018.00215

Gait Asymmetry in People With Parkinson's Disease Is Linked to Reduced Integrity of Callosal Sensorimotor Regions

Brett W. Fling[1,2], Carolin Curtze[3] and Fay B. Horak[3,4]*

[1] Department of Health and Exercise Science, Colorado State University, Fort Collins, CO, United States, [2] Molecular, Cellular and Integrative Neuroscience Program, Colorado State University, Fort Collins, CO, United States, [3] Department of Neurology, Oregon Health & Science University, Portland, OR, United States, [4] Veterans Affairs Portland Health Care System, Portland, OR, United States

Background: Individuals with Parkinson's disease (PD) often manifest significant temporal and spatial asymmetries of the lower extremities during gait, which significantly contribute to mobility impairments. While the neural mechanisms underlying mobility asymmetries within this population remain poorly understood, recent evidence points to altered microstructural integrity of white matter fiber tracts within the corpus callosum as potentially playing a substantial role.

Objectives: The purpose of this study was to quantify spatial and temporal gait asymmetries as well as transcallosal microstructural integrity of white matter fiber tracts connecting the primary and secondary sensorimotor cortices in people with PD and age-matched control participants.

Methods: Spatial and temporal gait asymmetry in the levodopa off state was assessed using an instrumented walkway. On the next day, diffusion-weighted images were collected to assess white matter microstructural integrity in transcallosal fibers connecting the homologous sensorimotor cortical regions.

Results: People with PD exhibited significantly more temporal and spatial gait asymmetry than healthy control subjects. Furthermore, people with PD had significantly reduced white matter microstructural integrity of transcallosal fibers connecting homologous regions of the pre-supplementary motor and supplementary motor areas (SMAs), but not the primary motor or somatosensory cortices. Finally, reduced transcallosal fiber tract integrity of the pre-SMA and S1 was associated with greater step length asymmetry in people with PD.

Conclusion: People with PD showed increased step length asymmetries and decreased microstructural integrity of callosal white matter tracts connecting the higher-order sensorimotor cortices (pre-SMA and SMA). The strong association between gait asymmetries and corpus collosum integrity, supports the hypothesis that reduced transcallosal structural connectivity is a significant mechanism underlying gait asymmetries in people with PD.

Keywords: MRI, diffusion-weighted imaging, gait, balance, transcallosal, mobility

OPEN ACCESS

Edited by:
Emily Keshner, Temple University, United States

Reviewed by:
Pedro Ribeiro, Universidade Federal do Rio de Janeiro, Brazil
Matteo Bologna, Sapienza Università di Roma, Italy

****Correspondence:***
Brett W. Fling
brett.fling@colostate.edu

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *31 January 2018*
Accepted: *20 March 2018*
Published: *04 April 2018*

Citation:
Fling BW, Curtze C and Horak FB (2018) Gait Asymmetry in People With Parkinson's Disease Is Linked to Reduced Integrity of Callosal Sensorimotor Regions. Front. Neurol. 9:215. doi: 10.3389/fneur.2018.00215

INTRODUCTION

Impaired walking ability is common in persons with Parkinson's disease (PD), typically manifesting as reduced gait velocity and step length, increased gait variability, and reduced automaticity (1). PD has also been associated with temporal and spatial asymmetries of the lower extremities during gait (2, 3). These lower extremity asymmetries significantly contribute to mobility impairments in neurologic populations who experience gait and balance dysfunction. Reduced coordination during gait (i.e., increased gait asymmetry) is associated with increased metabolic cost, postural instability, falls, and reduced quality of life in those living with PD or following a stroke (4–6). While significant asymmetries in lower extremity control typically arise from unilateral neurologic insult such as a stroke, spinal cord injury, or traumatic brain injury, the neural mechanisms underlying mobility asymmetries within people with PD remain poorly understood. Although sparsely investigated, recent work suggests that altered microstructural integrity of white matter fiber tracts within the corpus callosum may play(s) a role (7–9).

Transcallosal communication *via* the corpus callosum plays a key role in the production of integrated motor behavior to generate appropriate, coordinated motor responses on both sides of the body (10, 11). The primary motor cortices are connected to the contralateral muscles controlling movement and are also densely interconnected through the corpus callosum allowing for interhemispheric transfer of information. When precisely, bilaterally coordinating movements in time and space (e.g., walking or typing), activation of one limb has a cumulative, inhibitory effect on the ipsilateral motor cortex, obtained *via* interhemispheric communication (12, 13). The relationship between reduced transcallosal structural connectivity and impaired bimanual upper extremity control is clear and well studied (10, 11), but it remains unclear if these associations extend to bilateral control of the lower extremities as well. That is to say, reduced structural connectivity of the corpus callosum is common in PD (8, 14, 15), yet it remains to be tested how reduced transcallosal structure contributes to the lower limb asymmetries observed during gait and balance tasks.

The purpose of this study was to quantify spatial and temporal gait asymmetries (assessed *via* an instrumented walkway) as well as transcallosal microstructural integrity of white matter fiber tracts connecting the primary sensorimotor cortices and supplementary motor areas (SMAs) (assessed *via* diffusion-weighted imaging) in people with PD and age-matched control participants with no known neurologic conditions. Our overarching hypothesis was that those with PD would have increased spatial and temporal gait asymmetries during over-ground walking, associated with reduced sensorimotor corpus callosum structural connectivity compared with their age-matched counterparts.

MATERIALS AND METHODS

Participant Demographics

We recruited 39 people with idiopathic PD and 20 age-matched healthy controls (**Table 1**). The protocol was approved by the Institutional Review Board of Oregon Health and Science University. All subjects gave written informed consent in accordance with the Declaration of Helsinki. Clinical, mobility, and neuroimaging testing was performed over the course of two test sessions, separated by less than 1 week. All participants with PD were tested in the OFF medication state, that is, after withholding their dopaminergic medication for at least 12 h.

TABLE 1 | Participant demographics.

	Parkinson's disease	HC
n	39	20
Age (years)	68.7 (8.0)	71.4 (8.1)
Sex (M/F)	26/13	7/13
Disease duration (years)	7.1 (5.7)	
MDS-UPDRS III	40.1 (13.6)	
PIGD	5.5 (3.5)	
Hoehn and Yahr	2.4 (0.6)	
MoCA	24.4 (4.1)	27.1 (1.9)
Levodopa equivalent dose (mg)	1,024 (75–8,680)	

Mobility Assessment

Participants walked at preferred gait speed three times over an 8-m long instrumented walkway with an active area of 6 m × 0.6 m sampling at a frequency of 60 Hz (GAITRite, CIR System, Havertown, PA, USA). Spatial and temporal asymmetry in percent was calculated as follows:

$$|1 - \text{left/right}| * 100,$$

for step length and step time, respectively.

Image Acquisition

Neuroimaging data were collected at the Oregon Health and Science University's Advanced Imaging Research Center on a 3.0 T Siemens Magnetom Tim Trio scanner with a 12-channel head coil. Collection parameters were similar to previous research conducted by our lab (16). Briefly, a structural, high-resolution T1-weighted MP-RAGE sequence was collected (orientation = sagittal, echo time = 3.58 ms, repetition time = 2,300 ms, 256 × 256 matrix, resolution 1.0 mm × 1.0 mm × 1.1 mm). In addition, high angular resolution diffusion images were also acquired using a 72-gradient direction, whole-brain echo-planar imaging sequence (TR = 7,100 ms, TE = 112 ms, field of view = 230 mm × 230 mm, *b* value = 3,000 s/mm^2, isotropic voxel dimensions = 2.5 mm^3) and 10 non-diffusion-weighted images where the *b* value was equal to 0.

Diffusion Tensor Imaging Analysis

Diffusion data were processed using the tools implemented in FSL (Version 5.0; www.fmrib.ox.ac.uk/fslwww.fmrib.ox.ac.uk/fsl). Diffusion date were first corrected for eddy current distortions and motion artifacts, then averaged to improve signal-to-noise ratio (17) and subsequently skull stripped (using FSL's brain extraction tool). Non-diffusion-weighted images (B0) were also utilized for field map correction to reduce geometric distortions. Each participant's fractional anisotropy (FA) image was subsequently normalized into Montreal Neurological Institute (MNI) space *via* linear registration and Fourier interpolation through the FMRIB linear image registration tool.

Interhemispheric Callosal Tractography

Probabilistic fiber tractography to assess quantity and quality of interhemispheric structural connectivity for the body of the corpus callosum was carried out (**Figure 1A**). Similar to previous work (8, 18), we utilized a multiple ROI approach to provide specific fiber tract identification of callosal fibers connecting the primary and secondary sensorimotor areas. First, the Human Motor Area Template, which identifies the primary and secondary sensorimotor regions of the cortices (19), was co-registered to each individual's MNI-normalized FA image and then used as a mask (20). The HMAT is an oft-used sensorimotor template that was identified through a meta-analysis examining functional MRI-defined cortical activity. Four sensorimotor regions were subsequently used to identify homologous, transcallosal fiber tracts connecting the SMAs and pre-SMAs, respectively, as well as the primary motor (M1) and the primary somatosensory (S1) cortices. In addition, for each interhemispheric sensorimotor fiber tract we utilized a "waypoint" ROI within the corresponding region of the body of the corpus callosum as identified by previous work (**Figure 1B**) (20).

For all interhemispheric sensorimotor tracts, probabilistic fiber tracking was initiated from every voxel within the binarized cortical seed HMAT ROI in each participant's native diffusion space, was required to pass through the corresponding callosal ROI waypoint, and terminated in the contralateral hemisphere's homologous regions ROI. We identified four distinct interhemispheric fiber tracts connecting the: (1) pre = SMA, (2) SMA, (3) M1, and (4) S1, respectively. Due to the difficulty in delineating differences between the interhemispheric connections between the ventral and dorsal premotor cortices (20), we choose to omit these ROIs from the current analysis.

As previously described (21), implicitly modeling noise in a probabilistic model allows for fiber tracking without externally added constraints such as FA threshold or fiber angle. As a result, fiber tracking in or near cortical areas, as in this study, becomes more sensitive. Utilizing a two-fiber model (22), as in this study, also improves the identification of crossing fibers. For all tractography, a large number of samples (25,000) were initiated from each voxel within the HMAT mask with the following parameters: step length of 0.5 mm, curvature threshold of 0.2. Next, the probabilistic fibers were thresholded on individual maps to include voxels with a minimum of 50% of samples [i.e., selecting all connections where >12,500 of 25,000 samples passed; a very conservative level in comparison to previous work using a threshold of 5% (20, 23)]. Finally, the identified fiber tracts were binarized and affine-transferred into MNI space and summed across participants. Analysis of tract volume and FA was calculated for all tracts identified within the four interhemispheric pathways of interest, and analysis was subsequently restricted to each participant's 10 mid-sagittal slices (±5 slices from the mid-sagittal slice) to ensure that analysis was restricted to fiber tracts housed entirely within the corpus callosum.

Statistical Analysis

Diffusion derived metrics were compared *via* a repeated measures analysis of variance (2 groups × 4 tracts). Larger FA values are indicative of greater directional diffusivity, which is traditionally interpreted as better white matter microstructure, e.g., denser axonal packing and higher levels of myelination (21, 22). Cohen's *d* effect sizes to demonstrate the strength of group differences were calculated for all primary gait and fiber tract outcomes. Finally, fiber tract integrity of the four transcallosal fiber tracts were correlated with both spatial and temporal gait asymmetry in people with PD and HC, respectively. Correlations were Bonferroni-corrected for multiple comparisons and considered significant if $\alpha \leq 0.05/2$.

RESULTS

Mobility Performance

Many people with PD walked with greater temporal and spatial gait asymmetry than age-matched healthy controls (**Figure 2**).

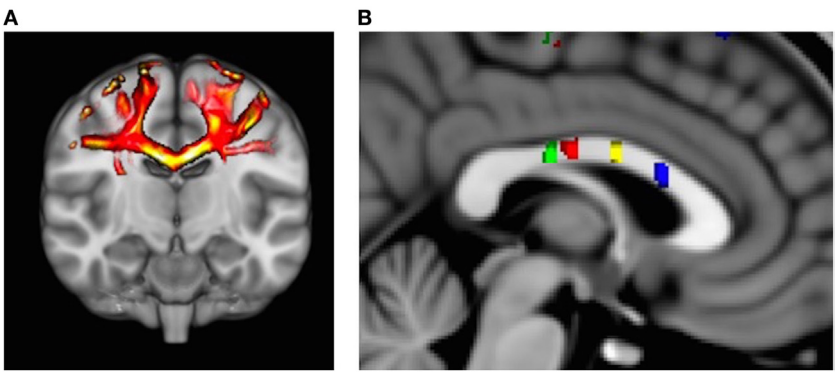


FIGURE 1 | **(A)** Representative example of identified transcallosal fiber tracts connecting the homologous right and left primary motor (M1) in a participant with Parkinson's disease. **(B)** Analysis of white matter tract microstructure was subsequently restricted to regions of interest identified on 10 mid-sagittal slices contained within the corpus callosum. Green = tracts connecting primary somatosensory; red = tracts connecting M1; yellow = tracts connecting supplementary motor area (SMA); and blue = tracts connecting pre-SMA.

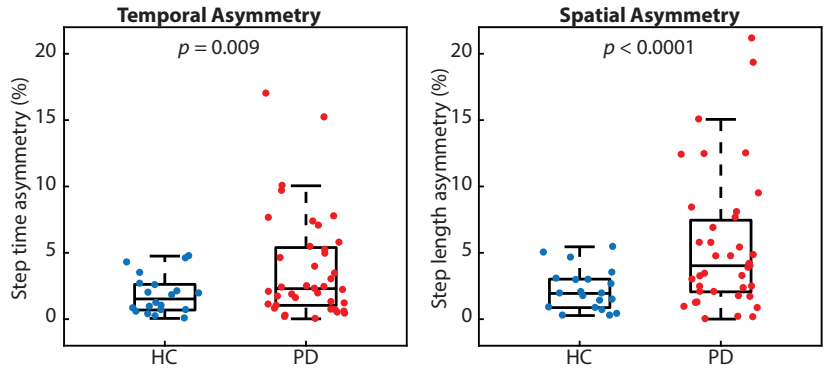


FIGURE 2 | People with Parkinson's disease (PD) exhibited significantly more temporal and spatial gait asymmetry than healthy controls ($p = 0.009$ and $p < 0.0001$, respectively).

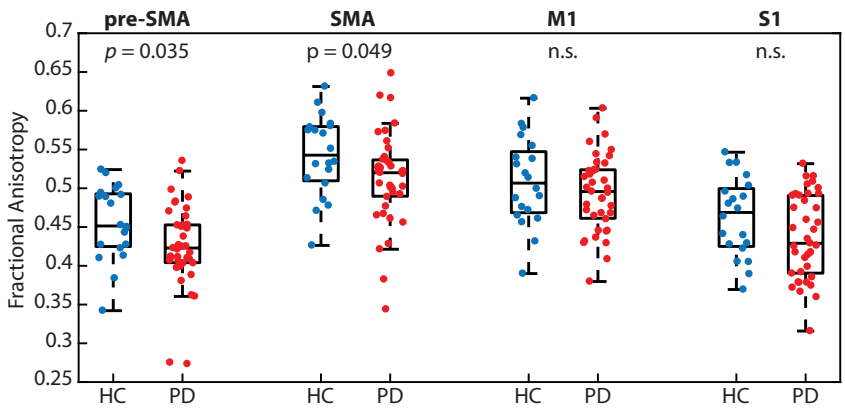


FIGURE 3 | People with Parkinson's disease (PD) had significantly reduced white matter microstructural integrity of the transcallosal fibers connecting homologous regions of the pre-supplementary motor area (SMA) and SMA, but not fibers connecting the primary motor (M1) and primary somatosensory (S1) cortices, when compared with age-matched control participants.

While both metrics of asymmetry were greater in people with PD, we report a stronger effect size for spatial asymmetry ($d = 0.78$) as compared with temporal asymmetry ($d = 0.59$). People with PD also walked slower ($p < 0.001$; PD 1.05 ± 0.19 m/s and HC 1.28 ± 0.16 m/s) and with a shorter step length ($p < 0.001$; PD 0.55 ± 0.09 m and HC 0.66 ± 0.06 m), but similar step time ($p < 0.48$; PD 0.53 ± 0.05 s and HC 52 ± 0.04 s) compared with healthy control subjects.

Transcallosal Fiber Tract Integrity

People with PD had significantly reduced white matter microstructural integrity (i.e., FA) of transcallosal fibers connecting homologous regions of the pre-SMA ($p < 0.05$; PD 0.42 ± 0.05 and HC 0.46 ± 0.05) and SMA ($p < 0.05$; PD 0.51 ± 0.06 and HC 0.54 ± 0.05), but not M1 ($p = 0.34$) or S1 ($p = 0.09$; **Figure 3**). We refer the reader to **Table 2** for effect sizes comparing the strength of group differences across the four fiber tracts, which ranged from small (0.28) to medium (0.59).

TABLE 2 | Cohen's *d* effect sizes calculated for the primary gait and fiber tract sizes between groups.

	Cohen's *d*
Temporal asymmetry	0.59
Spatial asymmetry	0.78
Pre-supplementary motor area (SMA)	0.59
SMA	0.54
Primary motor	0.28
Primary somatosensory	0.48

A large effect (≥0.75 and <1.10); medium effect (≥0.40 and <0.75); and small effect (≥0.15 and <0.40).

Associations Between Gait Asymmetry and Transcallosal Fiber Tract Integrity

Poorer transcallosal tract integrity of fibers connecting the pre-SMA ($r = -0.58$; $p < 0.001$) was associated with greater step length asymmetry in people with PD, but not in healthy controls

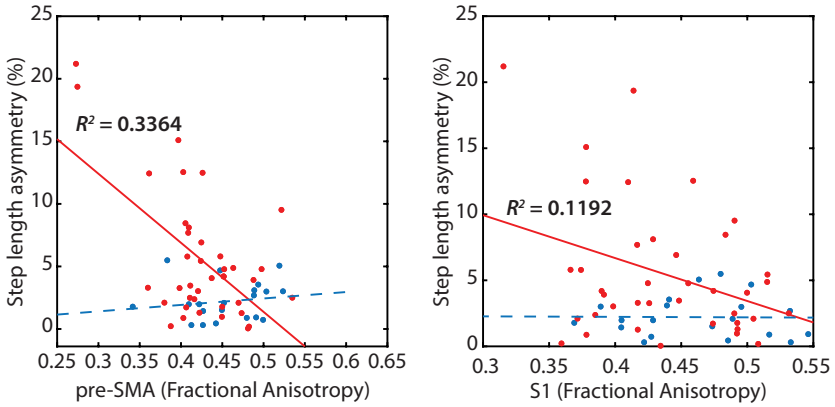


FIGURE 4 | Reduced transcallosal fiber tract integrity of the pre-supplementary motor area (SMA) and primary somatosensory (S1) were associated with greater step length asymmetry in people with Parkinson's disease, but not in healthy controls.

TABLE 3 | Correlation between the microstructural integrity of the callosal sensorimotor regions and spatial and temporal gait asymmetry (correlations with $p < 0.05$ are highlighted in bold).

	Spatial asymmetry		Temporal asymmetry	
	Parkinson's disease (PD)	**HC**	**PD**	**HC**
Pre-supplementary motor area (SMA)	**−0.5800**	0.1581	−0.0780	0.3425
SMA	−0.2699	0.2328	−0.0480	0.3744
Primary motor	−0.1367	−0.1162	0.1924	0.3813
Primary somatosensory	**−0.3452**	−0.0123	0.1923	0.0758

(**Figure 4**). In addition, FA of fiber tracts interhemispherically connecting the right and left S1 was strongly associated with spatial gait asymmetry in people with PD, although not significant when corrected for multiple comparisons ($r = -0.34$; $p = 0.03$). No significant association was observed between spatial asymmetry and tract integrity of fibers connecting either the SMA or the M1 in people with PD. In addition, no correlations were observed between temporal asymmetry and any of the four transcallosal fiber tracts ($r < 0.19$ for all) in those with PD nor were any significant correlations observed between fiber tract integrity and gait asymmetry for healthy control subjects (**Table 3**).

DISCUSSION

Differences in gait asymmetry between those with PD and HC were observed both spatially and temporally. Individuals with PD also had significantly reduced microstructural integrity of white matter fibers connecting the right and left pre-SMA and right and left SMA, regions responsible for higher-order motor control. Conversely, no differences in interhemispheric fiber integrity were found for those tracts connecting the right and left primary motor or somatosensory cortices. Finally, impaired neuroanatomy connecting the right and left higher-order motor planning regions of the sensorimotor cortical hemispheres (pre-SMA) and the S1 cortices resulted in a reduced capacity for spatially coordinating and controlling the legs during gait, specifically in people with PD.

Mobility Findings

While gait is generally considered to be symmetric, subtle asymmetries do exist, even in HC (24). Findings on gait asymmetry in PD are inconsistent, while some studies have shown that gait asymmetry is increased in people with PD, especially in PD who experience freezing of gait (25, 26) others found no difference in spatial or temporal step asymmetry during over-ground walking (27). Notably, while step length asymmetry has previously been shown to be weakly correlated with disease severity (27), but not associated with asymmetry of clinical motor symptoms (25). Similar to spatial gait asymmetry (25), temporal gait asymmetry has not been found to be associated with laterality of motor symptom presentation of the disease (25, 28). Our current results demonstrate significantly increased spatial (e.g., step length) and temporal (e.g., step time) gait asymmetry in people with PD, when measured in the OFF levodopa state, when gait is most affected. While previous work has offered descriptive metrics of gait asymmetry in people with PD, the current work also provides evidence for potential neural bases underlying this altered gait pattern that appears to be independent of disease laterality as typically assessed by clinical motor assessments.

Neuroimaging Findings

A recent meta-analysis by Atkinson-Clement et al. (15) reports consistent and significant reductions in white matter macrostructural integrity of the corpus callosum, as assessed by FA, in people with PD compared with age-matched healthy control subjects (15). While the individual contributions of axonal density and myelination to FA are not fully understood, recent work indicates that axonal membranes likely play the primary role, whereas myelination can modulate the degree of anisotropy (29). As an example, anisotropy is reduced in demyelinating disease [multiple sclerosis (30)] and in conditions of premyelination [children (31)]. While several studies have focused on the

anterior portions of the callosum (i.e., the genu) and its relation to cognitive decline in those with PD (32–34), there is a small, but growing body of literature indicating associations between callosal integrity and locomotor control in PD and the elderly (8, 35).

Interhemispheric communication *via* the corpus callosum is a well-known contributor to coordinated bimanual upper extremity control in healthy (10, 36, 37) and neurodegenerative (30, 38) populations. Specifically, intact transcallosal structure has been shown to prevent interference between the two hands, particularly during bimanual out-of-phase actions (similar to gait) as compared with bimanual simultaneous movements (36, 39, 40). Providing further confirmation for the specific relationship between transcallosal connectivity and asymmetric bilateral control, those patients who have received a callosotomy maintain the capacity to synchronously coordinate their two hands while performing discrete, simultaneous actions (41). This finding indicates that bilateral coordination remains possible, via pathways distinct from callosal communication. The current work extends this relationship between integrity of transcallosal sensorimotor fiber tracts to bilateral, out-of-phase control of the lower extremities in a large sample of people with PD. Specifically, these results point to transcallosal connections between the pre-SMA and the S1 cortices as important transcallosal fiber tracts associated with reduced symmetric control of gait in PD. Somatosensory cortices and medial motor areas like the pre-SMA have oft been implicated as serving prominent roles during complex bilateral movements.

Gerloff and Andres (42) have previously identified a complex cortical network underlying bimanual coordination, and they highlight the importance of the bilateral primary sensorimotor cortices, along with medial motor wall areas including the cingulate motor area and the pre-SMA. There are particularly dense homotopic transcallosal connections within the pre-SMA and SMAs (43), and these higher-order motor regions substantially influence M1 activity in both hemispheres during the execution of visually paced movements (44). For example, the pre-SMA significantly inhibits the opposite hemisphere's M1, thereby suppressing its activity. A growing body of literature investigating the effects of non-invasive brain stimulation (e.g., repetitive TMS) to reduce activity of the pre-SMA and SMA has shown that temporal pacing while bimanually tapping the fingers in an anti-phase pattern is selectively degraded, as compared with synchronously tapping (45). The authors suggest that deterioration of interhemispheric coupling due to stimulation likely reduces interhemispheric inhibition resulting in poorer motor performance on tasks requiring a higher level of interhemispheric inhibition. Similarly, our current results demonstrate that impaired neuroanatomy connecting the bilateral pre-SMAs results in a decreased ability to produce consistent steps with regards to the spatial domain in individuals with PD.

While the current literature is quite limited with regards to interhemispheric transfer of information between the primary somatosensory cortices, Geffen and colleagues (46) report that afferent feedback carries significant information regarding temporal control of movement and that it is a reduction in this sensory feedback that primarily impairs out-of-phase bilateral movement such as gait. Furthermore, recent work from Jung et al. (47) demonstrates that interhemispheric inhibition transmitted transcallosally between the bilateral somatosensory cortices is directly correlated with bimanual tactile performance, indicating that these interhemispheric sensory fiber tracts have behavioral importance for bimanual object manipulation and exploration. Structural findings within the brains of pianist's, a group that demands exquisite bilateral control and coordination, also demonstrates structural adaptations/enlargements of the SI hand representation (48). The current results are the first we are aware of that demonstrate the importance of transcallosal somatosensory fiber tracts and the ability to output consistent spatial bilateral gait patterns (i.e., steps). Collectively, the pre-SMA and S1 both exert an inhibitory influence on the contralateral M1, particularly for tasks where each limb undergoes independent spatiotemporal profiles that must be coordinated together, like gait in this study.

A limitation of the current manuscript is the amount of gait captured, comprising only three trials over an 8-m walkway per participant. While the use of an instrumented walkway is required to accurately assess spatial asymmetry during typical gait, this approach has been shown to be reflective of multiple gait characteristics including gait speed, cadence, and step length and time variables, as used in this study (49).

CONCLUSION

People with PD showed greater temporal and spatial gait asymmetry between the two legs along with decreased microstructural integrity of callosal white matter tracts connecting the pre-SMA and SMAs. Furthermore, strong associations were observed between callosal integrity of fiber tracts connecting pre-SMA and S1 cortical regions and step length asymmetries, solely in people with PD. These results indicate that reduced transcallosal sensorimotor structural connectivity may be a significant mechanism underlying bilateral gait asymmetries in those with PD.

ETHICS STATEMENT

All patients or their next of kin gave informed, written consent to a protocol approved by the Institutional Review Board of Oregon Health and Science University.

AUTHOR CONTRIBUTIONS

BF, FH, and CC all contributed to the conceptual design and interpretation of this study. BF and CC contributed to data collection and analysis.

FUNDING

This work was supported by the National Institutes of Health (2R01AG006457; KL2TR000152), the Department of Veterans Affairs grant # I01RX001075, the Collins Medical Trust, and the Medical Research Foundation of Oregon.

REFERENCES

1. Jankovic J. Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry* (2008) 79(4):368–76. doi:10.1136/jnnp.2007.131045
2. Morris ME, Matyas TA, Iansek R, Summers JJ. Temporal stability of gait in Parkinson's disease. *Phys Ther* (1996) 76(7):763–77; discussion 778–80. doi:10.1093/ptj/76.7.763
3. Almeida QJ, Frank JS, Roy EA, Patla AE, Jog MS. Dopaminergic modulation of timing control and variability in the gait of Parkinson's disease. *Mov Disord* (2007) 22(12):1735–42. doi:10.1002/mds.21603
4. Platts MM, Rafferty D, Paul L. Metabolic cost of over ground gait in younger stroke patients and healthy controls. *Med Sci Sports Exerc* (2006) 38(6):1041–6. doi:10.1249/01.mss.0000222829.34111.9c
5. Stoquart G, Detrembleur C, Lejeune TM. The reasons why stroke patients expend so much energy to walk slowly. *Gait Posture* (2012) 36(3):409–13. doi:10.1016/j.gaitpost.2012.03.019
6. Finley JM, Bastian AJ. Associations between foot placement asymmetries and metabolic cost of transport in hemiparetic gait. *Neurorehabil Neural Repair* (2017) 31(2):168–77. doi:10.1177/1545968316675428
7. Wang HC, Hsu JL, Leemans A. Diffusion tensor imaging of vascular parkinsonism: structural changes in cerebral white matter and the association with clinical severity. *Arch Neurol* (2012) 69(10):1340–8. doi:10.1001/archneurol.2012.633
8. Fling BW, Dale ML, Curtze C, Smulders K, Nutt JG, Horak FB. Associations between mobility, cognition and callosal integrity in people with parkinsonism. *Neuroimage Clin* (2016) 11:415–22. doi:10.1016/j.nicl.2016.03.006
9. Dale ML, Mancini M, Curtze C, Horak FB, Fling BW. Freezing of gait associated with a corpus callosum lesion. *J Clin Mov Disord* (2016) 3:2. doi:10.1186/s40734-016-0030-2
10. Fling BW, Seidler RD. Fundamental differences in callosal structure, neurophysiologic function, and bimanual control in young and older adults. *Cereb Cortex* (2012) 22(11):2643–52. doi:10.1093/cercor/bhr349
11. Gooijers J, Swinnen SP. Interactions between brain structure and behavior: the corpus callosum and bimanual coordination. *Neurosci Biobehav Rev* (2014) 43:1–19. doi:10.1016/j.neubiorev.2014.03.008
12. Sohn YH, Jung HY, Kaelin-Lang A, Hallett M. Excitability of the ipsilateral motor cortex during phasic voluntary hand movement. *Exp Brain Res* (2003) 148(2):176–85. doi:10.1007/s00221-002-1292-5
13. Stinear CM, Byblow WD. Role of intracortical inhibition in selective hand muscle activation. *J Neurophysiol* (2003) 89(4):2014–20. doi:10.1152/jn.00925.2002
14. Hall JM, Ehgoetz Martens KA, Walton CC, O'Callaghan C, Keller PE, Lewis SJ, et al. Diffusion alterations associated with Parkinson's disease symptomatology: a review of the literature. *Parkinsonism Relat Disord* (2016) 33:12–26. doi:10.1016/j.parkreldis.2016.09.026
15. Atkinson-Clement C, Pinto S, Eusebio A, Coulon O. Diffusion tensor imaging in Parkinson's disease: review and meta-analysis. *Neuroimage Clin* (2017) 16:98–110. doi:10.1016/j.nicl.2017.07.011
16. Fling BW, Cohen RG, Mancini M, Carpenter SD, Fair DA, Nutt JG, et al. Functional reorganization of the locomotor network in Parkinson patients with freezing of gait. *PLoS One* (2014) 9(6):e100291. doi:10.1371/journal.pone.0100291
17. Eickhoff SB, Jbabdi S, Caspers S, Laird AR, Fox PT, Zilles K, et al. Anatomical and functional connectivity of cytoarchitectonic areas within the human parietal operculum. *J Neurosci* (2010) 30(18):6409–21. doi:10.1523/JNEUROSCI.5664-09.2010
18. Fling BW, Benson BL, Seidler RD. Transcallosal sensorimotor fiber tract structure-function relationships. *Hum Brain Mapp* (2013) 34(2):384–95. doi:10.1002/hbm.21437
19. Mayka MA, Corcos DM, Leurgans SE, Vaillancourt DE. Three-dimensional locations and boundaries of motor and premotor cortices as defined by functional brain imaging: a meta-analysis. *Neuroimage* (2006) 31(4):1453–74. doi:10.1016/j.neuroimage.2006.02.004
20. Fling BW, Cohen RG, Mancini M, Nutt JG, Fair DA, Horak FB. Asymmetric pedunculopontine network connectivity in parkinsonian patients with freezing of gait. *Brain* (2013) 136(Pt 8):2405–18. doi:10.1093/brain/awt172
21. Behrens TE, Woolrich MW, Jenkinson M, Johansen-Berg H, Nunes RG, Clare S, et al. Characterization and propagation of uncertainty in diffusion-weighted MR imaging. *Magn Reson Med* (2003) 50(5):1077–88. doi:10.1002/mrm.10609
22. Behrens TE, Berg HJ, Jbabdi S, Rushworth MF, Woolrich MW. Probabilistic diffusion tractography with multiple fibre orientations: what can we gain? *Neuroimage* (2007) 34(1):144–55. doi:10.1016/j.neuroimage.2006.09.018
23. Gschwind M, Pourtois G, Schwartz S, Van De Ville D, Vuilleumier P. White-matter connectivity between face-responsive regions in the human brain. *Cereb Cortex* (2012) 22(7):1564–76. doi:10.1093/cercor/bhr226
24. Sadeghi H, Allard P, Prince F, Labelle H. Symmetry and limb dominance in able-bodied gait: a review. *Gait Posture* (2000) 12(1):34–45. doi:10.1016/S0966-6362(00)00070-9
25. Plotnik M, Giladi N, Balash Y, Peretz C, Hausdorff JM. Is freezing of gait in Parkinson's disease related to asymmetric motor function? *Ann Neurol* (2005) 57(5):656–63. doi:10.1002/ana.20452
26. Plotnik M, Giladi N, Hausdorff JM. A new measure for quantifying the bilateral coordination of human gait: effects of aging and Parkinson's disease. *Exp Brain Res* (2007) 181(4):561–70. doi:10.1007/s00221-007-0955-7
27. Nanhoe-Mahabier W, Snijders AH, Delval A, Weerdesteyn V, Duysens J, Overeem S, et al. Walking patterns in Parkinson's disease with and without freezing of gait. *Neuroscience* (2011) 182:217–24. doi:10.1016/j.neuroscience.2011.02.061
28. Yogev G, Plotnik M, Peretz C, Giladi N, Hausdorff JM. Gait asymmetry in patients with Parkinson's disease and elderly fallers: when does the bilateral coordination of gait require attention? *Exp Brain Res* (2007) 177(3):336–46. doi:10.1007/s00221-006-0676-3
29. Gulani V, Webb AG, Duncan ID, Lauterbur PC. Apparent diffusion tensor measurements in myelin-deficient rat spinal cords. *Magn Reson Med* (2001) 45(2):191–5. doi:10.1002/1522-2594(200102)45:2<191::AID-MRM1025>3.0.CO;2-9
30. Bonzano L, Tacchino A, Roccatagliata L, Abbruzzese G, Mancardi GL, Bove M. Callosal contributions to simultaneous bimanual finger movements. *J Neurosci* (2008) 28(12):3227–33. doi:10.1523/JNEUROSCI.4076-07.2008
31. Barnea-Goraly N, Menon V, Eckert M, Tamm L, Bammer R, Karchemskiy A, et al. White matter development during childhood and adolescence: a cross-sectional diffusion tensor imaging study. *Cereb Cortex* (2005) 15(12):1848–54. doi:10.1093/cercor/bhi062
32. Kamagata K, Motoi Y, Tomiyama H, Abe O, Ito K, Shimoji K, et al. Relationship between cognitive impairment and white-matter alteration in Parkinson's disease with dementia: tract-based spatial statistics and tract-specific analysis. *Eur Radiol* (2013) 23(7):1946–55. doi:10.1007/s00330-013-2775-4
33. Zheng Z, Shemmassian S, Wijekoon C, Kim W, Bookheimer SY, Pouratian N. DTI correlates of distinct cognitive impairments in Parkinson's disease. *Hum Brain Mapp* (2014) 35(4):1325–33. doi:10.1002/hbm.22256
34. Deng B, Zhang Y, Wang L, Peng K, Han L, Nie K, et al. Diffusion tensor imaging reveals white matter changes associated with cognitive status in patients with Parkinson's disease. *Am J Alzheimers Dis Other Demen* (2013) 28(2):154–64. doi:10.1177/1533317512470207
35. Chan LL, Ng KM, Rumpel H, Fook-Chong S, Li HH, Tan EK. Transcallosal diffusion tensor abnormalities in predominant gait disorder parkinsonism. *Parkinsonism Relat Disord* (2014) 20(1):53–9. doi:10.1016/j.parkreldis.2013.09.017
36. Fling BW, Seidler RD. Task-dependent effects of interhemispheric inhibition on motor control. *Behav Brain Res* (2012) 226(1):211–7. doi:10.1016/j.bbr.2011.09.018
37. Fling BW, Walsh CM, Bangert AS, Reuter-Lorenz PA, Welsh RC, Seidler RD. Differential callosal contributions to bimanual control in young and older adults. *J Cogn Neurosci* (2011) 23(9):2171–85. doi:10.1162/jocn.2010.21600
38. Bonzano L, Tacchino A, Roccatagliata L, Mancardi GL, Abbruzzese G, Bove M. Structural integrity of callosal midbody influences intermanual transfer in a motor reaction-time task. *Hum Brain Mapp* (2011) 32(2):218–28. doi:10.1002/hbm.21011
39. Stinear JW, Byblow WD. Disinhibition in the human motor cortex is enhanced by synchronous upper limb movements. *J Physiol* (2002) 543(Pt 1):307–16. doi:10.1113/jphysiol.2002.023986
40. Swinnen SP. Intermanual coordination: from behavioural principles to neural-network interactions. *Nat Rev Neurosci* (2002) 3(5):348–59. doi:10.1038/nrn807

41. Kennerley SW, Diedrichsen J, Hazeltine E, Semjen A, Ivry RB. Callosotomy patients exhibit temporal uncoupling during continuous bimanual movements. *Nat Neurosci* (2002) 5(4):376–81. doi:10.1038/nn822
42. Gerloff C, Andres FG. Bimanual coordination and interhemispheric interaction. *Acta Psychol (Amst)* (2002) 110(2–3):161–86. doi:10.1016/S0001-6918(02)00032-X
43. Rouiller EM, Babalian A, Kazennikov O, Moret V, Yu XH, Wiesendanger M. Transcallosal connections of the distal forelimb representations of the primary and supplementary motor cortical areas in macaque monkeys. *Exp Brain Res* (1994) 102(2):227–43. doi:10.1007/BF00227511
44. Grefkes C, Eickhoff SB, Nowak DA, Dafotakis M, Fink GR. Dynamic intra- and interhemispheric interactions during unilateral and bilateral hand movements assessed with fMRI and DCM. *Neuroimage* (2008) 41(4):1382–94. doi:10.1016/j.neuroimage.2008.03.048
45. Serrien DJ, Strens LH, Oliviero A, Brown P. Repetitive transcranial magnetic stimulation of the supplementary motor area (SMA) degrades bimanual movement control in humans. *Neurosci Lett* (2002) 328(2):89–92. doi:10.1016/S0304-3940(02)00499-8
46. Geffen GM, Jones DL, Geffen LB. Interhemispheric control of manual motor activity. *Behav Brain Res* (1994) 64(1–2):131–40. doi:10.1016/0166-4328(94)90125-2
47. Jung P, Klein JC, Wibral M, Hoechstetter K, Bliem B, Lu MK, et al. Spatiotemporal dynamics of bimanual integration in human somatosensory cortex and their relevance to bimanual object manipulation. *J Neurosci* (2012) 32(16):5667–77. doi:10.1523/JNEUROSCI.5957-11.2012
48. Gaser C, Schlaug G. Brain structures differ between musicians and non-musicians. *J Neurosci* (2003) 23(27):9240–5.
49. Webster KE, Wittwer JE, Feller JA. Validity of the GAITRite walkway system for the measurement of averaged and individual step parameters of gait. *Gait Posture* (2005) 22(4):317–21. doi:10.1016/j.gaitpost.2004.10.005

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

PERSPECTIVE
published: 02 May 2018
doi: 10.3389/fneur.2018.00313

What If Low Back Pain Is the Most Prevalent Parkinsonism in the World?

Jesse V. Jacobs[1], Sharon M. Henry[1,2] and Fay B. Horak[3]*

[1] Department of Rehabilitation and Movement Science, University of Vermont, Burlington, VT, United States, [2] Department of Rehabilitation Therapy, University of Vermont Medical Center, Burlington, VT, United States, [3] Department of Neurology, School of Medicine, Oregon Health & Science University, Veterans Affairs Portland Health Care System, Portland, OR, United States

Low back pain (LBP) has a point prevalence of nearly 10% and ranks highest in global disease burden for years lived with disability; Parkinson's disease (PD) ranks in the top 100 most disabling health conditions for years lost and years lived with disability (1). Recent evidence suggests that people with chronic, recurrent LBP exhibit many postural impairments reminiscent of a neurological postural disorder such as PD. We compare and contrast postural impairments associated with LBP and PD in order to inform treatment strategies for both conditions. The literature suggests that both LBP and PD associate with impaired proprioceptive function, sensory orientation during standing balance, anticipatory postural adjustments, automatic postural responses, and striatal-cortical function. Although postural impairments are similar in nature for LBP and PD, the postural impairments with LBP appear more specific to the trunk than for PD. Likewise, although both health conditions associate with altered striatal-cortical function, the nature of the altered neural structure or function differ for PD and LBP. Due to the high prevalence of LBP associated with PD, focused treatment of LBP in people with PD may render benefit to their postural impairments and disabilities. In addition, LBP would likely benefit from being considered more than just a musculoskeletal injury; as such, clinicians should consider including approaches that address impairments of postural motor control.

Keywords: Parkinson's disease, low back pain, posture, anticipatory postural adjustment, postural response, balance

OPEN ACCESS

Edited by:
Emily Keshner, Temple University, United States

Reviewed by:
Erwin Montgomery, University of Alabama at Birmingham, United States
Laura Avanzino, Università di Genova, Italy

****Correspondence:***
Jesse V. Jacobs
jesse.jacobs@med.uvm.edu

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *21 December 2017*
Accepted: *19 April 2018*
Published: *02 May 2018*

Citation:
Jacobs JV, Henry SM and Horak FB (2018) What If Low Back Pain Is the Most Prevalent Parkinsonism in the World? Front. Neurol. 9:313. doi: 10.3389/fneur.2018.00313

INTRODUCTION

Low back pain (LBP) represents one of the most prevalent health conditions worldwide, having a point prevalence of nearly 10% and ranking first in global disease burden for years lived with disability (1). Parkinson's disease (PD) also represents a significant health concern as the second-most prevalent neurodegenerative disease in older adults and ranking in the top 100 most disabling health conditions for years lost and years lived with disability (1). Although LBP is a musculoskeletal condition and PD is a neurodegenerative condition, both health conditions present with impairments of postural control and associated alterations of central neurophysiology. For both conditions, these postural impairments span multiple domains of postural control, including (a) reduced somatosensory perception and altered somatosensory integration for balance control; (b) excessive axial postural tone and stiffness; (c) delayed and non-specific anticipatory postural adjustments (APAs) to stabilize and facilitate voluntary movement; (d) non-specific and less effectual automatic postural responses (APRs) to external perturbations; and (e) slowness of walking and other activities. Further, altered structure and function of cortex and basal ganglia is evident for

both health conditions. The purpose of this perspective paper is to compare and contrast the postural impairments and related changes in neurophysiology associated with LBP and PD and to discuss the potential implications of their shared impairments on the treatment strategies for both health conditions.

SENSORY ACUITY, KINESTHESIA, AND DYNAMIC CENTRAL SENSORY INTEGRATION

Any type of physical activity optimally requires accurate sensation and perception of one's own position and movement (i.e., kinesthesia), and both PD and LBP associate with impaired kinesthesia. People with PD exhibit impaired tactile sensation and impaired kinesthesia to detect limb position during active motion as well as to detect passive limb and trunk rotation (2–8). People with LBP exhibit impaired two-point discrimination and can be unable to kinesthetically perceive their lumbar trunk based on body image traces (9). In contrast to the global somatosensory impairment exhibited by people with PD, the impaired tactile discrimination of people with LBP appears to be isolated to the area of the LBP (9). Impaired lumbosacral repositioning accuracy has also been reported for people with LBP (10). Further, similar to the impaired detection of trunk motion exhibited by people with PD, people with LBP exhibit increased thresholds for detecting passive trunk flexion and lateral bending (11). Thus, although the extent of impairment may differ between people with PD versus LBP, both health conditions associate with impaired tactile acuity and kinesthesia.

The act of maintaining standing balance requires integrating visual, somatosensory, and vestibular inputs. The central nervous system must also modulate each modality's influence on standing balance when transitioning to different sensory conditions. People with PD exhibit an impaired ability to limit postural sway during standing balance when somatosensory input is incongruent with visual and/or vestibular input (12, 13). Likewise, people with LBP also exhibit increased postural sway under conditions in which somatosensory input is incongruent with the other modalities (14). An enhanced use of ankle proprioception and the ankle strategy for postural sway, rather than a flexible control strategy to utilize trunk proprioception and hip motion under challenging conditions, has also been reported for people with LBP (15). These results suggest that, for people with LBP, the postural impairment may be localized to the processing of trunk proprioception and trunk control, with perhaps compensation through enhanced afferent processing and use of the distal limbs for the control of standing postural sway. Thus, people with LBP and PD alike exhibit an impaired ability to modulate the influence of surface somatosensory input in order to maintain standing balance.

MECHANICAL CONSTRAINT OF RIGIDITY

Rigidity (resistance to passive movement) is one of the cardinal symptoms of PD and can be evident across axial, proximal, and distal body segments. Although largely neural rather than peripheral in its generation (16), the rigidity associated with PD elicits a significant mechanical constraint that associates with impaired gait quality (17), turning (18), standing postural sway (19), and diminished quality of life (20). Direct measurement of axial rigidity by slow, passive trunk or hip rotation in stance demonstrates an increased rigidity with PD that correlates with clinical symptom scores (21) and with difficulty walking or rolling over (18). Thus, rigidity is a pervasive impairment in PD that influences mobility, balance, and daily life.

Axial or spinal-segmental rigidity is also common in people with LBP, and a change in LBP corresponds with a change in axial rigidity, but these results are not always consistent across studies (22). Although not the intent of a study by Cacciatore and colleagues (and therefore not powered to detect group differences), direct measurement of axial rigidity by slow, passive trunk and hip rotation during standing posture has been evaluated in people with and without LBP (23) using the same methods as those of Wright et al. (21) for people with PD. Cacciatore and colleagues reported nearly identical hip torques between a group of 8 people with LBP (mean $\pm$ SD = 3.06 $\pm$ 2.19) and a group of 15 control subjects without LBP (3.07 $\pm$ 1.66), but a statistically non-significant trend for increased trunk torque (6.26 $\pm$ 3.61 for LBP versus 5.00 $\pm$ 1.80 without LBP). Although requiring further study with a larger sample, the trend for increased mean rigidity with greater inter-individual variability in the group with LBP suggests that some, but not all, individuals with LBP exhibit axial rigidity (22). If the rigidity is evident, however, it is likely specific to the trunk. Therefore, although both LBP and PD have been associated with rigidity, this mechanical constraint is more consistent and pervasive for PD than for LBP.

ANTICIPATORY POSTURAL ADJUSTMENTS

Anticipatory postural adjustments represent learned, centrally programmed muscle activations of supporting body segments to counteract anticipated perturbing forces associated with voluntary movement in order to maintain posture and balance (24). Efficient movement thus depends upon appropriate movement-specific timing and amplitude of APAs.

For PD, impaired APAs appear evident across multiple tasks, such as step initiation and arm raising. During step initiation, for example, people with PD exhibit prolonged and diminished APAs that are poorly scaled to initial mechanical constraints (25, 26). During arm raises, people with PD exhibit APAs that can be delayed beyond a time window of anticipatory control prior to movement-related perturbation, and these delayed postural activations are not specific to the movement (27). Thus, PD associates with delayed, diminished, prolonged, and unspecified APAs across tasks that elicit APAs from axial or distal musculature.

For LBP, the primary impairment of the APA appears to be a delay in activation that can extend beyond a window of anticipatory control prior to movement-related perturbation (28, 29). Interestingly, similar to the findings on people with PD, people with LBP also exhibit a delayed APA that is not specific to the requirements of the movement (30). One notable difference,

however, is that the impairment is particularly limited to specific axial muscles and can actually be enhanced or earlier in onset at distal muscles (29). Thus, although delayed and contextually non-specific APAs are shared by both PD and LBP, prolonged duration and generalized impairment across body segments appears more evident with PD than with LBP.

AUTOMATIC POSTURAL RESPONSES

The ability to maintain balance and posture in response to an externally induced postural perturbation is also essential for efficiency and safety during daily activity. APRs represent rapid, automatic, but functionally specific responses to postural perturbations in order to maintain posture and balance.

For PD, the APR results in impaired stability marked by greater induced center-of-mass displacement and diminished corrective center-of-pressure displacement (31, 32). PD is also marked by impaired directional specificity of the APR, in which a non-specific stiffening strategy of antagonistic muscle co-contraction is evident (32, 33).

People with LBP exhibit remarkably similar impairments of the APR as people with PD, demonstrating increased center-of-mass displacements (34), muscle co-contraction (35, 36), and impaired directional specificity of the APR (37, 38). As previously described for both quiet stance and the control of the APA, however, people with LBP also exhibit a redistribution of control for the APR via compensation at distal body segments (36, 37, 39) that is not evident with PD. Thus, both health conditions exhibit diminished stability, co-contraction, and directionally non-specific APRs, but the impairment is more pervasive across body segments for PD, whereas the impairment appears localized to the trunk with compensation elsewhere for LBP.

BRADYKINESIA

Bradykinesia is a hallmark feature of parkinsonism. For people with PD, bradykinesia can span movements across body segments, such as finger tapping, smiling, and gait (40–42). For PD, bradykinetic gait is marked by slowed gait velocity, decreased step length, step asymmetries, and variability, and recent studies have also identified altered trunk coordination (42–44).

Interestingly, people with LBP also exhibit slowed gait velocity, decreased step length, step asymmetries, and altered trunk coordination (45–47). Further, as with PD, bradykinesia is not isolated to gait for people with LBP, as they also exhibit slowed trunk motion and lifting behaviors (48, 49). Although the extent of bradykinesia with PD appears greater than for people with LBP when evaluating differences compared to matched control subjects, both health conditions share similar characteristics of bradykinesia.

ASSOCIATED NEUROPATHOLOGY

Dysfunction of circuits involving the basal ganglia represents a hallmark pathophysiology associated with the development of motor symptoms in PD, which associates with clinical symptom severity, including postural instability and gait disturbance (50). LBP also associates with pathology of the basal ganglia. The transition from acute to chronic LBP associates with diminished striatal gray matter across multiple nuclei as well as with increased functional connectivity between prefrontal cortex and the nucleus accumbens; this increased connectivity also correlated with reported pain intensity (51). In subjects with established chronic LBP, however, there are many associated changes in neural structures and functions that do not necessarily resemble those of PD (52), including non-overlapping regions of diminished cortical gray matter and increased striatal gray matter (53, 54). Thus, corticostriatal pathology may affect both PD and LBP, but the nature of the pathology is quite different.

Beyond the existence of corticostriatal pathology, more specific alterations of cortical neurophysiology during postural tasks are evident with both PD and LBP. As determined by repetitive transcranial magnetic stimulation, the prolonged APA durations of people with PD during step initiation associate with the function of circuits involving the supplementary motor area, and the influence of stimulation at the supplementary motor area on APA duration appears to increase with increasing disease severity (26). Further, prior to initiating an APA for step initiation, greater amplitudes of electroencephalographic (EEG) preparatory cortical potentials associate with increasing disease severity for people with PD (55). With regard to the APR, people with PD exhibit enhanced preparatory EEG potentials, and the modulation of these potentials associates with the extent of APR modulation between conditions of differing perturbation amplitudes (56). During walking, people with PD exhibit enhanced frontal lobe activity (57). In sum, the results suggest an enhanced influence of the cerebral cortex on postural control for people with PD.

People with LBP likewise exhibit evidence of an increased influence of the cerebral cortex on postural control. As determined by transcranial magnetic stimulation, larger areas of the transversus abdominus muscle's cortical representation correlate with the onset delay of that muscle's APA activation during an arm-raise task (58). People with LBP also exhibit increased preparatory EEG potentials (29) as well as an increased topographical area of the potentials (59) prior to arm raises that require an APA. Amplitudes of preparatory EEG potentials have also been reported to correlate with APA onset time for subjects with LBP when performing an arm-raise task (59). With regard to the APR, people with LBP exhibit increased amplitudes of evoked EEG potentials in response to postural perturbation, and the amplitude of these enhanced potentials correlated with evoked center-of-mass displacement as well as the subjects' reported pain-related disability and fear of physical activity (39). Therefore, people with PD and people with LBP exhibit altered cortical functions that significantly correlate with their postural behavior and clinical symptoms, and this altered cortical function suggests an increased influence of the cerebral cortex on postural control for both health conditions.

Given the complex systems that control posture and gait (60), these few neuropathological similarities do not demonstrate that they are necessary and sufficient to produce the shared motor behaviors of LBP and PD. Although isolated characteristics of LBP could also relate to isolated characteristics of other neurological

conditions to suggest other mechanisms of neuropathological involvement, we preliminarily argue that the similarities in overall presentation of posture and gait between LBP and PD are greater than for LBP with other neurological conditions (e.g., cerebellar, vestibular, peripheral neuropathy, stroke), which differ in sensory conditions of impaired standing balance, truncal rigidity, the contextual specificity, scaling, and timing of APAs and APRs, as well as parkinsonian versus ataxic, neuropathic, or hemiparetic gait patterns (61–64). Therefore, relating the control of posture and gait of LBP to that of PD appears more robust than other options.

LBP CONFOUNDS PD

Based on the above sections, many shared postural impairments exist for both PD and LBP. These shared impairments are so extensive that PD can be misdiagnosed as LBP (65). It is important to note, however, that LBP confounds PD, because LBP is often coincident with PD. In almost 30% of cases, LBP is an initial presenting symptom of PD (66, 67). In addition, the prevalence of LBP with PD is approximately 60–83% compared to approximately 25% in matched control subjects (68–70). Thus, it is possible that the postural impairments of PD are exacerbated by the coexistence of LBP, and LBP may be exacerbated by the postural impairments of PD.

IMPLICATIONS FOR TREATMENT

Although multidisciplinary treatment strategies are espoused for both PD and LBP (71, 72), the conservative physical treatment of postural impairment differs considerably between these two conditions. First, despite the prevalence of pain with PD, pain is rarely a focus of treatment for people with PD (69, 70). The treatment of motor impairment, however, is more common for people with PD. For example, physical therapy is utilized by about 63% of cases with PD, and the majority of its use is focused on retraining gait, balance, and posture (73). In contrast, physical therapy is utilized by less than 20% of cases with LBP, and its use comprises approximately six visits that prioritize pain management, strength, and flexibility rather than gait, balance, and postural training (74, 75). Treatment outcomes for LBP with this approach have been variable, although the use of motor control retraining hasn't yet demonstrated superior treatment outcomes to general exercise (76). The lack of superior treatment outcomes for LBP with motor control retraining therapy, however, may be because the treatment does not adhere to principles of motor

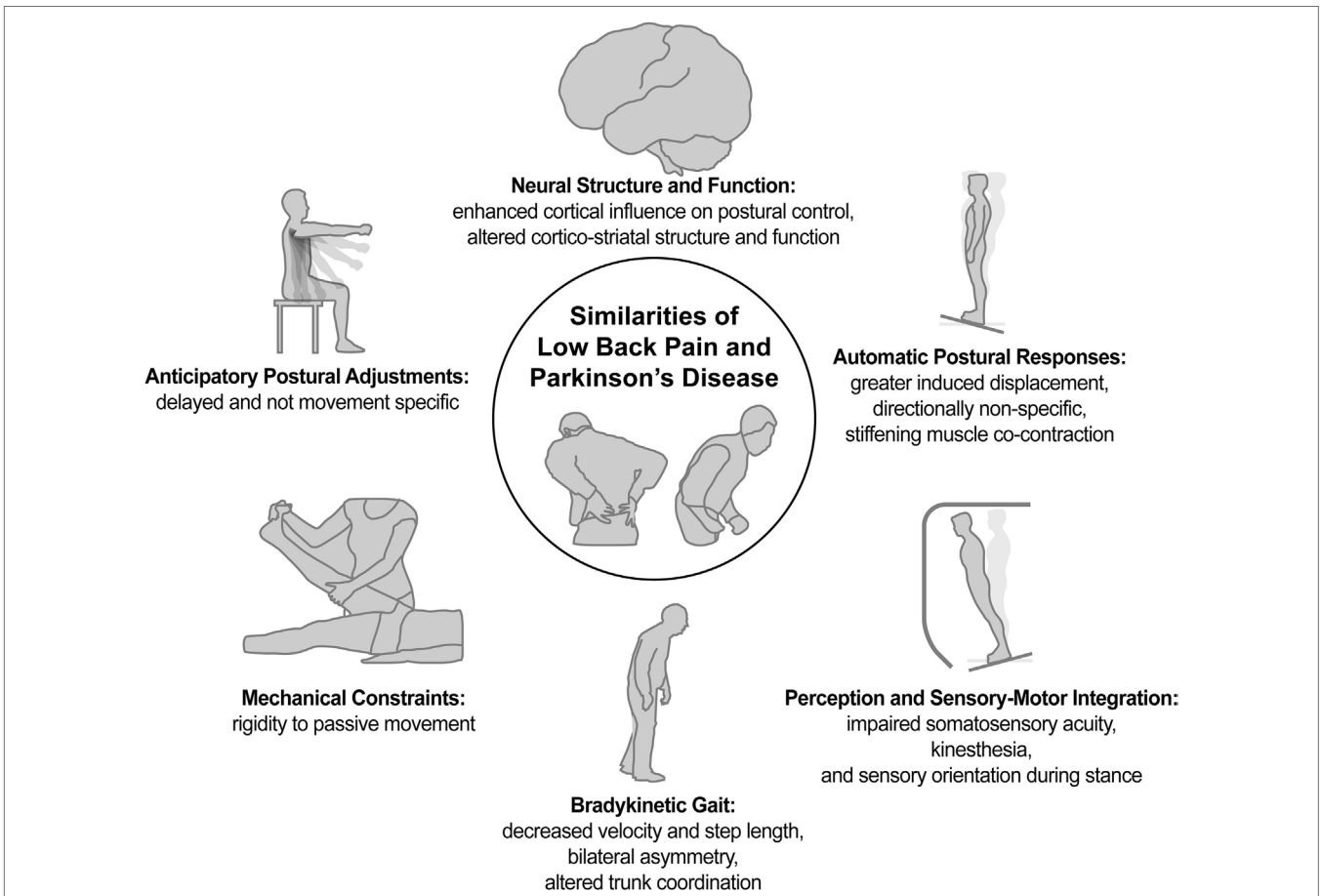


FIGURE 1 | Similarities of low back pain and Parkinson's disease.

rehabilitation that have been more thoroughly researched and considered in practice for neurological rehabilitation (77).

Therefore, despite the many shared postural impairments between PD and LBP, as well as the high prevalence of LBP in people with PD, the treatment approaches of these two health conditions are highly divergent. The coexistence of LBP with PD suggests focused management of pain, strength, and flexibility could potentially, at least partially, help alleviate postural impairment with PD. Similarly, the shared motor impairments of LBP to PD suggests that the management of LBP could optimally include a postural motor retraining approach that is of sufficient focus and training exposure that motor patterns can be modified across multiple domains of postural control. Although important to substantiate mechanisms of pathology associated with LBP as an axial parkinsonism of postural tone and dynamic control, that substantiation does not preclude exploring postural motor retraining for LBP as a potential treatment to improve patient outcomes.

SUMMARY

Review of the literature indicates that both PD and LBP exhibit many shared impairments in postural control as well as some similar changes in neural pathology or function (**Figure 1**). Notably, for LBP (a) the impairments appear less pervasive and more localized to the trunk, (b) the impairments seem less consistent across individuals, and (c) despite some shared characteristics, the neural pathology is holistically of a different nature than for PD. Nevertheless, motor impairments seem more alike than different, suggesting that treatment strategies for LBP could benefit from those provided for PD, and treatment strategies that ameliorate LBP have the potential to benefit the treatment of motor dysfunction and lumbar pain in people with PD. Overall, the similarities of LBP and PD in postural impairment and associated neurophysiology suggest it may not be so implausible to consider LBP as an axial parkinsonism, rendering it the most prevalent parkinsonism in the world.

AUTHOR CONTRIBUTIONS

All authors contributed to generating the scientific arguments of this perspective paper. First draft was generated by JJ, and critical review and editing was provided by all other authors.

ACKNOWLEDGMENTS

The authors thank the many contributors to the cited work that generated this perspective paper.

FUNDING

Articles with contributions by the authors who were cited in this perspective were supported by NIH grants R37AG06457, F31NS048800, T32AR07568-09, T32AG023477, F32HD070796, F32HD008520, K01HD01134, 2R01HD040909, and 5P20RR0 16435.

REFERENCES

1. Stovner LJ, Hoff JM, Svalheim S, Gilhus NE. Neurological disorders in the global burden of disease 2010 study. *Acta Neurol Scand Suppl* (2014) 198:1–6. doi:10.1111/ane.12229
2. Klockgether T, Borutta M, Rapp H, Spieker S, Dichgans J. A defect of kinesthesia in Parkinson's disease. *Mov Disord* (1995) 10:460–5. doi:10.1002/mds.870100410
3. Demirci M, Grill S, Mcshane L, Hallett M. A mismatch between kinesthetic and visual perception in Parkinson's disease. *Ann Neurol* (1997) 41:781–8. doi:10.1002/ana.410410614
4. Sathian K, Zangaladze A, Green J, Vitek JL, Delong MR. Tactile spatial acuity and roughness discrimination: impairments due to aging and Parkinson's disease. *Neurology* (1997) 49:168–77. doi:10.1212/WNL.49.1.168
5. Adamovich SV, Berkinblit MB, Hening W, Sage J, Poizner H. The interaction of visual and proprioceptive inputs in pointing to actual and remembered targets in Parkinson's disease. *Neuroscience* (2001) 104:1027–41. doi:10.1016/S0306-4522(01)00099-9
6. Jacobs JV, Horak FB. Abnormal proprioceptive-motor integration contributes to hypometric postural responses of subjects with Parkinson's disease. *Neuroscience* (2006) 141:999–1009. doi:10.1016/j.neuroscience.2006.04.014
7. Konczak J, Corcos DM, Horak F, Poizner H, Shapiro M, Tuite P, et al. Proprioception and motor control in Parkinson's disease. *J Mot Behav* (2009) 41:543–52. doi:10.3200/35-09-002
8. Wright WG, Gurfinkel VS, King LA, Nutt JG, Cordo PJ, Horak FB. Axial kinesthesia is impaired in Parkinson's disease: effects of levodopa. *Exp Neurol* (2010) 225:202–9. doi:10.1016/j.expneurol.2010.06.016
9. Moseley GL. I can't find it! Distorted body image and tactile dysfunction in patients with chronic back pain. *Pain* (2008) 140:239–43. doi:10.1016/j.pain.2008.08.001
10. Brumagne S, Cordo P, Lysens R, Verschueren S, Swinnen S. The role of paraspinal muscle spindles in lumbosacral position sense in individuals with and without low back pain. *Spine (Phila Pa 1976)* (2000) 25:989–94. doi:10.1097/00007632-200004150-00015
11. Lee AS, Cholewicki J, Reeves NP, Zazulak BT, Mysliwiec LW. Comparison of trunk proprioception between patients with low back pain and healthy controls. *Arch Phys Med Rehabil* (2010) 91:1327–31. doi:10.1016/j.apmr.2010.06.004
12. Chong RK, Horak FB, Frank J, Kaye J. Sensory organization for balance: specific deficits in Alzheimer's but not in Parkinson's disease. *J Gerontol A Biol Sci Med Sci* (1999) 54:M122–8. doi:10.1093/gerona/54.3.M122
13. Frenklach A, Louie S, Koop MM, Bronte-Stewart H. Excessive postural sway and the risk of falls at different stages of Parkinson's disease. *Mov Disord* (2009) 24:377–85. doi:10.1002/mds.22358
14. Della Volpe R, Popa T, Ginanneschi F, Spidalieri R, Mazzocchio R, Rossi A. Changes in coordination of postural control during dynamic stance in chronic low back pain patients. *Gait Posture* (2006) 24:349–55. doi:10.1016/j.gaitpost.2005.10.009
15. Brumagne S, Janssens L, Knapen S, Claeys K, Suuden-Johanson E. Persons with recurrent low back pain exhibit a rigid postural control strategy. *Eur Spine J* (2008) 17:1177–84. doi:10.1007/s00586-008-0709-7
16. Zetterberg H, Frykberg GE, Gaverth J, Lindberg PG. Neural and nonneural contributions to wrist rigidity in Parkinson's disease: an explorative study using the NeuroFlexor. *Biomed Res Int* (2015) 2015:276182. doi:10.1155/2015/276182
17. Kwon KY, Kim M, Lee SM, Kang SH, Lee HM, Koh SB. Is reduced arm and leg swing in Parkinson's disease associated with rigidity or bradykinesia? *J Neurol Sci* (2014) 341:32–5. doi:10.1016/j.jns.2014.03.041
18. Franzen E, Paquette C, Gurfinkel VS, Cordo PJ, Nutt JG, Horak FB. Reduced performance in balance, walking and turning tasks is associated with increased neck tone in Parkinson's disease. *Exp Neurol* (2009) 219:430–8. doi:10.1016/j.expneurol.2009.06.013
19. Bartolic A, Pirtosek Z, Rozman J, Ribaric S. Postural stability of Parkinson's disease patients is improved by decreasing rigidity. *Eur J Neurol* (2005) 12:156–9. doi:10.1111/j.1468-1331.2004.00942.x
20. Cano-De-La-Cuerda R, Vela-Desojo L, Miangolarra-Page JC, Macias-Macias Y, Munoz-Hellin E. Axial rigidity and quality of life in patients with Parkinson's disease: a preliminary study. *Qual Life Res* (2011) 20:817–23. doi:10.1007/s11136-010-9818-y

21. Wright WG, Gurfinkel VS, Nutt J, Horak FB, Cordo PJ. Axial hypertonicity in Parkinson's disease: direct measurements of trunk and hip torque. *Exp Neurol* (2007) 208:38–46. doi:10.1016/j.expneurol.2007.07.002
22. Wong AY, Kawchuk GN. The clinical value of assessing lumbar posteroanterior segmental stiffness: a narrative review of manual and instrumented methods. *PM R* (2016) 9(8):816–30. doi:10.1016/j.pmrj.2016.12.001
23. Cacciatore TW, Gurfinkel VS, Horak FB, Cordo PJ, Ames KE. Increased dynamic regulation of postural tone through Alexander technique training. *Hum Mov Sci* (2011) 30:74–89. doi:10.1016/j.humov.2010.10.002
24. Massion J. Movement, posture and equilibrium: interaction and coordination. *Prog Neurobiol* (1992) 38:35–56. doi:10.1016/0301-0082(92)90034-C
25. Rocchi L, Chiari L, Mancini M, Carlson-Kuhta P, Gross A, Horak FB. Step initiation in Parkinson's disease: influence of initial stance conditions. *Neurosci Lett* (2006) 406:128–32. doi:10.1016/j.neulet.2006.07.027
26. Jacobs JV, Lou JS, Kraakevik JA, Horak FB. The supplementary motor area contributes to the timing of the anticipatory postural adjustment during step initiation in participants with and without Parkinson's disease. *Neuroscience* (2009) 164:877–85. doi:10.1016/j.neuroscience.2009.08.002
27. Bazalgette D, Zattara M, Bathien N, Bouisset S, Rondot P. Postural adjustments associated with rapid voluntary arm movements in patients with Parkinson's disease. *Adv Neurol* (1987) 45:371–4.
28. Hodges PW, Richardson CA. Altered trunk muscle recruitment in people with low back pain with upper limb movement at different speeds. *Arch Phys Med Rehabil* (1999) 80:1005–12. doi:10.1016/S0003-9993(99)90052-7
29. Sadeghi M, Talebian S, Olyaei GR, Attarbashi Moghadam B. Preparatory brain activity and anticipatory postural adjustments accompanied by externally cued weighted-rapid arm rise task in non-specific chronic low back pain patients and healthy subjects. *Springerplus* (2016) 5:674. doi:10.1186/s40064-016-2342-y
30. Lomond KV, Jacobs JV, Hitt JR, Desarno MJ, Bunn JY, Henry SM. Effects of low back pain stabilization or movement system impairment treatments on voluntary postural adjustments: a randomized controlled trial. *Spine J* (2015) 15:596–606. doi:10.1016/j.spinee.2014.10.020
31. Horak FB, Dimitrova D, Nutt JG. Direction-specific postural instability in subjects with Parkinson's disease. *Exp Neurol* (2005) 193:504–21. doi:10.1016/j.expneurol.2004.12.008
32. Jacobs JV, Dimitrova DM, Nutt JG, Horak FB. Can stooped posture explain multidirectional postural instability in patients with Parkinson's disease? *Exp Brain Res* (2005) 166:78–88. doi:10.1007/s00221-005-2346-2
33. Dimitrova D, Horak FB, Nutt JG. Postural muscle responses to multidirectional translations in patients with Parkinson's disease. *J Neurophysiol* (2004) 91:489–501. doi:10.1152/jn.00094.2003
34. Henry SM, Hitt JR, Jones SL, Bunn JY. Decreased limits of stability in response to postural perturbations in subjects with low back pain. *Clin Biomech (Bristol, Avon)* (2006) 21:881–92. doi:10.1016/j.clinbiomech.2006.04.016
35. Radebold A, Cholewicki J, Panjabi MM, Patel TC. Muscle response pattern to sudden trunk loading in healthy individuals and in patients with chronic low back pain. *Spine (Phila Pa 1976)* (2000) 25:947–54. doi:10.1097/00007632-200004150-00009
36. Jones SL, Henry SM, Raasch CC, Hitt JR, Bunn JY. Individuals with non-specific low back pain use a trunk stiffening strategy to maintain upright posture. *J Electromyogr Kinesiol* (2012) 22:13–20. doi:10.1016/j.jelekin.2011.10.006
37. Jacobs JV, Henry SM, Jones SL, Hitt JR, Bunn JY. A history of low back pain associates with altered electromyographic activation patterns in response to perturbations of standing balance. *J Neurophysiol* (2011) 106:2506–14. doi:10.1152/jn.00296.2011
38. Jacobs JV, Lomond KV, Hitt JR, Desarno MJ, Bunn JY, Henry SM. Effects of low back pain and of stabilization or movement-system-impairment treatments on induced postural responses: a planned secondary analysis of a randomised controlled trial. *Man Ther* (2016) 21:210–9. doi:10.1016/j.math.2015.08.006
39. Jacobs JV, Roy CL, Hitt JR, Popov RE, Henry SM. Neural mechanisms and functional correlates of altered postural responses to perturbed standing balance with chronic low back pain. *Neuroscience* (2016) 339:511–24. doi:10.1016/j.neuroscience.2016.10.032
40. Marsili L, Agostino R, Bologna M, Belvisi D, Palma A, Fabbrini G, et al. Bradykinesia of posed smiling and voluntary movement of the lower face in Parkinson's disease. *Parkinsonism Relat Disord* (2014) 20:370–5. doi:10.1016/j.parkreldis.2014.01.013
41. Bologna M, Leodori G, Stirpe P, Paparella G, Colella D, Belvisi D, et al. Bradykinesia in early and advanced Parkinson's disease. *J Neurol Sci* (2016) 369:286–91. doi:10.1016/j.jns.2016.08.028
42. Peterson DS, Horak FB. Neural control of walking in people with parkinsonism. *Physiology (Bethesda)* (2016) 31:95–107. doi:10.1152/physiol.00034.2015
43. Tan D, Danoudis M, Mcginley J, Morris ME. Relationships between motor aspects of gait impairments and activity limitations in people with Parkinson's disease: a systematic review. *Parkinsonism Relat Disord* (2012) 18:117–24. doi:10.1016/j.parkreldis.2011.07.014
44. Horak FB, Mancini M. Objective biomarkers of balance and gait for Parkinson's disease using body-worn sensors. *Mov Disord* (2013) 28:1544–51. doi:10.1002/mds.25684
45. Keefe FJ, Hill RW. An objective approach to quantifying pain behavior and gait patterns in low back pain patients. *Pain* (1985) 21:153–61. doi:10.1016/0304-3959(85)90285-4
46. Lamoth CJ, Daffertshofer A, Meijer OG, Beek PJ. How do persons with chronic low back pain speed up and slow down? Trunk-pelvis coordination and lumbar erector spinae activity during gait. *Gait Posture* (2006) 23:230–9. doi:10.1016/j.gaitpost.2005.02.006
47. Cimolin V, Vismara L, Galli M, Zaina F, Negrini S, Capodaglio P. Effects of obesity and chronic low back pain on gait. *J Neuroeng Rehabil* (2011) 8:55. doi:10.1186/1743-0003-8-55
48. Marras WS, Wongsam PE. Flexibility and velocity of the normal and impaired lumbar spine. *Arch Phys Med Rehabil* (1986) 67:213–7.
49. Boston JR, Rudy TE, Lieber SJ, Stacey BR. Measuring treatment effects on repetitive lifting for patients with chronic low back pain: speed, style, and coordination. *J Spinal Disord* (1995) 8:342–51. doi:10.1097/00002517-199510000-00002
50. Hsiao IT, Weng YH, Hsieh CJ, Lin WY, Wey SP, Kung MP, et al. Correlation of Parkinson disease severity and 18F-DTBZ positron emission tomography. *JAMA Neurol* (2014) 71:758–66. doi:10.1001/jamaneurol.2014.290
51. Baliki MN, Petre B, Torbey S, Herrmann KM, Huang L, Schnitzer TJ, et al. Corticostriatal functional connectivity predicts transition to chronic back pain. *Nat Neurosci* (2012) 15:1117–9. doi:10.1038/nn.3153
52. Kregel J, Meeus M, Malfliet A, Dolphens M, Danneels L, Nijs J, et al. Structural and functional brain abnormalities in chronic low back pain: a systematic review. *Semin Arthritis Rheum* (2015) 45:229–37. doi:10.1016/j.semarthrit.2015.05.002
53. Schmidt-Wilcke T, Leinisch E, Ganssbauer S, Draganski B, Bogdahn U, Altmeppen J, et al. Affective components and intensity of pain correlate with structural differences in gray matter in chronic back pain patients. *Pain* (2006) 125:89–97. doi:10.1016/j.pain.2006.05.004
54. Mao C, Wei L, Zhang Q, Liao X, Yang X, Zhang M. Differences in brain structure in patients with distinct sites of chronic pain: a voxel-based morphometric analysis. *Neural Regen Res* (2013) 8:2981–90. doi:10.3969/j.issn.1673-5374.2013.32.001
55. Popov RE, Gamache J, Hitt JR, Boyd JT, Jacobs JV. Effects of Parkinson's disease on neural preparation and step initiation in unpredictable conditions. *Society for Neuroscience Annual Meeting*. San Diego, CA (2016).
56. Smith BA, Jacobs JV, Horak FB. Effects of magnitude and magnitude predictability of postural perturbations on preparatory cortical activity in older adults with and without Parkinson's disease. *Exp Brain Res* (2012) 222:455–70. doi:10.1007/s00221-012-3232-3
57. Maidan I, Nieuwhof F, Bernad-Elazari H, Reelick MF, Bloem BR, Giladi N, et al. The role of the frontal lobe in complex walking among patients with Parkinson's disease and healthy older adults: an fNIRS study. *Neurorehabil Neural Repair* (2016) 30:963–71. doi:10.1177/1545968316650426
58. Tsao H, Galea MP, Hodges PW. Reorganization of the motor cortex is associated with postural control deficits in recurrent low back pain. *Brain* (2008) 131:2161–71. doi:10.1093/brain/awn154
59. Jacobs JV, Henry SM, Nagle KJ. Low back pain associates with altered activity of the cerebral cortex prior to arm movements that require postural adjustment. *Clin Neurophysiol* (2010) 121:431–40. doi:10.1016/j.clinph.2009.11.076
60. Takakusaki K. Functional neuroanatomy for posture and gait control. *J Mov Disord* (2017) 10:1–17. doi:10.14802/jmd.16062
61. Morton SM, Bastian AJ. Cerebellar control of balance and locomotion. *Neuroscientist* (2004) 10:247–59. doi:10.1177/1073858404263517
62. Horak FB. Postural compensation for vestibular loss. *Ann N Y Acad Sci* (2009) 1164:76–81. doi:10.1111/j.1749-6632.2008.03708.x
63. Beyaert C, Vasa R, Frykberg GE. Gait post-stroke: pathophysiology and rehabilitation strategies. *Neurophysiol Clin* (2015) 45:335–55. doi:10.1016/j.neucli.2015.09.005

64. Alam U, Riley DR, Jugdey RS, Azmi S, Rajbhandari S, D'aout K, et al. Diabetic neuropathy and gait: a review. *Diabetes Ther* (2017) 8:1253–64. doi:10.1007/s13300-017-0295-y
65. Burton RR. Parkinson's disease without tremor masquerading as mechanical back pain; a case report. *J Can Chiropr Assoc* (2008) 52:185–92.
66. Sandyk R. Back pain as an early symptom of Parkinson's disease. *S Afr Med J* (1982) 61:3.
67. Farnikova K, Krobot A, Kanovsky P. Musculoskeletal problems as an initial manifestation of Parkinson's disease: a retrospective study. *J Neurol Sci* (2012) 319:102–4. doi:10.1016/j.jns.2012.05.002
68. Etchepare F, Rozenberg S, Mirault T, Bonnet AM, Lecorre C, Agid Y, et al. Back problems in Parkinson's disease: an underestimated problem. *Joint Bone Spine* (2006) 73:298–302. doi:10.1016/j.jbspin.2005.05.006
69. Broetz D, Eichner M, Gasser T, Weller M, Steinbach JP. Radicular and nonradicular back pain in Parkinson's disease: a controlled study. *Mov Disord* (2007) 22:853–6. doi:10.1002/mds.21439
70. Beiske AG, Loge JH, Ronningen A, Svensson E. Pain in Parkinson's disease: prevalence and characteristics. *Pain* (2009) 141:173–7. doi:10.1016/j.pain.2008.12.004
71. Breen AC, Van Tulder MW, Koes BW, Jensen I, Reardon R, Bronfort G. Monodisciplinary or multidisciplinary back pain guidelines? How can we achieve a common message in primary care? *Eur Spine J* (2006) 15:641–7. doi:10.1007/s00586-005-0883-9
72. Van Der Marck MA, Bloem BR. How to organize multispecialty care for patients with Parkinson's disease. *Parkinsonism Relat Disord* (2014) 20 (Suppl 1):S167–73. doi:10.1016/S1353-8020(13)70040-3
73. Nijkrake MJ, Keus SH, Oostendorp RA, Overeem S, Mulleners W, Bloem BR, et al. Allied health care in Parkinson's disease: referral, consultation, and professional expertise. *Mov Disord* (2009) 24:282–6. doi:10.1002/mds.22377
74. Poitras S, Blais R, Swaine B, Rossignol M. Management of work-related low back pain: a population-based survey of physical therapists. *Phys Ther* (2005) 85:1168–81. doi:10.1093/ptj/85.11.1168.
75. Carey TS, Freburger JK, Holmes GM, Castel L, Darter J, Agans R, et al. A long way to go: practice patterns and evidence in chronic low back pain care. *Spine (Phila Pa 1976)* (2009) 34:718–24. doi:10.1097/BRS.0b013e31819792b0
76. Saragiotto BT, Maher CG, Yamato TP, Costa LO, Costa LC, Ostelo RW, et al. Motor control exercise for nonspecific low back pain: a Cochrane review. *Spine (Phila Pa 1976)* (2016) 41:1284–95. doi:10.1097/BRS.0000000000001645
77. Winstein C, Lewthwaite R, Blanton SR, Wolf LB, Wishart L. Infusing motor learning research into neurorehabilitation practice: a historical perspective with case exemplar from the accelerated skill acquisition program. *J Neurol Phys Ther* (2014) 38:190–200. doi:10.1097/NPT.0000000000000046

Conflict of Interest Statement: FH has an equity interest in APDM, a company that may have commercial interest in the results of this study. This potential conflict of interest has been managed by OHSU and the Portland VA. JJ is employed by Liberty Mutual Insurance. SH declares no commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 30 May 2018
doi: 10.3389/fneur.2018.00373

Gait Stability Has Phase-Dependent Dual-Task Costs in Parkinson's Disease

Peter C. Fino[1,2], Martina Mancini[1,2], Carolin Curtze[1], John G. Nutt[1] and Fay B. Horak[1,2]*

[1] Department of Neurology, Oregon Health & Science University, Portland, OR, United States, [2] Veterans Affairs Portland Health Care System, Portland, OR, United States

Dual-task (DT) paradigms have been used in gait research to assess the automaticity of locomotion, particularly in people with Parkinson's disease (PD). In people with PD, reliance on cortical control during walking leads to greater interference between cognitive and locomotor tasks. Yet, recent studies have suggested that even healthy gait requires cognitive control, and that these cognitive contributions occur at specific phases of the gait cycle. Here, we examined whether changes in gait stability, elicited by simultaneous cognitive DTs, were specific to certain phases of the gait cycle in people with PD. Phase-dependent local dynamic stability (LDS) was calculated for 95 subjects with PD and 50 healthy control subjects during both single task and DT gait at phases corresponding to (1) heel contact—weight transfer, (2) toe-off—early swing, and (3) single-support—mid swing. PD-related DT interference was evident only for the duration of late swing and LDS during the heel contact—weight transfer phase of gait. No PD-related DT costs were found in other traditional spatiotemporal gait parameters. These results suggest that PD-related DT interference occurs only during times where cortical activity is needed for planning and postural adjustments. These results challenge our understanding of DT costs while walking, particularly in people with PD, and encourage researchers to re-evaluate traditional concepts of DT interference.

Keywords: lyapunov exponents, locomotion, cognitive dual-task, local dynamic stability, dynamic postural control

OPEN ACCESS

Edited by:
Emily Keshner, Temple University, United States

Reviewed by:
Ruey-Meei WU, National Taiwan University, Taiwan
Pedro Ribeiro, Universidade Federal do Rio de Janeiro, Brazil

****Correspondence:***
Peter C. Fino
fino@ohsu.edu

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *19 January 2018*
Accepted: *07 May 2018*
Published: *30 May 2018*

Citation:
Fino PC, Mancini M, Curtze C, Nutt JG and Horak FB (2018) Gait Stability Has Phase-Dependent Dual-Task Costs in Parkinson's Disease. Front. Neurol. 9:373. doi: 10.3389/fneur.2018.00373

INTRODUCTION

Locomotor deficits have been widely reported in people with Parkinson's disease (PD) due to the degeneration of basal ganglia and brainstem structures that contribute to control of gait and balance (1–5). To compensate for disrupted subcortical pathways, individuals with PD exhibit more goal-directed locomotion (6–8), with greater reliance on cortical networks when walking (8, 9). In particular, people with PD exhibit increased gait variability (10–13) and abnormal gait dynamics (i.e., how gait parameters vary over time) (14), often attributed to this loss of automaticity and increased cortical control of locomotion (7, 8, 15).

The primary evidence for this compensatory cognitive control in people with PD stems from excessive dual-task (DT) cost (16, 17). DT paradigms involve a cognitive task performed concurrently with a locomotor task, producing interference between the tasks and leading to decreases in the performance of one or both tasks (18–20). While there are several prevailing theories to describe the nature of these performance deficits, called DT costs or dual-task changes (DTC) (21, 22), a common notion maintains that the regulation of the cognitive task and the regulation of gait

interfere with one another. In healthy people, walking normally requires little cortical attention and therefore shows little DTCs, whereas in people with PD, walking requires significant cortical compensation, resulting in large DTCs (18–20, 23, 24).

Larger DTCs in spatiotemporal measures such as stride time, stride length, and gait speed have been reported in people with PD compared to control subjects (25), and larger DTCs have been associated with PD severity (19, 26), or freezing of gait (27, 28). However, these spatiotemporal measures of gait do not separate specific phases within the gait cycle that may be critical to stable locomotion. For instance, electroencephalography studies have indicated that gait involves cortical contributions at specific phases to plan the next foot placement, transfer weight from one step to the next, and maintain stability (29–31). Therefore, the interference between the cognitive task demands and the compensatory cortical control of gait may be specific to certain phases of the gait cycle that depend most on cortical control.

To investigate whether people with PD have DTCs that are specific to certain phases of the gait cycle, we examined phase-dependent measures of gait stability and traditional spatiotemporal gait measures in subjects with idiopathic PD and healthy age-matched control subjects during self-paced, over-ground walking with and without a cognitive DT. Phase-dependent local dynamic stability (LDS) of trunk movements was calculated at three phases of the gait cycle, corresponding to: (1) heel contact—weight transfer, (2) toe-off—early swing, and (3) single-support—mid swing. Phase-dependent LDS quantifies the rate at which local perturbations are attenuated during specific phases of the gait cycle (32). Previous studies have shown that phase-dependent LDS during weight transfer, but not other phases, is a sensitive predictor of falls in elderly populations and can differentiate gait in young and older adults, suggesting that dynamic stability during weight transfer, specifically, is sensitive to neuromotor changes related to fall risk due to aging (32–35).

Greater knowledge of how cognitive tasks interfere with locomotor demands in people with PD may facilitate targeted intervention strategies that focus on specific, highly affected components of gait. Therefore, the purpose of this study was to examine if people with PD exhibit phase-specific DTCs in local dynamic gait stability. We hypothesized that people with PD would exhibit the most severe DTC in dynamic stability during the weight transfer phase of gait compared with controls. We anticipated that these PD-related DTCs in dynamic stability associated with weight transfer would differ between subjects with PD and healthy control subjects while the DTCs in other spatiotemporal gait would not.

MATERIALS AND METHODS

Participants

As part of a larger study (Clinical Trials NCT02231073 and NCT02236286), 100 individuals with idiopathic PD were recruited for this baseline analysis. All subjects with PD had clinically diagnosed idiopathic PD by a neurologist and were tested in the practical OFF levodopa state, after withholding anti-parkinsonian medication for ≥12 h. Inclusion criteria for subjects with PD were (1) between 50 and 90 years old, (2) no major musculoskeletal or peripheral disorders (other than PD) that could significantly affect their balance and gait, (3) ability to stand and walk unassisted, and (4) met criteria for idiopathic PD according to the according to the Brain Bank Criteria for PD (36). In addition, 56 healthy elderly adults were recruited from the community. Exclusion criteria for both groups were as follows: any other neurological disorders or musculoskeletal impairments that interfere with gait or balance, and inability to follow instructions.

Five individuals with PD and six healthy controls were excluded from the final analysis due to technical considerations (see Analysis). Demographic characteristics for subjects retained in the final analysis for each group are provided in **Table 1**. This study was carried out in accordance with the recommendations of the Oregon Health & Science University (OHSU) and Veterans Affairs Portland Health Care System (VAPORHCS) joint institutional review board (IRB) with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the OHSU (#4131) and the OHSU/VAPORHCS joint IRB (#8979).

Procedures

Subjects with PD were clinically rated by a trained examiner on the Motor Section (III) of the Unified PD Rating Scale (MDS-UPDRS), which consists of 23 items related to bradykinesia, rigidity, tremor, and posture and gait signs rated on a four-point scale (37), prior to the mobility assessment. The Posture Instability and Gait Disability (PIGD) subscore was also calculated from the MDS-UPDRS Part III (38).

At the beginning of the mobility assessment, each participant performed a seated cognitive task of reciting every other letter of the alphabet for 1 min. The number of total responses and the number of correct responses were recorded. Each participant was then outfitted with eight inertial sensors (APDM, Inc., Portland, OR, USA), worn on the sternum, lumbar spine, bilaterally on the wrists,

TABLE 1 | Demographic data.

	Controls	PD	*p*-Value
N	50	95	
% Female	38	32	
Age (years)	67.8 (8.0)	68.7 (7.7)	0.947
Height (cm)	171.7 (9.8)	174.2 (10.2)	0.176
Mass (kg)	73.8 (14.6)	79.5 (15.2)	**0.033**
miniBEST	24.6 (2.2)	18.4 (4.7)	**<0.001**
TUG time (s)	18.3 (3.1)	23.2 (10.0)	**0.001**
MoCA	26.8 (1.9)	25.5 (3.6)	**0.019**
SCOPA-COG	32.0 (3.5)	28.1 (5.6)	**<0.001**
Fall in the past year (%)	12	38	
Disease duration (years)	–	7.0 (5.2)	
MDS-UPDRS part III	–	40.4 (12.9)	
PIGD score	–	5.0 (3.2)	
H&Y (range)	–	2–3	
N with freezing of gait	–	26	

Where applicable, groups were compared using independent sample t-tests and a significance level of 0.05.

Bold values indicate significant differences between PD and control subjects.

PD, Parkinson's disease; miniBEST, mini Balance Evaluation Systems Test; MoCA, Montreal Cognitive Assessment; PIGD, Posture Instability and Gait Disability.

anterior distal region of the shanks, and feet. Each inertial sensor recorded tri-axial accelerations and angular velocities at 128 Hz. Data from the wrist-sensors were not used for this study. As part of the larger study, participants completed several tests of balance and mobility, including the Timed Up and Go (TUG), mini Balance Evaluation Systems Test (miniBEST), and self-paced walking trials (**Table 1**). In addition, each participant completed the Montreal Cognitive Assessment (MoCA) (39) and SCOPA-COG.

Analysis of phase-dependent gait stability was based on two self-paced, walking trials: one 2-min trial with no added cognitive task [single-task (ST)] and one 1-min trial with a simultaneous cognitive task (DT). In both conditions, participants were instructed to walk at a comfortable pace back and forth continuously between two lines 7.62 m apart. In the ST condition, participants were instructed to walk for the entire 2 min; no other task was given. In the DT condition, participants were instructed to walk for 1 min while reciting every other letter of the alphabet. The order of the conditions was not randomized; the ST condition was always completed before the DT condition. In the DT condition, participants were given no instruction regarding the prioritization of one task over the other. The number of correct responses during the DT condition was recorded.

Analysis

Raw 3-D accelerometer and gyroscope data were extracted from the sternum, lumbar spine, and shank inertial sensors for each walking trial. Each walking trial was segmented into multiple, straight walking bouts by removing turns and removing one stride immediately preceding and following each turn. Turns were identified using a threshold-based detection algorithm based on the axial angular velocity of the lumbar sensor (40). Heel-contact, toe-off, and mid-swing events were detected using the angular velocity of the shank as described by Salarian et al. (41). Each straight walking bout was then divided into non-overlapping segments of five consecutive, straight walking strides, with each stride time-normalized to 130 points to maintain equal data-length across segments. If a walking bout did not include at least five straight strides, it was excluded from the remainder of the analysis. Subjects were excluded entirely if they had no walking bouts with at least five consecutive straight strides in either the ST or DT conditions.

Phase-dependent LDS was calculated for each walking bout of five strides at three phases within the gait cycle, heel contact—weight transfer; toe off—early swing; and single-support—mid swing, based on procedures described by Ihlen et al. (34). Briefly, a 6D state space $\boldsymbol{X}(t) = [a_{AP}(t), a_{ML}(t), a_{ML}(t), \omega_{AP}(t), \omega_{ML}(t), \omega_{VT}(t)]$ was constructed using the 3D trunk accelerations $a(t)$ and 3D trunk angular velocities $\omega(t)$ from the sternum inertial sensor. Next, points corresponding to heel-contact, toe-off, and mid-swing events were found within the state space, and two nearest neighbors within the space were identified for each event. For each gait event, the average distances from the trajectories of the two nearest neighbors to the trajectory of gait event were tracked for one step, and mean log divergence curves were created by mapping the average distance across all similar gait events (e.g., all heel-contact events, all toe-off events, and all mid-swing events) as a function of the percentage of normalized stride. Phase-dependent LDS was then estimated for each segment using maximum finite-time Lyapunov exponents calculated from the slope of the mean log divergence curves from the initial gait event to the next 10% of the step cycle (i.e., 5% of the gait cycle) for each phase, heel contact (λ_{HC}), toe off (λ_{TO}), and mid swing (λ_{MS}) (e.g., heel contact + 5% of gait cycle, toe off + 5% of gait cycle, and mid swing + 5% of the gait cycle, respectively). This procedure can be described mathematically using the following equation:

$$\lambda_{bout} = \frac{\langle \ln \langle d_i(t) \rangle \rangle_{step}}{t},$$

where $\langle d_i(t) \rangle$ is the average Euclidean distance between the i nearest neighbor trajectories and the reference trajectory at each point in time t, where the gait event (e.g., heel contact, toe off, or mid swing) defined $t = 0$ within the state space, $\langle \ldots \rangle_{step}$ is the average over all steps within the bout, and λ_{bout} is the estimate of phase-dependent LDS for a single bout. The median λ_{HC}, λ_{TO}, and λ_{MS} across all walking bouts was used as the final estimate of phase-dependent LDS at heel contact, toe off, and mid swing, respectively.

Traditional LDS, λ_{Kantz}, was also calculated for each walking segment of five time-normalized strides following Kantz's algorithm (42) and previous reports for estimating local dynamics stability over short bouts of gait (43–45). A 9D state space was constructed from the three-dimensional trunk accelerations and their twice time-delayed copies using a fixed time delay of 0.25 of the average stride time. For each point, the average distance to the two nearest neighbors of the trajectory were tracked for one step, and mean log divergence curves were created by mapping the average distance across all points as a function of the percentage of normalized stride. Traditional LDS, λ_{Kantz}, was then estimated for each segment using maximum finite-time Lyapunov exponents calculated from the slope of the mean log divergence curves from the 0 to 0.5 strides, and the median across all walking segments was used as the final estimate of λ_{Kantz}. For all four stability outcomes, greater values of λ indicate faster divergence or nearby trajectories in state space and are therefore associated with less stability; smaller values of λ indicate slower divergence and are typically associated with increased stability (46, 47).

To compare the DTC of stability outcomes to the DTC of traditional gait measures, temporal gait measures of stride time, double support time, early swing time (toe off to mid swing), and late swing time (mid swing to heel contact) were calculated from the difference in time between respective gait events. Gait speed and stride length were calculated from Mobility Lab software using analysis version 3.0 (Mobility Lab v2, APDM, Inc., Portland, OR, USA).

To evaluate the performance on the cognitive task, the total number of responses and the number of correct responses were tabulated for both the seated and DT walking conditions. Accuracy was calculated as the number of correct responses divided by the total number of responses $\left(\text{Accuracy} = \frac{\#\text{Correct}}{\text{Total}} \right)$. For cognitive task outcomes of total responses, correct responses, and accuracy, the DTC was calculated as the change relative to seated.

Statistical Analysis

Independent sample *t*-tests compared age, height, mass, mini-BEST scores, MoCA scores, and SCOPA-COG scores between the PD and control groups. To investigate whether outcomes differed between groups, linear mixed models were fit for each stability outcome (λ_{HC}, λ_{TO}, λ_{MS}, and λ_{Kantz}), spatiotemporal measure of gait (gait speed, stride length, stride time, double support time, early swing time, and late swing time), and cognitive task outcome (total responses, correct responses, and accuracy). Each model was adjusted for group, task (ST versus DT), and the group*task interaction. The group*task interaction term was included in each model to test whether groups had different linear DTC between task conditions. Each model included a random intercept for each subject to account for the repeated measurements within each subject. For the cognitive outcomes, the task effect compared seated to walking conditions. Gait speed was included as a covariate in models for stability outcomes to account for variations in stability with gait speed (48, 49).

To confirm that any significant group*task interaction was robust to methods of calculating DTC (23), we performed *post hoc* analyses on any outcome with a significant group*task interaction. As the group*task interaction term in the linear mixed models assessed the linear DTC between tasks (DT − ST), group differences in the DTC as a percentage $\left(\%\mathrm{DTC} = \frac{\mathrm{DT}-\mathrm{ST}}{\mathrm{ST}} \times 100\%\right)$ were tested using independent sample *t*-tests. To limit the number of comparisons, the comparison of %DTC between groups was only performed on outcome measures with a significant group*task interaction.

To assess whether DTCs were associated with disease duration, severity, or cognitive function in PD, Spearman correlation coefficients compared the %DTCs of each outcome with a significant group*task interaction to disease duration, the MDS-UPDRS Part III subscore, the PIGD score from the MDS-UPDRS, the miniBEST score, the MoCA score, and the SCOPA-COG score. All statistical analysis was performed in MATLAB r2017a (The Mathworks Inc., Natick, MA, USA) using the Statistics and Machine Learning Toolbox. A significance level of 0.05 was used throughout.

RESULTS

Ninety-five subjects with PD and 50 healthy control subjects were retained in the final analysis after excluding five subjects with PD and six control subjects with no bouts of at least five strides during both ST and DT gait. The PD and control groups had medians (IQR) of 12 (2) and 14 (3) bouts of ST gait, respectively, and 6 (1) and 6 (2) bouts of DT gait, respectively, included in the analysis. There were no significant differences between groups in age or height. The PD group had significantly greater mass, lower miniBEST, MoCA, and SCOPA-COG scores, and had slower TUG times (**Table 1**). Univariate descriptive statistics for each outcome are shown in **Table 2**.

A significant group*task effect was found for phase-dependent stability at weight transfer (λ_{HC}) meaning that subjects with PD became less dynamically stable in the DT condition relative to the difference between conditions in the control subjects (**Table 3**, **Figure 1**). No group*task effect was found for stability at other phases (λ_{TO}, λ_{MS}) or when assessed without regards to phase (λ_{Kantz}). Phase-dependent stability at weight transfer (λ_{HC}) and mid swing (λ_{MS}) was significantly greater (i.e., less stable) with faster gait speeds, while non-phase-dependent stability (λ_{Kantz}) was significantly lower (i.e., more stable) with faster gait.

A significant group*task interaction effect was found for time spent in the late swing phase, where, relative to the ST condition, control subjects increased the time spent in late swing in the DT condition but subjects with PD did not change. No other spatiotemporal measure had a significant

TABLE 2 | Univariate means (SD) of each outcome stratified by group and condition.

	Single task		Dual task	
	Mean	**SD**	**Mean**	**SD**
Gait speed (m/s)				
Control	1.12	0.14	0.95	0.17
PD	0.93	0.20	0.78	0.19
Stride length (m)				
Control	1.19	0.08	1.11	0.10
PD	0.99	0.19	0.89	0.19
Stride time (s)				
Control	1.04	0.13	1.07	0.15
PD	1.07	0.16	1.09	0.15
Time in double support (%)				
Control	22.5	3.9	24.6	3.9
PD	23.9	4.8	26.7	6.2
Time in early swing (%)				
Control	51.2	4.8	48.1	5.4
PD	49.2	5.6	46.4	6.4
Time in late swing (%)				
Control	26.5	3.3	27.4	3.3
PD	27.0	3.3	27.0	3.7
Total cognitive responses (*n*)[a]				
Control	36	7	35	8
PD	32	10	29	8
Correct cognitive responses (*n*)[a]				
Control	34	8	31	8
PD	29	11	26	9
Cognitive task accuracy (%)[a]				
Control	93	9	89	10
PD	90	11	88	11
λ_{HC}				
Control	0.15	0.04	0.13	0.04
PD	0.13	0.04	0.12	0.04
λ_{TO}				
Control	0.07	0.02	0.08	0.02
PD	0.08	0.02	0.08	0.02
λ_{MS}				
Control	0.11	0.02	0.11	0.02
PD	0.12	0.02	0.11	0.02
λ_{Kantz}				
Control	0.30	0.07	0.34	0.08
PD	0.35	0.07	0.37	0.09

[a]*ST condition for cognitive responses refers to the seated condition.*
PD, Parkinson's disease.

TABLE 3 | Results from the linear mixed models for each stability measure.

	Beta	SE	Lower CI	Upper CI	*p*-Value
λ_{HC}					
Intercept	0.072	0.015	0.042	0.103	<0.001
Task (ref ST)	**−0.011**	**0.005**	**−0.020**	**−0.001**	**0.024**
Gait speed	**0.070**	**0.013**	**0.045**	**0.096**	**<0.001**
Group (ref controls)	−0.006	0.007	−0.019	0.007	0.390
Group*Task	**0.011**	**0.005**	**0.000**	**0.021**	**0.043**
λ_{TO}					
Intercept	0.077	0.009	0.060	0.094	<0.001
Task (ref ST)	0.001	0.003	−0.006	0.008	0.756
Gait speed	−0.003	0.007	−0.017	0.011	0.681
Group (ref controls)	**0.008**	**0.004**	**0.001**	**0.012**	**0.029**
Group*Task	−0.003	0.004	−0.011	0.004	0.412
λ_{MS}					
Intercept	0.072	0.009	0.054	0.089	<0.001
Task (ref ST)	0.004	0.003	−0.002	0.010	0.163
Gait speed	**0.031**	**0.008**	**0.016**	**0.046**	**<0.001**
Group (ref controls)	**0.015**	**0.004**	**0.008**	**0.023**	**<0.001**
Group*Task	−0.005	0.003	−0.011	0.002	0.178
λ_{Kantz}					
Intercept	0.471	0.031	0.410	0.533	0.000
Task (ref ST)	0.009	0.013	−0.017	0.035	0.486
Gait speed	**−0.151**	**0.026**	**−0.203**	**−0.100**	**<0.001**
Group (ref controls)	0.020	0.014	−0.007	0.048	0.142
Group*Task	−0.011	0.015	−0.041	0.018	0.452

Lower and upper 95% confidence intervals (CI) for beta are also presented. Bold values indicate significant effects at p < 0.05.

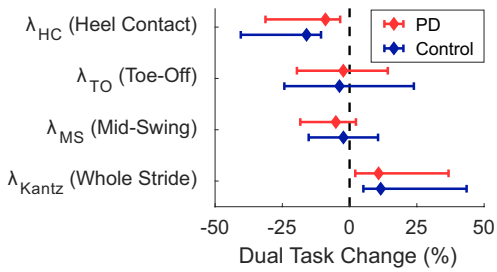


FIGURE 1 | Median dual-task changes (DTC) as percentages (%DTC) and IQRs for phase-dependent local dynamic stability (LDS) measures calculated at (1) heel contact—weight transfer, λ_{HC}, (2) toe off—early swing, λ_{TO}, and (3) single-support—mid swing, λ_{MS}, and traditional LDS calculated at all points within a stride, λ_{Kantz}. DTCs were calculated as a percentage change with respect to single-task gait. *Phase-dependent LDS during heel contact—weight transfer, λ_{HC}, was significantly different between groups whether calculated as a linear change (see **Table 3**), or as a percentage change. Group differences in DTCs as percentages were not tested on other stability outcomes as the group*task interactions were not significant in the initial linear mixed models.

group*task interaction effect indicative of PD-related DTCs. Subjects with PD had significantly slower gait speed, shorter stride lengths, and spent less time in early swing compared to controls (**Table 4**; **Figure 2**). The DT condition led to slower gait speeds, shorter stride lengths, more time spent in double support, and less time in early swing compared to the ST condition across all subjects.

TABLE 4 | Results from the linear mixed models for each spatiotemporal measure.

	Beta	SE	Lower CI	Upper CI	*p*-Value
Gait speed (m/s)					
Intercept	1.12	0.03	1.07	1.17	<0.001
Task (ref ST)	**−0.17**	**0.02**	**−0.20**	**−0.14**	**<0.001**
Group (ref controls)	**−0.20**	**0.03**	**−0.26**	**−0.13**	**<0.001**
Group*Task	0.02	0.02	−0.02	0.06	0.368
Stride length (m)					
Intercept	1.19	0.02	1.15	1.24	<0.001
Task (ref ST)	**−0.08**	**0.01**	**−0.11**	**−0.06**	**<0.001**
Group (ref controls)	**−0.20**	**0.03**	**−0.26**	**−0.14**	**<0.001**
Group*Task	−0.02	0.01	−0.05	0.00	0.090
Stride time (s)					
Intercept	1.04	0.02	0.99	1.08	<0.001
Task (ref ST)	0.03	0.03	−0.02	0.08	0.230
Group (ref controls)	0.04	0.03	−0.02	0.09	0.157
Group*Task	−0.02	0.03	−0.08	0.04	0.532
Time in double support (%)					
Intercept	22.5	0.7	21.1	23.9	<0.001
Task (ref ST)	**2.1**	**0.4**	**1.3**	**3.0**	**<0.001**
Group (ref controls)	1.4	0.9	−0.3	3.1	0.107
Group*Task	0.6	0.5	−0.4	1.7	0.231
Time in early swing (%)					
Intercept	51.1	0.8	49.6	52.7	<0.001
Task (ref ST)	**−3.0**	**0.5**	**−4.0**	**−2.0**	**<0.001**
Group (ref controls)	**−2.0**	**1.0**	**−3.9**	**−0.0**	**0.048**
Group*Task	−0.2	0.6	−0.9	1.4	0.732
Time in late swing (%)					
Intercept	26.5	0.5	25.6	27.5	<0.001
Task (ref ST)	**0.9**	**0.3**	**0.3**	**1.4**	**0.002**
Group (ref controls)	−0.5	0.6	−0.7	1.6	0.431
Group*Task	**−0.9**	**0.3**	**−1.5**	**−0.2**	**0.010**

Lower and upper 95% confidence intervals (CI) for beta are also presented. Bold values indicate significant effects at p < 0.05.

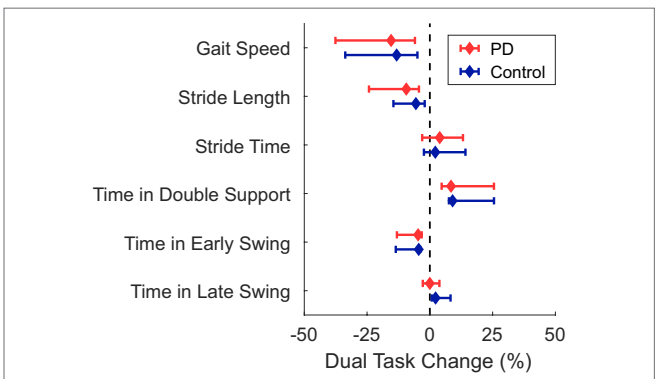


FIGURE 2 | Median dual-task changes (DTC) as percentages (%DTC) and IQRs for spatiotemporal measures of gait for people with Parkinson's disease (PD) (red) and healthy control subjects (blue). DTCs were calculated as a percentage change with respect to single-task gait. *Time spent in late swing was significantly different between groups whether calculated as a linear change (see **Table 4**), or as a percentage change. Group differences in DTCs as percentages were not tested on other spatiotemporal outcomes as the group*task interactions were not significant in the initial linear mixed models.

There was no significant group*task interaction for any cognitive task outcome (**Table 5**; **Figure 3**). Main effects of group and task were found for the number of correct responses, but not for

TABLE 5 | Results from the linear mixed models for measures of cognitive task performance.

	Beta	SE	Lower CI	Upper CI	*p*-Value
Number of total responses					
Intercept	35.99	1.23	33.45	38.30	<0.001
Task (ref ST)	−1.30	0.79	−2.86	0.26	0.103
Group (ref controls)	**−3.86**	**1.53**	**−6.87**	**−0.86**	**0.012**
Group*Task	−1.07	1.00	−3.00	0.92	0.299
Number of correct responses					
Intercept	33.5	1.29	30.96	36.04	<0.001
Task (ref seated)	**−2.60**	**0.81**	**−4.19**	**−1.02**	**0.001**
Group (ref controls)	**−4.29**	**1.60**	**−7.45**	**−1.14**	**0.008**
Group*Task	−0.29	1.01	−2.28	1.69	0.771
Cognitive task accuracy (%)					
Intercept	92.5	14.7	89.6	95.4	<0.001
Task (ref seated)	**−3.4**	**1.3**	**−5.9**	**−0.8**	**0.010**
Group (ref controls)	−2.6	1.8	−6.2	0.9	0.149
Group*Task	−1.4	1.6	−1.8	4.6	0.399

Lower and upper 95% confidence intervals (CI) for beta are also presented. Bold values indicate significant effects at p < 0.05.

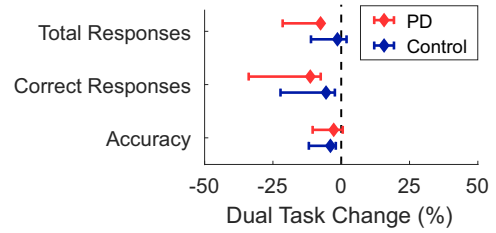


FIGURE 3 | Median dual-task changes (DTC) as percentages (%DTC) and IQRs for cognitive outcomes for people with Parkinson's disease (PD) (red) and healthy control subjects (blue). DTCs were calculated as a percentage change with respect to seated. Group differences in DTCs as percentages were not tested for any cognitive outcome as no group*task interactions were significant in the initial linear mixed models.

the number of total responses or accuracy. Subjects with PD had fewer correct responses than the control group across both conditions, and the walking condition had fewer correct responses than the seated condition across both groups.

Post hoc t-tests were only performed on the %DTC for two outcomes, λ_{HC} and time spent in late swing, as those were the only outcomes with significant group*task interactions in the linear mixed models. The %DTC for λ_{HC} was significantly smaller in subjects with PD compared with controls ($t = -2.56$, $p = 0.012$). Similarly, the %DTC for time spent in late swing was significantly smaller in subjects with PD compared to controls ($t = -2.78$, $p = 0.006$).

The %DTC for time in late swing was significantly associated with TUG time in controls only ($\rho = 0.41$, $p = 0.004$), but not in subjects with PD. The %DTCs of λ_{HC} and time in late swing were not significantly associated with disease duration, MDS-UPDRS Part III subscore, or UPDRS PIGD score in subjects with PD (**Table 6**). The %DTCs of λ_{HC} and time in late swing were not associated with miniBEST, MoCA, or SCOPA-COG scores, or with age, height, or mass in either group (**Figure 4**).

TABLE 6 | Spearman correlation coefficients and *p*-values for comparisons between the %DTC of λ_{HC} and clinical characteristics in subjects with Parkinson's disease.

	Disease duration		MDS-UPDRS part III		Posture Instability and Gait Disability	
	ρ	*p*-Value	ρ	*p*-Value	ρ	*p*-Value
%DTC λ_{HC}	−0.011	0.917	0.091	0.384	0.063	0.549
%DTC time in late swing	0.039	0.709	0.075	0.475	0.109	0.294

DISCUSSION

We compared the DTC on phase-dependent LDS during phases of the gait cycle beginning with heel contact, toe off, and mid swing in people with PD and healthy matched controls. Compared to controls, people with PD only demonstrated greater DTCs during the phase beginning at heel contact and corresponding to the weight transfer phase of gait. Many previous studies have described larger DTCs on spatiotemporal measures of gait in people with PD compared to controls [see review by Kelly et al. (25)], but these measures cannot examine intra-stride patterns. Our results suggest that cognitive DTs affect gait stability in an intra-stride, phase-specific pattern in people with PD.

Increasing evidence has suggested that gait has intermittent contributions from the cortex, and that these contributions are locked to specific phases of the gait cycle (29, 31, 50–52). Cortical activity in the premotor cortex is highest during single-limb stance prior to heel contact, representative of cortical planning of balance control and foot placement (30, 50). Others have reported elevated activity in the sensorimotor cortices during weight transfer (31, 52, 53), indicative of sensory feedback for state estimation of postural adjustments (54). While it is not clear how variations in cortical activity affect DT interference, our results suggest DTC can similarly fluctuate within a gait cycle.

We found significant DTCs, indicated by a significant main effect of task, in both the PD and control groups with slower gait speeds, shorter stride lengths, more time spent in double support, and less time spent in early swing compared to the ST condition. However, these DTCs did not differ between subjects with PD and healthy control subjects. Previous work by Rochester et al. (23) suggested that DT deficits in PD stem from two underlying causes: age-related DT declines in overall gait performance and PD-related DT deficits in specific measures of postural control. Specifically, PD-related DT deficits were apparent only in step width and step width variability (23), implying that cognitive tasks only have PD-related interference with measures pertaining to the unstable mediolateral (ML) direction during gait (55, 56). Stable gait is largely achieved by placing the swing limb to redirect the lateral movement of the center-of-mass (57, 58). While weight transfer occurs after placement of the swing limb, planning the placement of the swing limb occurs during second half of the swing phase (59), during a period of elevated activity

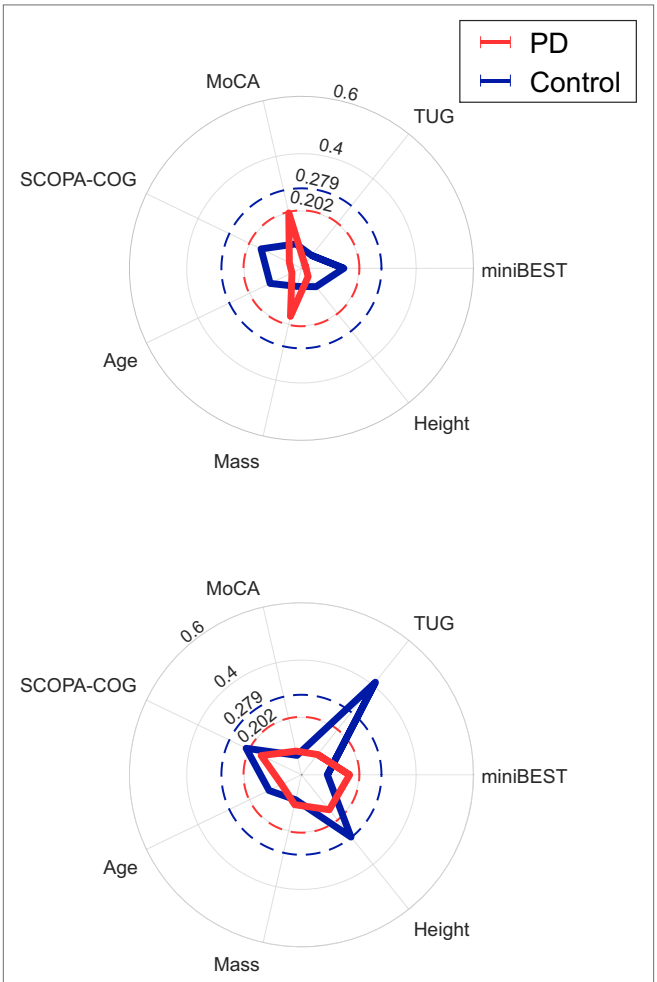


FIGURE 4 | Radar plots of the absolute value of Spearman's correlation coefficients between demographic and clinical outcomes and the %DTCs of λ_{HC} (top) or time in late swing (bottom). The dashed red and blue circles indicate the critical ρ value for $p = 0.05$ for Parkinson's disease (PD) and control groups, respectively. The %DTC for time in late swing was significantly associated with TUG time in controls only ($\rho = 0.41$, $p = 0.004$). There were no other significant correlations ($p > 0.05$).

in the premotor cortex (50). In a study of healthy elderly, Bruijn et al. (30) found that stabilizing healthy young participants in the ML direction significantly decreased step width, improved trunk stability, and reduced the activity in the premotor cortex immediately before and during weight transfer. Therefore, it appears that stability, particularly in the ML direction, might require significant activity from the premotor and supplementary motor areas (SMA) for correct limb placement and weight transfer. Thus, the PD-related DTCs specific to the duration of the late swing phase of gait and gait stability during weight transfer are consistent with the effects of basal ganglia degeneration on SMA connectivity and postural adjustments in people with PD (24, 60–62). While we lack data on cortical activation to make firm conclusions about the nature of the DTC-related deficits we observed, we speculate that the PD-related DTCs during the late swing phase and weight transfer (λ_{HC}) may be indicative of greater cortical involvement for locomotion in PD, due to reduced automaticity (7, 8). In people with PD, reduced automaticity and increased cortical control over action has been put forward to explain DT costs during gait (23). Our results suggest that DT interference, possibly due to increased reliance on cortical control in PD, may be more likely to occur at specific phases of gait that normally require cortical activity for stabilization, such as during late swing and weight transfer, as there may be less cognitive resources available for concurrent tasks at these phases.

We compared several spatiotemporal measures and measures of stability, but only phase-dependent LDS at weight transfer (λ_{HC}), and the time spent in late swing immediately prior to weight transfer, demonstrated PD-related DTCs. This result agrees with Rochester et al. (23), who similarly found differences in postural stability measures of step width, but failed to find PD-related differences in step length, step time, or step velocity. Furthermore, these results suggest that DT assessments may ignore temporal variation in the demands of the locomotor task. While several models of DT interference exist (e.g., bottleneck, resource limiting, and cross talk) (21), an implicit assumption across all models is that the two competing tasks occur simultaneously and uniformly. While studies have investigated how different cognitive tasks with variations in attentional focus over time influence DT costs during gait (63–65), few studies have examined the temporal variation of the demands of the locomotor task. Nonetheless, the idea that attentional demands vary across a gait cycle was suggested early on by Lajoie et al. (66), who found verbal reaction time was slower during single support compared to double support phases of the gait cycle. However, while Lajoie et al. (66), found reaction time varied by gait cycle in healthy young adults, they did not find DT differences in gait variables when assessing entire strides such as cadence, stride length, stride time, and gait speed. The general lack of consideration for intra-stride changes related to the locomotor task may help explain why DT assessments of gait have little added value over ST assessments when predicting future falls (67, 68). Supporting this notion, we found PD-related, DT interference on LDS only at a specific phase of gait, weight transfer. However, it is possible that severe PD-related DTCs, even if occurring only around weight transfer, could manifest in spatiotemporal measures of whole strides. Other studies have found PD-related DTCs in a variety of spatiotemporal measures, but there is variability about the magnitude of the effect and which spatiotemporal measures are affected (25). A phase-specific DTC in people with PD may explain some of this variability, where the PD-related DTC is blurred across the entire stride and only large magnitude DTCs are measurable. Combined, these results suggest that assessments should examine specific phases of gait, and that targeted interventions should specifically focus on improving the automaticity of foot placement and weight transfer during gait.

Few, if any, studies have compared phase-dependent LDS between people with PD and healthy controls. Yet, our results agree with previous studies that found phase-dependent LDS differences between young and older adults (33) and elderly fallers and non-fallers (34) specific to the weight transfer phase.

Notably, older adults had larger λ_{HC}, indicative of less stable dynamics, than young adults during steady-state treadmill walking (33). In a later analysis of data obtained during uncontrolled walking, Ihlen and colleagues (34, 35) found elderly with a history of falls had lower λ_{HC} values than non-fallers during daily living activities, indicating more stable dynamics. This disparity was attributed to fallers engaging in less complex tasks at home. A separate analysis found λ_{HC} increased with increasing gait speed (32), suggesting gait speed may have played a role in the lower λ_{HC} values in fallers compared to non-fallers. In our study, the control subjects decreased λ_{HC} and slowed down when walking with a cognitive task, while individuals with PD slowed down but did not proportionally change λ_{HC}. Therefore, after adjusting for changes in gait speed, our results can be interpreted similarly to the previous studies on steady-state gait and aligns with the larger body of literature on LDS, where larger λ values indicate less stability (47). Accordingly, cognitive tasks during gait induced less stable dynamics during weight transfer in people with PD compared with similar-aged, elderly control subjects.

While this study benefited from a large sample size, several limitations should be considered when generalizing the results. First, the analysis of LDS and phase-dependent LDS was performed on a small number of consecutive strides. The small number of stride may have increased the within-subject variability across bouts which was partially mitigated by obtaining many bouts of gait (44). In preliminary analyses, we excluded 26 subjects with PD and 16 control subjects who had less than four bouts—21% of the current sample—and we found identical results as presented here, suggesting that the current results are robust; the results do not appear to be driven by subjects with a small number of bouts. However, the present conclusions could be strengthened in future analyses considering a greater number of, and longer, bouts of consecutive strides.

Second, all subjects performed the same cognitive task, which introduced two confounding variables: between-subject differences in cognition and temporal variations in cognitive load as mentioned earlier. The PD group had significantly fewer correct responses across both seated and walking tasks, despite similar total responses, suggesting that our results may be associated with cognitive differences between groups. Yet, the DTC of λ_{HC} was not associated with the MoCA or the SCOPA-COG within either group, suggesting that cognitive differences alone do not explain our results. Furthermore, the lack of a significant group*task interaction for any of the cognitive outcomes suggests that the PD group did not prioritize the cognitive and motor tasks differently than controls. It is possible the fixed order of the conditions may have introduced an order effect. However, the order was consistent across groups and the primary inferences were drawn from the group*task interaction. Similarly, the difference in duration between the walking conditions (2 min ST versus 1 min DT) led to fewer strides and bouts within the DT condition. The shorter DT duration was selected to accommodate people with PD who had difficulty completing 2-min of continuous DT walking. It is possible the different durations influenced the main effect of task, but it is unlikely the main inferences drawn from the group*task interaction were affected.

Finally, it is unclear how freezing of gait influenced our results. While bouts of gait that included a freezing episode were excluded from any analysis, it is unclear whether people PD with and without freezing of gait differed in bouts without a freezing episode. The relatively small number of people with PD who exhibited freezing of gait in our sample prevented a sub-analysis examining this question. However, future studies may investigate whether freezing of gait is similarly associated with phase-dependent DT costs.

Overall, these results challenge our understanding of DT costs while walking, particularly in people with PD. With growing evidence that cortical control occurs during specific phases of gait, it is necessary to re-evaluate traditional concepts of DT interference that may neglect the phasic structure of control during locomotion. Our results suggest that PD-related DT interference occurs only immediately before and during postural adjustments at weight transfer. Interventions, particularly those utilizing DT and multi-task training paradigms, may benefit from focusing on postural adjustments during gait, and future research should directly examine this question using mobile neuroimaging modalities time-locked to phases of the gait cycle.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Oregon Health & Science University (OHSU) and Veterans Affairs Portland Health Care System (VAPORHCS) joint institutional review board (IRB) with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the OHSU (#4131) and the OHSU/VAPORHCS joint IRB (#8979).

AUTHOR CONTRIBUTIONS

PF, MM, and FH conceptualized the question and hypothesis. FH, JN, and MM designed the study from which the data originates. PF, MM, and CC contributed to data collection and analysis. PF, MM, CC, JN, and FH contributed to the interpretation, writing and editing of the manuscript. PF wrote the first draft.

ACKNOWLEDGMENTS

The authors would like to thank Graham Harker, Natassja Pal, Michael Fleming, Heather Schlueter, and Peter Martin for their assistance during data collection and subject recruitment, and special thanks to Dr. Patty Carlson-Kuhta for her contributions throughout the study. This study was supported through funding from the NIH 2R01AG006457 (FH), R00HD078492 01A1 (MM), and VA Merit 5I01RX001075 (FH).

REFERENCES

1. Morris ME, Iansek R, Matyas TA, Summers JJ. The pathogenesis of gait hypokinesia in Parkinson's disease. *Brain* (1994) 117(Pt 5):1169–81. doi:10.1093/brain/117.5.1169
2. Hanakawa T, Katsumi Y, Fukuyama H, Honda M, Hayashi T, Kimura J, et al. Mechanisms underlying gait disturbance in Parkinson's disease: a single photon emission computed tomography study. *Brain* (1999) 122(Pt 7):1271–82. doi:10.1093/brain/122.7.1271
3. Braak H, Del Tredici K, Rub U, De Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* (2003) 24:197–211. doi:10.1016/S0197-4580(02)00065-9
4. Bohnen NI, Albin RL. The cholinergic system and Parkinson disease. *Behav Brain Res* (2011) 221:564–73. doi:10.1016/j.bbr.2009.12.048
5. Galna B, Lord S, Burn DJ, Rochester L. Progression of gait dysfunction in incident Parkinson's disease: impact of medication and phenotype. *Mov Disord* (2015) 30:359–67. doi:10.1002/mds.26110
6. Bohnen NI, Jahn K. Imaging: what can it tell us about parkinsonian gait? *Mov Disord* (2013) 28:1492–500. doi:10.1002/mds.25534
7. Wu T, Hallett M, Chan P. Motor automaticity in Parkinson's disease. *Neurobiol Dis* (2015) 82:226–34. doi:10.1016/j.nbd.2015.06.014
8. Gilat M, Bell PT, Ehgoetz Martens KA, Georgiades MJ, Hall JM, Walton CC, et al. Dopamine depletion impairs gait automaticity by altering cortico-striatal and cerebellar processing in Parkinson's disease. *Neuroimage* (2017) 152:207–20. doi:10.1016/j.neuroimage.2017.02.073
9. Maidan I, Nieuwhof F, Bernad-Elazari H, Reelick MF, Bloem BR, Giladi N, et al. The role of the frontal lobe in complex walking among patients with Parkinson's disease and healthy older adults: an fNIRS study. *Neurorehabil Neural Repair* (2016) 30:963–71. doi:10.1177/1545968316650426
10. Hausdorff JM, Cudkowicz ME, Firtion R, Wei JY, Goldberger AL. Gait variability and basal ganglia disorders: stride-to-stride variations of gait cycle timing in Parkinson's disease and Huntington's disease. *Mov Disord* (1998) 13:428–37. doi:10.1002/mds.870130310
11. Hausdorff JM, Balash J, Giladi N. Effects of cognitive challenge on gait variability in patients with Parkinson's disease. *J Geriatr Psychiatry Neurol* (2003) 16:53–8. doi:10.1177/0891988702250580
12. Schaafsma JD, Giladi N, Balash Y, Bartels AL, Gurevich T, Hausdorff JM. Gait dynamics in Parkinson's disease: relationship to Parkinsonian features, falls and response to levodopa. *J Neurol Sci* (2003) 212:47–53. doi:10.1016/S0022-510X(03)00104-7
13. Moon Y, Sung J, An R, Hernandez ME, Sosnoff JJ. Gait variability in people with neurological disorders: a systematic review and meta-analysis. *Hum Mov Sci* (2016) 47:197–208. doi:10.1016/j.humov.2016.03.010
14. Hausdorff JM. Gait dynamics in Parkinson's disease: common and distinct behavior among stride length, gait variability, and fractal-like scaling. *Chaos* (2009) 19:026113. doi:10.1063/1.3147408
15. Morris ME, Iansek R, Matyas TA, Summers JJ. Stride length regulation in Parkinson's disease. Normalization strategies and underlying mechanisms. *Brain* (1996) 119(Pt 2):551–68. doi:10.1093/brain/119.2.551
16. Wu T, Kansaku K, Hallett M. How self-initiated memorized movements become automatic: a functional MRI study. *J Neurophysiol* (2004) 91:1690–8. doi:10.1152/jn.01052.2003
17. Clark DJ. Automaticity of walking: functional significance, mechanisms, measurement and rehabilitation strategies. *Front Hum Neurosci* (2015) 9:246. doi:10.3389/fnhum.2015.00246
18. O'Shea S, Morris ME, Iansek R. Dual task interference during gait in people with Parkinson disease: effects of motor versus cognitive secondary tasks. *Phys Ther* (2002) 82:888–97.
19. Rochester L, Hetherington V, Jones D, Nieuwboer A, Willems AM, Kwakkel G, et al. Attending to the task: interference effects of functional tasks on walking in Parkinson's disease and the roles of cognition, depression, fatigue, and balance. *Arch Phys Med Rehabil* (2004) 85:1578–85. doi:10.1016/j.apmr.2004.01.025
20. Rochester L, Nieuwboer A, Baker K, Hetherington V, Willems AM, Kwakkel G, et al. Walking speed during single and dual tasks in Parkinson's disease: which characteristics are important? *Mov Disord* (2008) 23:2312–8. doi:10.1002/mds.22219
21. Pashler H. Dual-task interference in simple tasks: data and theory. *Psychol Bull* (1994) 116:220–44. doi:10.1037/0033-2909.116.2.220
22. Tombu M, Jolicoeur P. A central capacity sharing model of dual-task performance. *J Exp Psychol Hum Percept Perform* (2003) 29:3–18. doi:10.1037/0096-1523.29.1.3
23. Rochester L, Galna B, Lord S, Burn D. The nature of dual-task interference during gait in incident Parkinson's disease. *Neuroscience* (2014) 265:83–94. doi:10.1016/j.neuroscience.2014.01.041
24. Peterson DS, Horak FB. Neural control of walking in people with Parkinsonism. *Physiology (Bethesda)* (2016) 31:95–107. doi:10.1152/physiol.00034.2015
25. Kelly VE, Eusterbrock AJ, Shumway-Cook A. A review of dual-task walking deficits in people with Parkinson's disease: motor and cognitive contributions, mechanisms, and clinical implications. *Parkinsons Dis* (2012) 2012:918719. doi:10.1155/2012/918719
26. Lord S, Rochester L, Hetherington V, Allcock LM, Burn D. Executive dysfunction and attention contribute to gait interference in 'off' state Parkinson's disease. *Gait Posture* (2010) 31:169–74. doi:10.1016/j.gaitpost.2009.09.019
27. Peterson DS, Fling BW, Mancini M, Cohen RG, Nutt JG, Horak FB. Dual-task interference and brain structural connectivity in people with Parkinson's disease who freeze. *J Neurol Neurosurg Psychiatry* (2015) 86:786–92. doi:10.1136/jnnp-2014-308840
28. de Souza Fortaleza AC, Mancini M, Carlson-Kuhta P, King LA, Nutt JG, Chagas EF, et al. Dual task interference on postural sway, postural transitions and gait in people with Parkinson's disease and freezing of gait. *Gait Posture* (2017) 56:76–81. doi:10.1016/j.gaitpost.2017.05.006
29. Gwin JT, Gramann K, Makeig S, Ferris DP. Electrocortical activity is coupled to gait cycle phase during treadmill walking. *Neuroimage* (2011) 54:1289–96. doi:10.1016/j.neuroimage.2010.08.066
30. Bruijn SM, Van Dieen JH, Daffertshofer A. Beta activity in the premotor cortex is increased during stabilized as compared to normal walking. *Front Hum Neurosci* (2015) 9:593. doi:10.3389/fnhum.2015.00593
31. Wagner J, Makeig S, Gola M, Neuper C, Muller-Putz G. Distinct beta band oscillatory networks subserving motor and cognitive control during gait adaptation. *J Neurosci* (2016) 36:2212–26. doi:10.1523/JNEUROSCI.3543-15.2016
32. Ihlen EAF, Goihl T, Wik PB, Sletvold O, Helbostad J, Vereijken B. Phase-dependent changes in local dynamic stability of human gait. *J Biomech* (2012) 45:2208–14. doi:10.1016/j.jbiomech.2012.06.022
33. Ihlen EAF, Sletvold O, Goihl T, Wik PB, Vereijken B, Helbostad J. Older adults have unstable gait kinematics during weight transfer. *J Biomech* (2012) 45:1559–65. doi:10.1016/j.jbiomech.2012.04.021
34. Ihlen EA, Weiss A, Helbostad JL, Hausdorff JM. The discriminant value of phase-dependent local dynamic stability of daily life walking in older adult community-dwelling fallers and nonfallers. *Biomed Res Int* (2015) 2015:402596. doi:10.1155/2015/402596
35. Ihlen EA, Weiss A, Beck Y, Helbostad JL, Hausdorff JM. A comparison study of local dynamic stability measures of daily life walking in older adult community-dwelling fallers and non-fallers. *J Biomech* (2016) 49(9):1498–503. doi:10.1016/j.jbiomech.2016.03.019
36. Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. *Arch Neurol* (1999) 56:33–9. doi:10.1001/archneur.56.1.33
37. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord* (2008) 23:2129–70. doi:10.1002/mds.22340
38. Stebbins GT, Goetz CG, Burn DJ, Jankovic J, Khoo TK, Tilley BC. How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: comparison with the unified Parkinson's disease rating scale. *Mov Disord* (2013) 28:668–70. doi:10.1002/mds.25383
39. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* (2005) 53:695–9. doi:10.1111/j.1532-5415.2005.53221.x
40. El-Gohary M, Pearson S, Mcnames J, Mancini M, Horak F, Mellone S, et al. Continuous monitoring of turning in patients with movement disability. *Sensors (Basel)* (2013) 14:356–69. doi:10.3390/s140100356
41. Salarian A, Russmann H, Vingerhoets FJ, Dehollain C, Blanc Y, Burkhard PR, et al. Gait assessment in Parkinson's disease: toward an ambulatory system for long-term monitoring. *IEEE Trans Biomed Eng* (2004) 51:1434–43. doi:10.1109/TBME.2004.827933

42. Kantz H. A robust method to estimate the maximal Lyapunov exponent of a time series. *Phys Lett A* (1994) 185:77–87. doi:10.1016/0375-9601(94)90991-1
43. Sloot LH, Van Schooten KS, Bruijn SM, Kingma H, Pijnappels M, Van Dieën JH. Sensitivity of local dynamic stability of over-ground walking to balance impairment due to galvanic vestibular stimulation. *Ann Biomed Eng* (2011) 39:1563–9. doi:10.1007/s10439-010-0240-y
44. van Schooten KS, Rispens SM, Elders PJ, Van Dieen JH, Pijnappels M. Toward ambulatory balance assessment: estimating variability and stability from short bouts of gait. *Gait Posture* (2014) 39:695–9. doi:10.1016/j.gaitpost.2013.09.020
45. Fino PC. A preliminary study of longitudinal differences in local dynamic stability between recently concussed and healthy athletes during single and dual-task gait. *J Biomech* (2016) 49:1983–8. doi:10.1016/j.jbiomech.2016.05.004
46. Dingwell JB, Cusumano JP, Cavanagh PR, Sternad D. Local dynamic stability versus kinematic variability of continuous overground and treadmill walking. *J Biomech Eng* (2001) 123:27–32. doi:10.1115/1.1336798
47. Bruijn S, Meijer O, Beek P, Van Dieën J. Assessing the stability of human locomotion: a review of current measures. *J R Soc Interface* (2013) 10:20120999. doi:10.1098/rsif.2012.0999
48. Hak L, Houdijk H, Beek PJ, Van Dieen JH. Steps to take to enhance gait stability: the effect of stride frequency, stride length, and walking speed on local dynamic stability and margins of stability. *PLoS One* (2013) 8:e82842. doi:10.1371/journal.pone.0082842
49. Terrier P, Reynard F. Effect of age on the variability and stability of gait: a cross-sectional treadmill study in healthy individuals between 20 and 69 years of age. *Gait Posture* (2015) 41:170–4. doi:10.1016/j.gaitpost.2014.09.024
50. Seeber M, Scherer R, Wagner J, Solis-Escalante T, Muller-Putz GR. EEG beta suppression and low gamma modulation are different elements of human upright walking. *Front Hum Neurosci* (2014) 8:485. doi:10.3389/fnhum.2014.00485
51. Bulea TC, Kim J, Damiano DL, Stanley CJ, Park HS. Prefrontal, posterior parietal and sensorimotor network activity underlying speed control during walking. *Front Hum Neurosci* (2015) 9:247. doi:10.3389/fnhum.2015.00247
52. Seeber M, Scherer R, Wagner J, Solis-Escalante T, Muller-Putz GR. High and low gamma EEG oscillations in central sensorimotor areas are conversely modulated during the human gait cycle. *Neuroimage* (2015) 112:318–26. doi:10.1016/j.neuroimage.2015.03.045
53. Wagner J, Solis-Escalante T, Grieshofer P, Neuper C, Muller-Putz G, Scherer R. Level of participation in robotic-assisted treadmill walking modulates midline sensorimotor EEG rhythms in able-bodied subjects. *Neuroimage* (2012) 63:1203–11. doi:10.1016/j.neuroimage.2012.08.019
54. Bent LR, Inglis JT, Mcfadyen BJ. When is vestibular information important during walking? *J Neurophysiol* (2004) 92:1269–75. doi:10.1152/jn.01260.2003
55. Bauby CE, Kuo AD. Active control of lateral balance in human walking. *J Biomech* (2000) 33:1433–40. doi:10.1016/S0021-9290(00)00101-9
56. O'Connor SM, Kuo AD. Direction-dependent control of balance during walking and standing. *J Neurophysiol* (2009) 102:1411–9. doi:10.1152/jn.00131.2009
57. Townsend MA. Biped gait stabilization via foot placement. *J Biomech* (1985) 18:21–38. doi:10.1016/0021-9290(85)90042-9
58. Hof AL, Gazendam MG, Sinke WE. The condition for dynamic stability. *J Biomech* (2005) 38:1–8. doi:10.1016/j.jbiomech.2004.03.025
59. Wang Y, Srinivasan M. Stepping in the direction of the fall: the next foot placement can be predicted from current upper body state in steady-state walking. *Biol Lett* (2014) 10:20140405. doi:10.1098/rsbl.2014.0405
60. Rosin R, Topka H, Dichgans J. Gait initiation in Parkinson's disease. *Mov Disord* (1997) 12:682–90. doi:10.1002/mds.870120509
61. Hanakawa T. Neuroimaging of standing and walking: special emphasis on Parkinsonian gait. *Parkinsonism Relat Disord* (2006) 12:S70–5. doi:10.1016/j.parkreldis.2006.05.009
62. Gallea C, Ewenczyk C, Degos B, Welter ML, Grabli D, Leu-Semenescu S, et al. Pedunculopontine network dysfunction in Parkinson's disease with postural control and sleep disorders. *Mov Disord* (2017) 32:693–704. doi:10.1002/mds.26923
63. Beauchet O, Dubost V, Aminian K, Gonthier R, Kressig RW. Dual-task-related gait changes in the elderly: does the type of cognitive task matter? *J Mot Behav* (2005) 37:259–64.
64. Hausdorff JM, Schweiger A, Herman T, Yogev-Seligmann G, Giladi N. Dual-task decrements in gait: contributing factors among healthy older adults. *J Gerontol A Biol Sci Med Sci* (2008) 63:1335–43. doi:10.1093/gerona/63.12.1335
65. Montero-Odasso M, Muir SW, Speechley M. Dual-task complexity affects gait in people with mild cognitive impairment: the interplay between gait variability, dual tasking, and risk of falls. *Arch Phys Med Rehabil* (2012) 93:293–9. doi:10.1016/j.apmr.2011.08.026
66. Lajoie Y, Teasdale N, Bard C, Fleury M. Attentional demands for static and dynamic equilibrium. *Exp Brain Res* (1993) 97:139–44. doi:10.1007/BF00228824
67. Smulders K, Esselink RA, Weiss A, Kessels RP, Geurts AC, Bloem BR. Assessment of dual tasking has no clinical value for fall prediction in Parkinson's disease. *J Neurol* (2012) 259:1840–7. doi:10.1007/s00415-012-6419-4
68. Menant JC, Schoene D, Sarofim M, Lord SR. Single and dual task tests of gait speed are equivalent in the prediction of falls in older people: a systematic review and meta-analysis. *Ageing Res Rev* (2014) 16:83–104. doi:10.1016/j.arr.2014.06.001

Conflict of Interest Statement: FBH has a significant financial interest in APDM, a company that may have a commercial interest in the results of this research and technology. This potential conflict has been reviewed and managed by OHSU. All other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

PERSPECTIVE
published: 21 September 2018
doi: 10.3389/fneur.2018.00789

New Insights on Emotional Contributions to Human Postural Control

Allan L. Adkin[1]* *and Mark G. Carpenter*[2,3,4]

[1] Department of Kinesiology, Brock University, St. Catharines, ON, Canada, [2] School of Kinesiology, University of British Columbia, Vancouver, BC, Canada, [3] Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver, BC, Canada, [4] International Collaboration on Repair Discoveries, University of British Columbia, Vancouver, BC, Canada

It has been just over 20 years since the effects of height-induced threat on human postural control were first investigated. Raising the height of the support surface on which individuals stood increased the perceived consequences of instability and generated postural control changes. Since this initial work, converging evidence has accumulated supporting the efficacy of using height-induced threat to study the effects of emotions on postural control and confirming a direct influence of threat-related changes in arousal, anxiety, and fear of falling on all aspects of postural control, including standing, anticipatory, and reactive balance. In general, threat-related postural changes promote a greater physical safety margin while maintaining upright stance. We use the static balance literature to critically examine the current state of knowledge regarding: (1) the extent to which threat-related changes in postural control are sensitive to threat-related changes in emotions; (2) the underlying neurophysiological and cognitive mechanisms that may contribute to explaining the relationship between emotions and postural control; and (3) the generalizability of threat-related changes across different populations and types of threat. These findings have important implications for understanding the neuromechanisms that control healthy balance, and highlight the need to recognize the potential contributions of psychological and physiological factors to balance deficits associated with age or pathology. We conclude with a discussion of the practical significance of this research, its impact on improving diagnosis and treatment of postural control deficits, and potential directions for future research.

Keywords: postural control, balance, emotions, fear, anxiety, threat, surface height

OPEN ACCESS

Edited by:
Emily Keshner,
Temple University, United States

Reviewed by:
William Richard Young,
Brunel University London, United Kingdom
Laura Avanzino,
Università di Genova, Italy

***Correspondence:**
Allan L. Adkin
aadkin@brocku.ca

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *29 June 2018*
Accepted: *31 August 2018*
Published: *21 September 2018*

Citation:
Adkin AL and Carpenter MG (2018) New Insights on Emotional Contributions to Human Postural Control. Front. Neurol. 9:789. doi: 10.3389/fneur.2018.00789

BACKGROUND

Fear of falling is frequently reported in older adults (1, 2) and patients with balance deficits (3–8) and is a significant predictor of future falls risk (9, 10). Maki et al. (11) were the first to report significant differences in balance control between fearful and non-fearful older adults, followed by evidence of balance control changes in individuals with anxiety disorders and phobias (12, 13). While these observational studies provided important evidence for a link between balance deficits and emotions, such as fear and anxiety, the direction of the relationship was not determined due to limitations of the cross-sectional design (i.e., individuals may be fearful because they have underlying balance deficits, or have balance deficits because they have an underlying fear of falling).

Brown and Frank (14) were the first to use an experimental design to examine the direct effect of postural threat on human balance control. These researchers employed a modified version of an elevated surface height paradigm used extensively to study fear and anxiety behaviors in animals [elevated plus maze, (15)]. When young healthy adults stood on an elevated (0.8 m) platform and responded to an unpredictable forward push to the trunk, they leaned back away from the platform edge and stiffened to constrain the forward movement of the body's center of mass (COM). A series of studies followed to examine the effects of postural threat on standing postural control in young healthy adults (16–18). Collectively, these studies revealed threat-related postural changes that included leaning away from the platform edge (or away from the direction of the perceived threat), and decreased amplitude and increased frequency of center of pressure (COP) displacements during quiet standing. These threat-related responses were more pronounced with the eyes open and when forward stepping was restricted by the edge of the platform (16). Furthermore, these threat-related changes were scaled to the level of postural threat with progressive decreases in sway amplitude and increases in sway frequency observed with increasing surface heights up to 1.6 m (17). The combination of decreased amplitude and increased frequency of COP displacements suggested the adoption of an ankle stiffening strategy (19). With the body modeled as an inverted pendulum when standing quietly, increased muscle activity around the ankle joints would act to tighten control of the COM within the limits of the base-of-support (19, 20). This hypothesis was experimentally confirmed by observations of increased ankle muscle stiffness when standing at height, coupled with EMG changes consistent with increased co-contraction of lower leg muscles, and decreased COM displacements (18). Together, these early studies revealed that threat-related postural changes provided protection against a loss of balance by limiting body position and movement in the direction of the perceived risk associated with the threat. These changes in humans coincide with freezing and stiffening behavior observed in anxious animals when moving on elevated surfaces (21).

Since these initial studies, physically raising the height of the support surface on which individuals stand has been used extensively to: (1) confirm the effects on standing balance control in young and older healthy adults (22–36), and patient populations such as individuals with unilateral vestibular loss (37) and Parkinson's disease (38, 39); (2) extend the effects of threat on different types of postural tasks including anticipatory postural control (34, 40–42), reactive postural control (43, 44), functional balance tasks [e.g., one leg stance; (28)], and normal and adaptive gait (45–53); and (3) explore the neural mechanisms underlying these threat effects (44, 54–67). Studies have also provided converging evidence to confirm that the threat of standing on elevated surfaces (i.e., real or virtual) can evoke psychological (e.g., self-reported increases in perceived anxiety and fear) and physiological responses (e.g., increases in electrodermal activity, blood pressure) typically observed in fearful or anxious conditions [e.g., (25, 28–30, 32, 34, 35, 40)]. Furthermore, significant relationships have been observed between threat-induced emotional as well as cognitive changes (e.g., conscious control of posture) and modifications in postural control [e.g., (28, 30, 64)].

EVALUATING THE EFFECTS OF HEIGHT-INDUCED POSTURAL THREAT ON STANDING BALANCE CONTROL

Given the breadth of research on this topic over the past 20 years, we chose to focus on height-induced postural threat effects on standing balance control, as this represents the majority of studies conducted to date, and has the potential to influence anticipatory and reactive postural adjustments. In order to critically evaluate and allow for a direct comparison between the studies, we controlled for key factors known to influence standing balance control. A search of PubMed, PsychINFO, EMBASE, CINAHL (search terms: postural threat or anxiety, and height, and standing), and hand searches, identified 89 original research articles (non-duplicate). Manual screening removed 51 articles that did not include a manipulation of postural threat/anxiety or a standing task in the study design. The remaining 38 studies were examined, and a subset of studies was selected based on the following five criteria: (1) young or older healthy adults; (2) height threat; (3) quiet standing task; (4) sample duration ($\geq$60 s); and (5) psychological or physiological measure to confirm the efficacy of the threat manipulation. Stance duration was considered a critical factor because it has been shown to significantly affect COP summary measures (68–70) and varies widely across studies. At least one physiological (e.g., increased electrodermal activity) or psychological (e.g., increased perceived anxiety) measure was required to confirm that the height manipulation generated a significant emotional effect; this was important given the variability of heights and conditions used to manipulate threat across studies. Based on these criteria, eight studies were identified (**Table 1**), with six studies focusing specifically on young adults (28–30, 32, 34, 35) and two involving older adults (25, 39).

A consistent postural strategy emerged from the collective results of the eight studies that met our criteria. All studies revealed that young and older healthy adults leaned significantly away from the edge of the platform and significantly increased their COP sway frequency (25, 28–30, 32, 34, 35, 39). The majority of the studies also showed that young and healthy older adults decreased their COP sway amplitude (25, 28, 29, 32, 34, 35); two exceptions to this observation reported no significant change in sway amplitude when threatened (30, 39). These observations reinforced the findings of earlier work on standing balance control in young healthy adults (16–18) and extended the findings to older healthy adults. All selected studies were performed with eyes open and gaze fixed on near targets (<4-m) to control for effects of postural height vertigo that may occur with longer (>6-m) viewing distances (71, 72). Yet, similar height-induced postural changes have been observed with eyes closed, and also when peripheral vision was occluded (16, 18, 29). The selected studies focused predominantly on anterior-posterior COP changes (which align with the direction of the threat), with similar effects also reported in the medial-lateral

TABLE 1 | Height-induced postural threat effects on quiet standing.

Study	Group	Maximum threat	Sampling duration	AP COP MP	AP COP MPF	AP COP RMS
Carpenter et al. (25)	14 YA	1.6 m	120 s	Posterior lean	Increased	Decreased
	13 OA	1.6 m	120 s	Posterior lean	Increased	Decreased
Hauck et al. (28)	31 YA	1.4 m	60 s	Posterior lean	Increased	Decreased
Davis et al. (29)	26 YA	3.2 m	60 s	Posterior lean	Increased	Decreased
Huffman et al. (30)	48 YA	3.2 m	60 s	Posterior lean	Increased	*No change*
Pasman et al. (39)	14 OA	1.6 m	120 s	Posterior lean	Increased	*No change*
Cleworth et al. (32)	18 YA	3.2 m	120 s	Posterior lean	Increased	Decreased
Zaback et al. (34)	82 YA	3.2 m	60 s	Posterior lean	Increased	Decreased
Cleworth et al. (35)	20 YA	3.2 m	60 s	Posterior lean	Increased	Decreased

Table includes studies that met the following criteria: (1) healthy young adults (YA) or older adults (OA), (2) height threat, (3) quiet standing task, (4) sampling duration (≥60 s), and (5) psychological or physiological measure to confirm efficacy of threat manipulation. Significant anterior-posterior (AP) center of pressure (COP) mean position (MP), mean power frequency (MPF), and root mean square (RMS) effects (maximum threat compared to lowest threat condition) for eyes open conditions are reported. Participants stood at the platform edge in the maximum threat condition for all studies except Carpenter et al. (25). Effects reported for Davis et al. (29) do not include results from the fearful sub-group.

direction, albeit to a lesser degree (17, 31), potentially due to the threat direction (42) or biomechanical constraints of controlling anterior-posterior versus medial-lateral sway (20).

CONTEXT-DEPENDENT THREAT-RELATED CHANGES IN STANDING BALANCE CONTROL

Studies have utilized other methods to manipulate threat or emotions, to confirm if the effects of height are generalizable to other threat sources, and to avoid some of the context-specific limitations associated with standing on an elevated surface. One common alternative is to manipulate the threat of an impending perturbation, during which individuals are required to stand with or without the threat of experiencing a sudden, unpredictable balance disturbance, such as a push or pull to the upper trunk (73) or a support surface translation (74, 75) or rotation (57). Like height-induced threat, the threat of perturbation has been shown to significantly increase arousal, anxiety, and fear (57). Using the threat of multi-directional perturbations has the advantage of reducing the likelihood of individuals adopting any directionally specific strategies that are inherent to elevated surface paradigms (14). COP displacements during quiet standing when anticipating the threat of forward or backward perturbation are found to significantly increase in frequency and amplitude, with a significant shift of mean position forward instead of backward (75).

Initial comparisons between reported effects of height and perturbation-related threat reveal a common effect of increased frequency of COP displacements during quiet stance (**Figure 1A**). In contrast, the amplitude of COP displacements and leaning seems context dependent, with smaller amplitude displacements and backwards leaning specific to height-induced threat, and larger amplitude displacements more commonly observed with the threat of a perturbation. While direct comparisons are made difficult by the shorter sample durations typically used in threat of perturbation studies, more recent studies using 60-s durations confirmed the increased amplitude and frequency of COP displacements with this type of threat (76), which are also dependent on the orientation of stance relative to the perceived direction of the threat (**Figure 1A**). An increase in COP frequency has also been consistently reported in other contexts, including "white coat" effects observed in older women standing under the perceived threat of negative evaluation (78), and young adults standing while viewing affective pictures that elicited increases in arousal, independent of valence (79). In contrast, the increased arousal elicited by mental arithmetic, appears to influence mean position (80), but not COP frequency or amplitude (80, 81), unless coupled with a social evaluative threat (81). Thus, standing balance changes appear to be highly specific to the context, direction, and nature of the perceived threat, which coincides with other threat-avoidance behaviors (82).

POTENTIAL MECHANISMS UNDERLYING THREAT-RELATED POSTURAL CHANGES

The mechanisms that may contribute to, or explain threat-related changes in postural control remain poorly understood. In general, theories can be divided along the lines of emotionally-evoked neurophysiological changes, and/or changes in attention.

Neurophysiological theories are based on the existence of highly-integrated neural networks responsible for processing emotional information, such as fear and anxiety, and sensorimotor control of upright stance (83) and gait (84). Neuroanatomical evidence for direct influences of emotion onto balance control systems has been well-established in animal models (83, 85, 86). Supporting evidence has been established in standing humans, with threat-induced increases observed in: (1) muscle-spindle sensitivity (56, 57, 87); (2) 1b reflex gain (65); and (3) vestibular gain of balance, head and eye-reflexes (60–63, 66). While early cortical potentials seem unaffected by threat (55, 56), later cortical changes thought to be responsible for

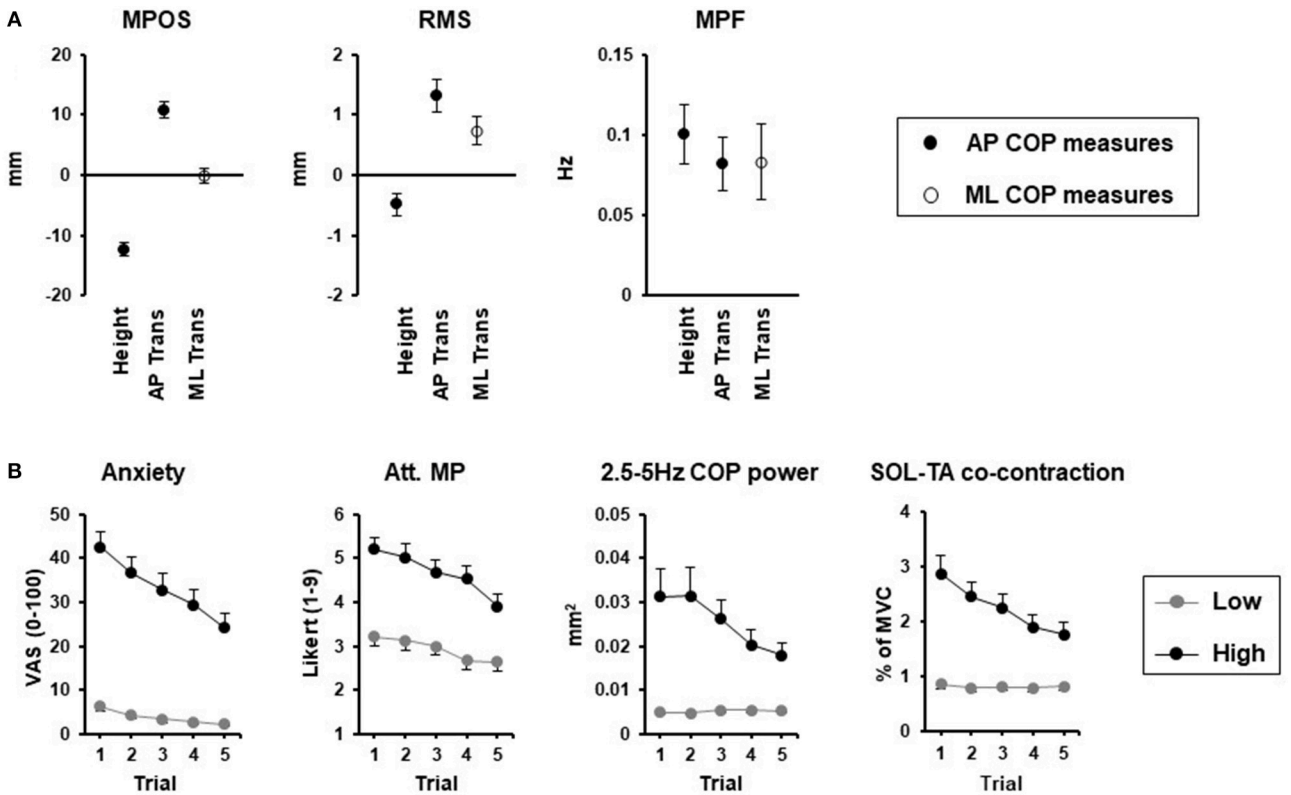


FIGURE 1 | Threat context **(A)** and adaptation **(B)** effects. **(A)** Change in center of pressure (COP) mean position (MP), mean power frequency (MPF), and root mean square (RMS) between threat and no threat conditions for height, [0.8 and 3.2 m surface; 60-s stance duration; modified from (34)] and support surface translations (Trans) in the anterior-posterior (AP) direction [30 s stance duration; modified from (75)] and medial-lateral (ML) direction [60-s stance duration; (76)]. Closed circles reflect AP COP measures while open circles reflect ML COP measures. **(B)** Adaptation of emotional, cognitive (attention focus to movement processes; Att. MP) and postural responses for low (gray circles) and high (black circles) surface heights over 5 repeated 120-s standing trials (77).

processing sensory information are significantly influenced with threat (44, 55, 88).

Alternatively, changes in attention may mediate threat-related postural changes (82, 84). It is possible that threat influences how attention resources are allocated (e.g., individuals choosing to direct attention to their posture) contributing to the postural changes. Huffman et al. (30) demonstrated that with height-induced threat: (1) individuals had a greater tendency to consciously control and monitor their posture; and (2) an increase in conscious control of posture was related to leaning further back away from the platform edge, independent of any changes in amplitude or frequency of COP displacements. Zaback et al. (64) used open-ended questions to categorize how individuals directed their attention under non-threatening and threatening conditions, with five attention focus categories emerging. When standing at a high compared to low height, individuals directed more attention to movement processes, threat-related stimuli, and self-regulatory or coping strategies, and less attention to task objectives and task-irrelevant information. Again, these threat-related attention focus changes were associated with changes in postural control. For example, individuals who directed more attention to movement processes were more likely to demonstrate increases in frequency of COP displacements, and decreases in amplitude of COP displacements when directing less attention to movement processes. In addition, participants that reported increased attention focus to self-regulatory strategies were more likely to show greater decreases in amplitude of postural displacements. Differences in the approach used to assess attention focus in Zaback et al. (64) and Huffman et al. (30) likely contributed to the differences in reported relationships between attention focus and COP measures across studies. This work linking changes in attention focus and postural control provides preliminary evidence that threat-related changes in attention focus may be a mechanism underlying the postural changes (82).

It is most likely that the effects of threat on balance control rely on a complex interaction between neurophysiological changes and changes in attentional processes. With repeated exposure to height, emotional and attentional changes are attenuated, and correspond to reduced changes in high frequency COP displacements and co-contraction of lower leg muscles. In contrast, initial height-induced posterior leaning and decreases in COP amplitude do not appear to attenuate with repeated exposure and thus may be influenced by other mechanisms (e.g., sensory changes, vigilance) not accounted for in the study [**Figure 1B**; (77)]. Likewise, changes in perception of

balance, which relies on a combination of neurophysiological and cognitive-attentional processes, could also contribute to threat-related changes in postural control. Cleworth et al. (35) demonstrated no change in perceived sway (both self-reported, and tracked in real-time using a hand-held device), in contrast to significant reductions in COP and COM amplitude when standing at a high compared to low height. The incongruency of perceived and actual sway with threat (35) mirrors the reported increase in perceived instability of individuals standing on elevated surfaces, despite no change or an actual decrease in sway amplitude (28, 32, 35).

CLINICAL RELEVANCE

It is crucial to understand how emotional factors can directly and indirectly influence balance control, as these changes have the potential to mask or modify underlying balance deficits. This is particularly important given the high prevalence of fear and anxiety in populations with balance deficits due to age or pathology such as Parkinson's disease, vestibular disorders, stroke, and multiple sclerosis (1–8), and links with postural instability and gait deficits (4, 84). Studies have shown that older adults, individuals with vestibular loss and Parkinson's disease have a similar postural response as young healthy adults to a height-induced threat (24–26, 36, 37, 39). However, the extent to which balance control deficits in these individuals may be attributed to high levels of state and trait fear or anxiety are still unknown (11, 29, 34, 36).

The capacity for fear and anxiety to directly influence balance in healthy adults provides important insight into potential mechanisms through which clinical balance deficits may present without any clear physiological dysfunction. For example, Chronic Dizziness Disorder and Phobic Postural Vertigo (now unified under the diagnosis of Persistent Postural-Perceptual Dizziness; PPPD) are functional dizziness disorders characterized by non-spinning vertigo and subjective balance instability in the absence of any neurological or structural findings, and often have secondary psychological co-morbidities including fear of falling, anxiety or depressive disorders (89). Postural changes in patients with PPPD include increased high frequency (>1 Hz) sway and increased co-contraction of lower-leg muscles under normal standing conditions (90, 91). These changes become less distinct from healthy controls under conditions of threat (92) or attentional distraction tasks (90). These changes correspond to threat-related changes in healthy adults that adapt to repeated exposure and correlate with changes in conscious attention to movement [(77); **Figure 1B**]. Overall, these observations support the hypothesis that postural changes with PPPD reflect a maladaptation of high-risk postural control strategies triggered by an initial stimulus that persists due, in part to, excessive self-observation and anxiety (89). Likewise, individuals with visual height intolerance (VHI) have been identified in ∼30% of the population, defined as those with "an unpleasant feeling caused by visual exposure to heights" (93). When standing on elevated surfaces (15 m), individuals with VHI have increased tibialis anterior activity, greater co-contraction of lower leg muscles, increased ranges of COP sway, and no change in COP RMS (33). However, in the absence of a control group without VHI, it is unclear to what extent the postural changes reported in VHI differ from an otherwise normal manifestation of balance changes observed in healthy individuals standing under conditions of increased postural threat (**Table 1**).

The potential for fear and anxiety to influence balance is also important to account for when designing intervention studies that require longitudinal measures of balance-related performance in comparison to a baseline measure. Given known white-coat effects (78) and potential first trial effects (17) on balance, it is important that multiple baseline measures be recorded, and/or a control group incorporated to address potential order effects that may be mediated by adaptation of fear/anxiety with repeated exposure (77). Finally, it is important to recognize, and understand, how clinical balance treatments and interventions may be impacted by emotional-balance interactions (83).

FUTURE RESEARCH DIRECTIONS

Most studies that used a height manipulation to understand how threat affects normal balance excluded participants with height phobias for safety/ethical concerns; however, there is some reason to believe that a true fear response may have distinct balance changes compared to an anxious response. For example, individuals standing at extreme surface heights [over 9-m high, (22, 23)] are shown to have significant increases in amplitude of postural sway, in contrast to the reduced sway seen in most individuals at lower surface heights (up to 3.2-m high, see **Table 1**). However, Davis et al. (29) showed that a subgroup of their subjects, who reported a robust fear response to the moderate (3.2 m) surface height threat (>50% change from ground) had a significantly larger amplitude and frequency of COP displacements compared to anxious but less fearful (<50% change) subjects. Thus, more work needs to be done to determine how fear and anxiety may differentially impact unique aspects of balance control, and distinguish those from the context-specific changes which may or may not translate from a lab setting to daily-life situations experienced by those with a fear of falling. Future work also needs to continue to investigate the potential neurophysiological and attentional mechanisms that contribute to postural changes with threat. This includes probing how different sensori-motor systems respond to different threat conditions, and investigating whether specific instructions or tasks designed to shift attention from posture can modify the postural response to threat. Finally, there is a need for exploration of novel techniques such as virtual reality/augmented reality as a means to test and treat individuals with fear of falling, and develop more effective types of balance interventions that are designed to influence both the psychological and physiological aspects of a balance deficit.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

ACKNOWLEDGMENTS

The authors acknowledge funding from the Natural Sciences and Engineering Research Council of Canada (NSERC) to AA (#288164) and MC (#326910). The authors wish to acknowledge the contributions of Martin Zaback, Taylor Cleworth, and Kyle Johnson for their valuable assistance in preparing the manuscript and figures.

REFERENCES

1. Legters K. Fear of falling. *Phys Ther.* (2002) 82:264–72. doi: 10.1093/ptj/82.3.264
2. Scheffer AC, Schuurmans MJ, Van Dijk N, Van Der Hooft T, De Rooij SE. Fear of falling: measurement strategy, prevalence, risk factors and consequences among older persons. *Age Ageing* (2008) 37:19–24. doi: 10.1093/ageing/afm169
3. Bloem BR, Grimbergen YA, Cramer M, Willemsen M, Zwinderman AH. Prospective assessment of falls in Parkinson's disease. *J Neurol.* (2001) 248:950–8. doi: 10.1007/s004150170047
4. Adkin AL, Frank JS, Jog MS. Fear of falling and postural control in Parkinson's disease. *Mov Disord.* (2003) 18:496–502. doi: 10.1002/mds.10396
5. Watanabe Y. Fear of falling among stroke survivors after discharge from inpatient rehabilitation. *Int J Rehabil Res.* (2005) 28:149–52. doi: 10.1097/00004356-200506000-00008
6. Finlayson ML, Peterson EW, Cho CC. Risk factors for falling among people aged 45 to 90 years with multiple sclerosis. *Arch Phys Med Rehab.* (2006) 87:1274–9. doi: 10.1016/j.apmr.2006.06.002
7. Schmid AA, Van Puymbroeck M, Knies K, Spangler-Morris C, Watts K, Damush T, et al. Fear of falling among people who have sustained a stroke: a 6-month longitudinal pilot study. *Am J Occup Ther.* (2011) 65:125–32. doi: 10.5014/ajot.2011.000737
8. Schlick C, Schniepp R, Loidl V, Wuehr M, Hesselbarth K, Jahn, K. Falls and fear of falling in vertigo and balance disorders: a controlled cross-sectional study. *J Vestib Res.* (2015) 25, 241–51. doi: 10.3233/VES-150564
9. Cumming RG, Salkeld G, Thomas M, Szonyi G. Prospective study of the impact of fear of falling on activities of daily living, SF-36 scores, and nursing home admission. *J Gerontol A Biol Sci Med Sci.* (2000) 55:M299–305. doi: 10.1093/gerona/55.5.M299
10. Friedman SM, Munoz B, West SK, Rubin GS, Fried LP. Falls and fear of falling: which comes first? A longitudinal prediction model suggests strategies for primary and secondary prevention. *J Am Geriatr Soc.* (2002) 50:1329–35. doi: 10.1046/j.1532-5415.2002.50352.x
11. Maki BE, Holliday PJ, Topper AK. Fear of falling and postural performance in the elderly. *J Gerontol.* (1991) 46:M123–31. doi: 10.1093/geronj/46.4.M123
12. Jacob RG, Furman JM, Durrant JD, Turner SM. Surface dependence: a balance control strategy in panic disorder with agoraphobia. *Psychosom Med.* (1997) 59:323–30. doi: 10.1097/00006842-199705000-00016
13. Redfern MS, Furman JM, Jacob RG. Visually induced postural sway in anxiety disorders. *J Anxiety Disord.* (2007) 21:704–16. doi: 10.1016/j.janxdis.2006.09.002
14. Brown LA, Frank JS. Postural compensations to the potential consequences of instability: kinematics. *Gait Posture* (1997) 6:89–97. doi: 10.1016/S0966-6362(96)01106-X
15. Hogg S. A review of the validity and variability of the elevated plus-maze as an animal model of anxiety. *Pharmacol Biochem Behav.* (1996) 54:21–30. doi: 10.1016/0091-3057(95)02126-4
16. Carpenter MG, Frank JS, Silcher CP. Surface height effects on postural control: a hypothesis for a stiffness strategy for stance. *J Vestib Res.* (1999) 9:277–86.
17. Adkin AL, Frank JS, Carpenter MG, Peysar GW. Postural control is scaled to level of postural threat. *Gait Posture* (2000) 12:87–93. doi: 10.1016/S0966-6362(00)00057-6
18. Carpenter MG, Frank JS, Silcher CP, Peysar GW. The influence of postural threat on the control of upright stance. *Exp Brain Res.* (2001) 138:210–8. doi: 10.1007/s002210100681
19. Winter DA, Patla AE, Prince F, Ishac M, Gielo-Perczak K. Stiffness control of balance in quiet standing. *J Neurophysiol.* (1998) 80:1211–21. doi: 10.1152/jn.1998.80.3.1211
20. Winter DA. Human balance and posture control during standing and walking. *Gait Posture* (1995) 3:193–214. doi: 10.1016/0966-6362(96)82849-9
21. Lepicard EM, Venault P, Perez-Diaz F, Joubert C, Berthoz A, Chapouthier G. Balance control and posture differences in the anxious BALB/cByJ mice compared to the non- anxious C57BL/6J mice. *Behav Brain Res.* (2000) 117:185–95. doi: 10.1016/S0166-4328(00)00304-1
22. Nakahara H, Takemori S, Tsuruoka H. Influence of height on the spatial orientation and equilibrium of the body. *Otolaryngol Head Neck Surg.* (2000) 123:501–4. doi: 10.1067/mhn.2000.107316
23. Simeonov P, Hsiao H. Height, surface firmness, and visual reference effects on balance control. *Inj Prev.* (2001) 7:i50–3. doi: 10.1136/ip.7.suppl_1.i50
24. Brown LA, Polych MA, Doan JB. The effect of anxiety on the regulation of upright standing among younger and older adults. *Gait Posture* (2006) 24:397–405. doi: 10.1016/j.gaitpost.2005.04.013.
25. Carpenter MG, Adkin AL, Brawley LR, Frank JS. Postural, physiological and psychological reactions to challenging balance: does age make a difference? *Age Ageing* (2006) 35:298–303. doi: 10.1093/ageing/afl002
26. Laufer Y, Barak Y, Chemel I. Age-related differences in the effect of a perceived threat to stability on postural control. *J Gerontol A Biol Sci Med Sci.* (2006) 61:500–4. doi: 10.1093/gerona/61.5.500
27. Alpers GW, Adolph D. Exposure to heights in a theme park: fear, dizziness, and body sway. *J Anxiety Disord.* (2008) 22:591–601. doi: 10.1016/j.janxdis.2007.05.008
28. Hauck LJ, Carpenter MG, Frank JS. Task-specific measures of balance efficacy, anxiety, and stability and their relationship to clinical balance performance. *Gait Posture* (2008) 27:676–82. doi: 10.1016/j.gaitpost.2007.09.002
29. Davis JR, Campbell AD, Adkin AL, Carpenter MG. The relationship between fear of falling and human postural control. *Gait Posture* (2009) 29:275–9. doi: 10.1016/j.gaitpost.2008.09.006
30. Huffman JL, Horslen BC, Carpenter MG, Adkin AL. Does increased postural threat lead to more conscious control of posture? *Gait Posture* (2009) 30:528–32. doi: 10.1016/j.gaitpost.2009.08.001
31. Stins JF, Roerdink M, Beek PJ. To freeze or not to freeze? Affective and cognitive perturbations have markedly different effects on postural control. *Hum Mov Sci.* (2011) 30:190–202. doi: 10.1016/j.humov.2010.05.013
32. Cleworth TW, Horslen BC, Carpenter MG. Influence of real and virtual heights on standing balance. *Gait Posture* (2012) 36:172–6. doi: 10.1016/j.gaitpost.2012.02.010
33. Wuehr M, Kugler G, Schniepp R, Eckl M, Pradhan C, Jahn K, et al. (2014). Balance control and anti-gravity muscle activity during the experience of fear at heights. *Physiol Rep.* 2:e00232. doi: 10.1002/phy2.232
34. Zaback M, Cleworth TW, Carpenter MG, Adkin AL. Personality traits and individual differences predict threat-induced changes in postural control. *Hum Mov Sci.* (2015) 40:393–409. doi: 10.1016/j.humov.2015.01.015
35. Cleworth TW, Carpenter MG. Postural threat influences conscious perception of postural sway. *Neurosci Lett.* (2016) 620:127–31. doi: 10.1016/j.neulet.2016.03.032
36. Sturnieks DL, Delbaere K, Brodie MA, Lord SR. The influence of age, anxiety and concern about falling on postural sway when standing at an elevated level. *Hum Mov Sci.* (2016) 49:206–15. doi: 10.1016/j.humov.2016.06.014
37. Young LR, Bernard-Demanze L, Dumitrescu M, Magnan J, Borel L, Lacour M. Postural performance of vestibular loss patients under increased postural threat. *J Vestib Res.* (2012) 22:129–38. doi: 10.3233/VES-2012-0449
38. Brown LA, Doan JB, Whishaw IQ, Suchowersky O. Parkinsonian deficits in context-dependent regulation of standing postural control. *Neurosci Lett.* (2007) 418:292–7. doi: 10.1016/j.neulet.2007.03.040
39. Pasman EP, Murnaghan CD, Bloem BR, Carpenter MG. Balance problems with Parkinson's disease: are they anxiety-dependent? *Neuroscience* (2011) 177:283–91. doi: 10.1016/j.neuroscience.2010.12.050

40. Adkin AL, Frank JS, Carpenter MG, Peysar GW. Fear of falling modifies anticipatory postural control. *Exp Brain Res.* (2002) 143:160–70. doi: 10.1007/s00221-001-0974-8
41. Yiou E, Deroche T, Do MC, Woodman T. Influence of fear of falling on anticipatory postural control of medio-lateral stability during rapid leg flexion. *Eur J Appl Physiol.* (2011) 111:611–20. doi: 10.1007/s00421-010-1680-7
42. Gendre M, Yiou E, Gélat T, Honeine J, Deroche T. Directional specificity of postural threat on anticipatory postural adjustments during lateral leg raising. *Exp Brain Res.* (2016) 234:659–71. doi: 10.1007/s00221-015-4471-x
43. Carpenter MG, Frank JS, Adkin AL, Paton A, Allum JHJ. Influence of postural anxiety on postural reactions to multi-directional surface rotations. *J Neurophysiol.* (2004) 92:3255–65. doi: 10.1152/jn.00724.2004
44. Adkin AL, Campbell AD, Chua R, Carpenter MG. The influence of postural threat on the cortical response to unpredictable and predictable postural perturbations. *Neurosci Lett.* (2008) 435:120–5. doi: 10.1016/j.neulet.2008.02.018
45. Brown LA, Gage WH, Polych MA, Sleik RJ, Winder TR. Central set influences on gait: Age-dependent effects of postural threat. *Exp Brain Res.* (2002) 145:286–96. doi: 10.1007/s00221-002-1082-0
46. Gage WH, Sleik RJ, Polych MA, McKenzie NC, Brown LA. The allocation of attention during locomotion is altered by anxiety. *Exp Brain Res.* (2003) 150:385–94. doi: 10.1007/s00221-003-1468-7
47. McKenzie NC, Brown LA. Obstacle negotiation kinematics: age-dependent effects of postural threat. *Gait Posture* (2004) 19:226–34. doi: 10.1016/S0966-6362(03)00060-2
48. Brown LA, Doan JB, McKenzie NC, Cooper SA. Anxiety-mediated gait adaptations reduce errors of obstacle negotiation among younger and older adults: implications for fall risk. *Gait Posture* (2006) 24:418–23. doi: 10.1016/j.gaitpost.2005.09.013
49. Delbaere K, Sturnieks DL, Crombez G, Lord SR. Concern about falls elicits changes in gait parameters in conditions of postural threat in older people. *J Gerontol A Biomed Sci Med Sci.* (2009) 64:237–42. doi: 10.1093/gerona/gln014
50. Caetano MJD, Gobbi LTB, del Rosario Sánchez-Arias M, Stella F, Gobbi S. Effects of postural threat on walking features of Parkinson's disease patients. *Neurosci Lett.* (2009) 452:136–40. doi: 10.1016/j.neulet.2009.01.053
51. Tersteeg MCA, Marple-Horvat DE, Loram ID. Cautious gait in relation to knowledge and vision of height: is altered visual information the dominant influence? *J Neurophysiol.* (2012) 107:2686–91. doi: 10.1152/jn.00875.2011
52. Schniepp R, Kugler G, Wuehr M, Eckl M, Huppert D, Huth S, et al. Quantification of gait changes in subjects with visual height intolerance when exposed to heights. *Front Hum Neurosci.* (2014) 8:963. doi: 10.3389/fnhum.2014.00963
53. Hackney AL, Cinelli ME, Denomme LT, Frank JS. The effects of narrow and elevated path walking on aperture crossing. *Hum Mov Sci.* (2015) 41:295–306. doi: 10.1016/j.humov.2015.04.002
54. Sibley KM, Carpenter MG, Perry JC, Frank JS. Effects of postural anxiety on the soleus H-reflex. *Hum Mov Sci.* (2007) 26:103–12. doi: 10.1016/j.humov.2006.09.004
55. Sibley KM, Mochizuki G, Frank JS, McIlroy WE. The relationship between physiological arousal and cortical and autonomic responses to postural instability. *Exp Brain Res.* (2010) 203:533–40. doi: 10.1007/s00221-010-2257-8
56. Davis JR, Horslen BC, Nishikawa K, Fukushima K, Chua R, Inglis JT, et al. Human proprioceptive adaptations during states of height-induced fear and anxiety. *J Neurophysiol.* (2011) 106:3082–90. doi: 10.1152/jn.01030.2010
57. Horslen BC, Murnaghan CD, Inglis JT, Chua, R, Carpenter MG. Effects of postural threat on spinal stretch reflexes: evidence for increased muscle spindle sensitivity? *J Neurophysiol.* (2013) 110:899–906. doi: 10.1152/jn.00065.2013
58. Osler CJ, Tersteeg MCA, Reynolds RF, Loram ID. Postural threat differentially affects the feedforward and feedback components of the vestibular-evoked balance response. *Eur J Neurosci.* (2013) 38:3239–47. doi: 10.1111/ejn.12336
59. Tanaka T, Matsugi A, Kamata N, Hiraoka K. Postural threat increases corticospinal excitability in the trunk flexor muscles in the upright stance. *J Psychophysiol.* (2013) 27:165. doi: 10.1027/0269-8803/a000101
60. Horslen BC, Dakin CJ, Inglis JT, Blouin JS, Carpenter MG. Modulation of human vestibular reflexes with increased postural threat. *J Physiol.* (2014) 592:3671–85. doi: 10.1113/jphysiol.2014.270744
61. Naranjo EN, Allum JHJ, Inglis JT, Carpenter MG. Increased gain of vestibulospinal potentials evoked in neck and leg muscles when standing under height-induced postural threat. *Neuroscience* (2015) 293:45–54. doi: 10.1016/j.neuroscience.2015.02.026
62. Naranjo EN, Cleworth TW, Allum JHJ, Inglis JT, Lea J, Westerberg BD, et al. Vestibulo-spinal and vestibulo-ocular reflexes are modulated when standing with increased postural threat. *J Neurophysiol.* (2015) 115:833–42. doi: 10.1152/jn.00626.2015
63. Lim SB, Cleworth TW, Horslen BC, Blouin JS, Inglis JT, Carpenter MG. Postural threat influences vestibular-evoked muscular responses. *J Neurophysiol.* (2016) 117:604–11. doi: 10.1152/jn.00712.2016
64. Zaback M, Carpenter MG, Adkin AL. Threat-induced changes in attention during tests of static and anticipatory postural control. *Gait Posture* (2016) 45:19–24. doi: 10.1016/j.gaitpost.2015.12.033
65. Horslen BC, Inglis JT, Blouin JS, Carpenter MG. Both standing and postural threat decrease Achilles' tendon reflex inhibition from tendon electrical stimulation. *J Physiol.* (2017) 595:4493–506. doi: 10.1113/JP273935
66. Naranjo EN, Cleworth TW, Allum JHJ, Inglis JT, Lea J, Westerberg BD, et al. Threat effects on human oculo-motor function. *Neuroscience* (2017) 359:289–98. doi: 10.1016/j.neuroscience.2017.07.024
67. Cleworth TW, Chua R, Inglis JT, Carpenter MG. Influence of virtual height exposure on postural reactions to support surface translations. *Gait Posture* (2016) 47:96–102. doi: 10.1016/j.gaitpost.2016.04.006
68. Le Clair K, Riach C. Postural stability measures: what to measure and for how long. *Clin Biomech.* (1996) 11:176–8. doi: 10.1016/0268-0033(95)00027-5
69. Carpenter MG, Frank JS, Winter DA, Peysar GW. Sampling duration effects on centre of pressure summary measures. *Gait Posture* (2001) 13:35–40. doi: 10.1016/S0966-6362(00)00093-X
70. van der Kooij H, Campbell AD, Carpenter MG. Sampling duration effects on centre of pressure descriptive measures. *Gait Posture* (2011) 34:19–24. doi: 10.1016/j.gaitpost.2011.02.025
71. Brandt T, Bles W, Arnold F, Kapteyn TS. Height vertigo and human posture. *Adv Otorhinolaryngol.* (1979) 25:88–92.
72. Bles W, Kapteyn TS, Brandt T, Arnold F. The mechanism of physiological height vertigo: II. *Posturography Acta Otolaryngol.* (1980) 89:534–40.
73. Shaw JA, Stefanyk LE, Frank JS, Jog MS, Adkin AL. Effects of age and pathology on stance modifications in response to increased postural threat. *Gait Posture* (2012) 35:658–61. doi: 10.1016/j.gaitpost.2011.12.020
74. Phanthanourak AL, Cleworth TW, Adkin AL, Carpenter MG, Tokuno CD. The threat of a support surface translation affects anticipatory postural control. *Gait Posture* (2016) 50:145–50. doi: 10.1016/j.gaitpost.2016.08.031
75. Johnson KJ, Zaback M, Tokuno CD, Carpenter MG, Adkin AL. Exploring the relationship between threat-related changes in anxiety, attention focus, and postural control. *Psychol Res.* (2017). doi: 10.1007/s00426-017-0940-0. [Epub ahead of print].
76. Johnson KJ, Zaback M, Tokuno CD, Carpenter MG, Adkin AL. Cognitive, emotional, and postural adaptations to repeated postural threat exposure. In: *12th Annual Canadian Neuroscience Meeting* (2018). Available online at: https://can-acn.org/documents/2018/CAN2018-final-program.pdf
77. Zaback M, Adkin AL, Carpenter MG. Repeated exposure to height-related postural threat: how do humans adapt? In: *International Society of Posture and Gait Research World Congress* (2017). Available online at: https://silkstart.s3.amazonaws.com/59415e0f68621305b714ddfc.pdf
78. Geh CL, Beauchamp MR, Crocker PR, Carpenter MG. Assessed and distressed: white-coat effects on clinical balance performance. *J Psychosom Res.* (2011) 70:45–51. doi: 10.1016/j.jpsychores.2010.09.008
79. Horslen BC, Carpenter MG. Arousal, valence and their relative effects on postural control. *Exp Brain Res.* (2011) 215:27. doi: 10.1007/s00221-011-2867-9
80. Maki BE, Mcllroy WE. Influence of arousal and attention on the control of postural sway. *J Vestib Res.* (1996) 6:53–9.
81. Doumas M, Morsanyi K, Young WR. Cognitively and socially induced stress affects postural control. *Exp Brain Res.* (2018) 236:305–14. doi: 10.1007/s00221-017-5128-8
82. Young WR, Williams AM. How fear of falling can increase fall-risk in older adults: applying psychological theory to practical observations. *Gait Posture* (2015) 41:7–12. doi: 10.1016/j.gaitpost.2014.09.006

83. Staab JP, Balaban CD, Furman JM. Threat assessment and locomotion: clinical applications of an integrated model of anxiety and postural control. *Semin Neurol.* (2013) 33:297–306. doi: 10.1055/s-0033-1356462
84. Avanzino L, Lagravinese G, Abbruzzese G, Pelosin, E. Relationships between gait and emotion in Parkinson's disease: A narrative review. *Gait Posture* (2018) 65:57–64. doi: 10.1016/j.gaitpost.2018.06.171
85. Balaban CD, Thayer JF. Neurological bases for balance-anxiety links. *J Anxiety Disord.* (2001) 15:53–79. doi: 10.1016/S0887-6185(00)00042-6
86. Balaban CD. Neural substrates linking balance control and anxiety. *Physiol Behav.* (2002) 77:469–75. doi: 10.1016/S0031-9384(02)00935-6
87. Horslen BC, Zaback M, Inglis JT, Blouin JS, Carpenter MG. *Static and Dynamic Soleus Stretch Reflex Responses in Standing Humans are Independently Modulated by Postural Threat*. San Diego, CA: Society for Neuroscience (2016).
88. Horslen, B. C. *Vestibular, Proprioceptive, and Cutaneous Reflex Modulation Explored Through a Height-Induced Postural Threat.* Doctoral dissertation, University of British Columbia (2016).doi: 10.14288/1.0319265
89. Popkirov S, Staab JP, Stone J. Persistent postural-perceptual dizziness (PPPD): a common, characteristic and treatable cause of chronic dizziness. *Pract Neurol.* (2018) 18:5–13. doi: 10.1136/practneurol-2017-001809
90. Wuehr M, Brandt T, Schniepp R. Distracting attention in phobic postural vertigo normalizes leg muscle activity and balance. *Neurology* (2016). 88:284–8. doi: 10.1212/WNL.0000000000003516
91. Dieterich M, Staab JP. Functional dizziness: from phobic postural vertigo and chronic subjective dizziness to persistent postural-perceptual dizziness. *Curr Opin Neurol.* (2017) 30:107–13. doi: 10.1097/WCO.0000000000000417
92. Holmberg J, Tjernstrom F, Karlberg M, Fransson PA, Magnusson M. Reduced postural differences between phobic postural vertigo patients and healthy subjects during a postural threat. *J Neurol.* (2009) 256:1258–62. doi: 10.1007/s00415-009-5110-x
93. Huppert D, Grill E, Brandt T. Down on heights? One in three has visual height intolerance. *J Neurol.* (2013) 260:597–604. doi: 10.1007/s00415-012-6685-1

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 10 October 2018
doi: 10.3389/fneur.2018.00850

Unveiling Intermittency in the Control of Quiet Upright Standing: Beyond Automatic Behavior

John F. Stins and Melvyn Roerdink*

Department of Human Movement Sciences, Faculty of Behavioural and Movement Sciences, Vrije Universiteit Amsterdam, Amsterdam Movement Sciences, Amsterdam, Netherlands

The control of posture, as in quiet upright standing, is distributed among postural reflexes and higher (cortical) centers. According to the theory of "intermittent control," the control of posture involves a rapid succession of brief periods of postural stability, during which the body dwells relatively motionless in a particular posture, and postural instability, during which the body rapidly transits to a new stable point. This theory assumes a combination of stiffness control, keeping the body in the same position, and top-down ballistic control, moving the body to a new reference position. We tested the prediction that exerting ballistic control consumes more attention, relative to stiffness control, using variations in reaction time as our index of attention load. Slower reactions to external stimulus events were expected if these events happen to coincide with ballistic control regimes compared to stiffness regimes, as unveiled from local features of the posturogram. Thirty-two participants stood on a force plate, and were instructed to press a hand-held button as soon as they heard a stimulus tone. About 40 stimuli were presented at random instances during a 3-min trial. Postural control regimes were characterized using sway-density analysis for each stimulus-response interval, by computing local dwell times from the corresponding center-of-pressure samples. We correlated stimulus-response durations with the corresponding local dwell times, and also with local velocity and local eccentricity (distance from the origin). As predicted, an overall negative correlation was observed, meaning that shorter dwell times are associated with longer stimulus-response intervals, as well as a positive correlation with local center-of-pressure velocity. The correlation between reaction times and local eccentricity was not significant. Thus, by mapping stimulus-response intervals to local center-of-pressure features we demonstrated attentional fluctuations in the control of quiet upright standing, thereby validating a core assumption underlying the notion of intermittent postural control.

Keywords: postural control, intermittency, dual-tasking, postural sway, attention, reaction time, sway density curve

OPEN ACCESS

Edited by:
Emily Keshner,
Temple University, United States

Reviewed by:
Patrick Sparto,
University of Pittsburgh, United States
Taishin Nomura,
Osaka University, Japan

****Correspondence:***
John F. Stins
j.f.stins@vu.nl

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *29 June 2018*
Accepted: *21 September 2018*
Published: *10 October 2018*

Citation:
Stins JF and Roerdink M (2018) Unveiling Intermittency in the Control of Quiet Upright Standing: Beyond Automatic Behavior. Front. Neurol. 9:850. doi: 10.3389/fneur.2018.00850

INTRODUCTION

Body sway during quiet upright standing reflects attempts of the actor to control the unstable "inverted pendulum," i.e., the erect human body. In theory, it would be possible to apply a constant mechanical stiffness of the muscle-tendon complex acting around the ankle joint. If stiffness is sufficiently high, then the inverted pendulum will stay in place. However, empirical measurements performed by Loram and Lakie (1) showed that ankle stiffness was lower than the gravitational toppling torque, implying that an additional mechanism was required to maintain quiet upright standing.

This mechanism arguably involved serial ballistic, neurally generated, torques that "kick" the body center of mass in a particular direction. This form of postural control has been labeled intermittent or "saccadic" control [e.g., (2)]. An important characteristic of intermittent control is its anticipatory nature. Phasic neural commands, sent out to the muscles, generate anticipatory torques based on a prediction of imminent destabilization, and bring the center of mass back to a stable state. Intermittent control thus implies a neural representation of the "inverted pendulum" dynamics that predicts the postural consequences of phasic applied torques.

Is it possible to identify such intermittent or discrete instances of control in the trajectory of the center of pressure (COP) during an actual quiet standing episode? Yes, according to an inventive sway-density analysis method proposed by Baratto et al. (2), and adopted by others since then [e.g., (3–5)]. This method involves constructing so-called sway-density curves, unveiling instances when the COP is relatively stationary or transient (see section Materials and Methods for details). Briefly, the approach assumes a "waxing and waning" between episodes wherein the center of mass (and the COP) is relatively motionless (i.e., high density, long dwell times) and episodes wherein the COP quickly shifts position (i.e., low density, short dwell times). This process has been likened to sequences of saccades and fixations, which alternate and repeat in quick succession (3). During the "fixations" the COP shows little activity, likely representing the contribution of ankle stiffness. On the other hand, the "saccades" involve quick displacements of the COP, likely representing phasic neural commands generating anticipatory torques to bring the erect body back to a stable state, which is then again followed by a period of postural inactivity, ad infinitum.

In a recent paper, Villarrasa-Sapiña et al. (4) described intermittent control as consisting of two control mechanisms; one involving the mechanical properties of the ankle muscles (a.k.a. intrinsic feedback, or "passive control"), and one involving anticipatory activation of the muscles (feedforward control, or "active control"). It is assumed that episodes in the posturogram with short dwell times represent anticipatory top-down balance control that drive the COP (and hence the center of mass) back to a stable state (4). According to Baratto et al. (2), these episodes represent complex sensory processing, for example estimating a stable future (intended) state of the center-of-mass. The sway-density analysis has been successfully applied to demonstrate that the sensory regulation of postural control is affected in individuals with idiopathic scoliosis (6) and in individuals with obesity (4, 7).

Despite the promising empirical and theoretical embedding of this analysis [but see (5)], there has been no independent test of one of its core assumptions, namely that during quiet standing there is a quick back-and-forth of two control regimes; the passive feedback control and active feedforward control, as outlined above. In this paper we argue that the two control strategies likely differ in their computational and attentional complexity. More specifically, feedforward control is applied by the central nervous system based on an internal model of the body dynamics, which likely comes with an associated computational cost. In contrast, stiffness control is peripheral by nature and is likely not—or considerably less—computationally demanding. If this holds, then it should be possible to observe differences in computational cost using a concurrent stimulus-response reaction-time task, thereby taxing the differential attentional demands of the respective control modes, represented by specific local posturographic state variables (i.e., position, velocity, dwell times).

To this end, we first briefly describe a study by Teasdale et al. (8) which served as inspiration for our current study. That study asked whether young and older (otherwise healthy) participants differed in their attentional requirements to maintain static balance. During the quiet standing task, participants heard a tone at unpredictable instances upon which they had to press a handheld button as quickly as possible. Stimulus-response reaction times (RT) served as an index of the attentional requirements needed to perform the task, i.e., upright standing while responding to the tone. Teasdale et al. (8) reasoned that if the COP happened to be in a more eccentric position (relative to the origin of the posturogram), posture was presumably less stable, requiring deployment of attentional resources to bring the COP toward a more central (and putatively more stable) position. Thus, if an auditory stimulus happened to coincide with a more eccentric COP position, then—following Teasdale et al.'s (8) reasoning—this should give rise to longer RTs. This was indeed the case, but only for the group of older participants (8).

Teasdale et al. (8) focused exclusively on postural eccentricity. However, they did not consider the possibility that episodes of relatively stationary and transient COP excursions may occur anywhere in the posturogram, that is, at eccentric and central positions alike. As argued above, some episodes involve rapid, self-generated anticipatory COP displacements and likely reflect attention-demanding postural computations, whereas other episodes are relatively stationary and not (or less) computationally demanding. We adopted the experimental paradigm developed by Teasdale et al. (8) to test the hypothesis that the attentional requirements of postural control "wax and wane" during quiet upright standing, with greater requirements for active compared to passive control regimes. We used stimulus-response RTs as an index for the required attentional involvement (higher RTs represent greater attentional requirements) and related them to local posturographic state features like local COP eccentricity, local COP velocity and local dwell times derived from sway-density curves. Local COP eccentricity was included to replicate Teasdale et al.'s (8) findings.

Local COP velocity and local dwell times were included to unveil passive and active control episodes. Episodes in which the COP is relatively stationary are characterized by low velocity and high dwell times, which are assumed to reflect episodes of passive control. Vice versa, COP episodes with high velocity and low dwell times are assumed to reflect episodes of active control. By correlating RT values to local COP velocities and local dwell times, we could evaluate the hypothesis that the attentional requirement for controlling upright quiet stance fluctuates depending on the relative contribution of the two control regimes. More precisely, we predict (a) an overall positive association between RT and local COP velocity and (b) an overall negative association between RT and local dwell times.

MATERIALS AND METHODS

Participants

We tested 32 healthy young participants (15 females and 17 males). Their mean (±SD) age was 21.7 (±2.1) years. The study was approved by the local ethics committee and informed consent was obtained from all participants.

Procedure

Participants were instructed to stand still on a force plate (1 × 1 m, custom made) and to pay attention to a sequence of tones that was presented over computer loud speakers, positioned behind the participant at a distance of 1.5 m. Tones (8 kHz) were presented at random intervals ranging between 2 and 6 s. Participants had to press a small response key that was held in the right hand, as soon as they heard the tone. The computer sampled the stimulus tones, the response events, and the anterior-posterior (AP) and mediolateral (ML) COP data at 1 kHz.

The experiment was divided into four trials; (1) standing on a firm surface (i.e., the metal surface of the force plate), (2) standing on a piece of foam (40 × 40 × 8 cm, medium density) laying atop the force plate, (3) standing on a firm surface again, and (4) standing again on foam. Each trial lasted 181 s, thus yielding 181.000 data samples per trial. During each trial there were about 40 stimuli. Between trials there was a break of ∼1 min, during which the experimenter attached or removed the piece of foam.

Data Analysis

Stimulus-Response Reaction Times

We had to exclude three participants from the analyses because of a measurement error (i.e., failure to record the responses). For the 29 remaining participants, we ensured that the recorded stimulus-response pairs were valid by (1) excluding responses faster than 100 ms, (2) excluding responses slower than 600 ms, and (3) by excluding stimuli without a recorded response. Two participants exhibited RTs that were considerably slower than the rest with responses lasting well over 600 ms on many occasions. We decided to discard these participants from further analyses. For the remaining 27 participants (our final sample) we found that (1) there were never responses below 100 ms, (2) there were twelve responses slower than 600 ms, and (3) there was one stimulus without a recorded response. These events were discarded from further analyses. Furthermore, we discarded stimulus-response pairs falling in the first 5 or final 5 s of a trial to prevent the influence of starting or stopping the trials. From the remaining 4,515 valid stimulus-response pairs (yielding on average 42 valid pairs per trial, range 37–44), the mean stimulus-response reaction-time interval was determined, separately for each trial.

Global Posturographic Outcomes: Eccentricity, Velocity, and Dwell Time

AP and ML COP time series were filtered with a bi-directional, second-order low-pass Butterworth filter with a cut-off frequency of 12.5 Hz. We then removed the first and last 5 s of each trial (see above). For each trial, the mean eccentricity (defined as mean distance to the origin of the posturogram, in mm) and the mean sway velocity (traveled distance in the posturogram per unit time, in mm/s) were determined. Greater eccentricity and velocity were expected for standing on foam. Dwell times were determined from sway-density curves derived by counting, for each sample *i*, the number of consecutive samples on the posturogram falling inside a circle of given radius *R*, yielding, for each sample *i*, the duration in ms that the COP remained inside that circle [see, for example, (4) for a graphical illustration of the method]. These durations, also known as dwell times, critically depend on the overall magnitude of the posturogram (i.e., shorter durations for larger posturograms, thus supposedly shorter dwell times for foam than firm surfaces) and the size of the radius *R* (i.e., longer dwell times for larger radii). Although not the main topic of our research, we decided to investigate the effect of choice of radius on overall dwell times. The default setting for the radius in the literature is 2.5 mm [e.g., (2)], but some studies [e.g., (9)] have manipulated the size of *R* and examined its effect on the number of peaks and associated heights (i.e., peak dwell times) of the sway density curve. Since we were particularly interested in episodes at a specific time scale, namely episodes similar to the stimulus-response reaction times, we computed sway-density curves for ten different radii (0.25, 0.50, . . . , 2.50 mm), from which the mean dwell times were determined. The radius yielding dwell times similar to the stimulus-response durations will be used for the subsequent relational analyses, as described next.

Local Posturopgraphic Outcomes and Their Relation to Stimulus-Response Reaction Times

Figure 1 shows two individual posturograms (firm and foam), in which the red traces represent segments in the posturogram corresponding to the stimulus-response intervals. Our main interest was in the relationship between local posturographic outcomes (i.e., computed over segments in the posturogram corresponding to the stimulus-response intervals, i.e., the red traces in **Figure 1**) and stimulus-response reaction times, because this may reveal whether certain episodes within the posturogram have heightened attentional costs. To this end, we determined eccentricity, velocity and dwell times locally from COP episodes corresponding to individual stimulus-response intervals. If, for example, a given stimulus-response pair had a RT value of 200 ms, we used the posturographic data spanning this interval to determine local eccentricity, velocity and dwell times (thus

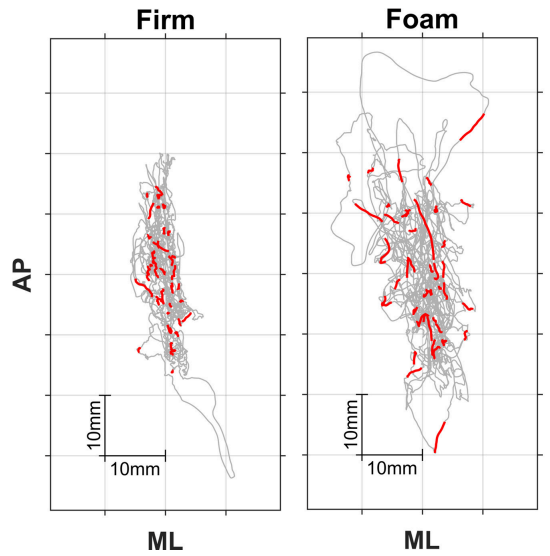


FIGURE 1 | Posturograms for firm **(Left)** and foam **(Right)** surface conditions. Trials lasted 181 s. Anterior-posterior (AP) vs. mediolateral (ML) center-of-pressure trajectories are depicted in gray, while superimposed red traces represent the 42 or so stimulus-response episodes during a trial.

based on 200 posturographic samples, starting with the sample corresponding to stimulus onset and ending with the sample corresponding to key press). We did this for each valid stimulus-response pair (see above), resulting in 37–44 values for local eccentricity, velocity, and dwell time per trial.

For each trial, Pearson's correlation coefficients and the slopes of the linear fits among these local posturographic values, as well as between local posturographic values and stimulus-response reaction times were determined and used for further statistical analyses (see below). The method of determining local dwell times and its association with stimulus-response reaction times (from which the slope was taken) is shown in **Figure 2**, for a representative trial (i.e., data corresponds to the left posturogram of **Figure 1**).

Statistical Analyses

We first tested the effect of surface (firm vs. foam) on stimulus-response reaction times and on the posturographic outcomes eccentricity and velocity. We performed two statistical analyses contrasting the two surface conditions, namely (1) a paired-samples t-test (alpha = 0.05) and (2) a Bayesian comparison of means (with default Cauchy prior of 0.707) performed in JASP (Version 0.8.6). The tests were performed on the average over the two trial repetitions per surface condition, except for one participant for which we used the second firm surface trial to represent the firm condition because of an error in data collection for the first firm trial. Bayesian hypothesis testing is rapidly gaining popularity [e.g., (10)]. It can be used to quantify the relative predictive value of two competing hypotheses, operationalized with so-called Bayes factors (BF) quantifying the relative evidence for the null hypothesis vis-à-vis the alternative hypothesis. The BF_{01} indicates how much more likely the data support the null-hypothesis (the means do not differ) compared to the alternative hypothesis (the means differ). BF_{10} equals $1/BF_{01}$, and quantifies how much more likely the data support the alternative hypothesis. It has been suggested to treat BFs between 1 and 3 as anecdotal (hence, inconclusive) evidence, BFs between 3 and 10 as moderate evidence, and BFs > 10 as strong evidence (11); we regard these qualifications as convenient shorthands to an underlying continuum of evidence.

With regard to the dwell times derived from the sway density analysis, we conducted a 2 (surface: firm, foam) by 10 (radius: 0.25, 0.50, …, 2.50 mm) repeated-measures ANOVA to (1) confirm the effects of magnitude of the posturogram and radius on the overall dwell times (smaller posturograms and larger radii would result in longer dwell times) and (2) to identify the radius yielding overall dwell times representative of the time scale of interest (i.e., dwell times similar to stimulus-response reaction-time intervals).

Third, we analyzed the statistical relationships among our local posturographic outcomes (local eccentricity, local velocity and local dwell times) as well as between these local outcomes and reaction times. We did this by analyzing the sign, magnitude and significance of the correlation coefficient as well as the slope of the linear fit. Since we were primarily interested in the nature and direction of the effect (positive, zero or negative), we entered the values of the correlation coefficient and the slope (averaged over the two trial repetitions) into one-sample t-tests against 0; correlations and slopes significantly different from zero would indicate an overall consistent positive or negative relationship. We likewise computed Bayes factors to quantify how much more likely the data supports the null hypothesis (correlations and slopes do not differ from 0, BF_{01}) or the alternative hypothesis (correlations and slopes differ from 0; BF_{10}). We did this separately for the firm and foam conditions.

RESULTS

Reaction Times

For the RTs we found no significant difference between responding on a firm surface (210 ± 25 ms) and on a foam surface [208 ± 28 ms; $t_{(26)} = 0.531$, $p = 0.60$, $d = 0.102$; **Figure 3**, top left panel]. The Bayesian analysis yielded a BF_{01} of 4.31, thus indicating moderate evidence in favor of the null hypothesis, i.e., no effect of the foam manipulation on RT.

Global Posturography

Figure 3 further summarizes the effects of support surface on global posturographic outcomes. As predicted, standing on foam had very strong effects, in expected directions, with greater eccentricity, faster velocity and shorter dwell times on foam compared to standing on the firm surface. Specifically, significant effects were found for eccentricity [firm: 4.5 ± 1.6 mm, foam 6.1 ± 1.2 mm; $t_{(26)} = -5.913$, $p < 0.001$, $d = -1.138$; $BF_{10} > 1{,}000$) and velocity (firm: 8.8 ± 1.6 mm/s, foam: 12.1 ± 2.9 mm/s; $t_{(26)} = -8.578$, $p < 0.001$, $d = -1.651$; $BF_{10} > 1{,}000$). Furthermore, both surface and radius significantly affected the overall dwell time of the sway density analysis. That is, the 2 (surface: firm,

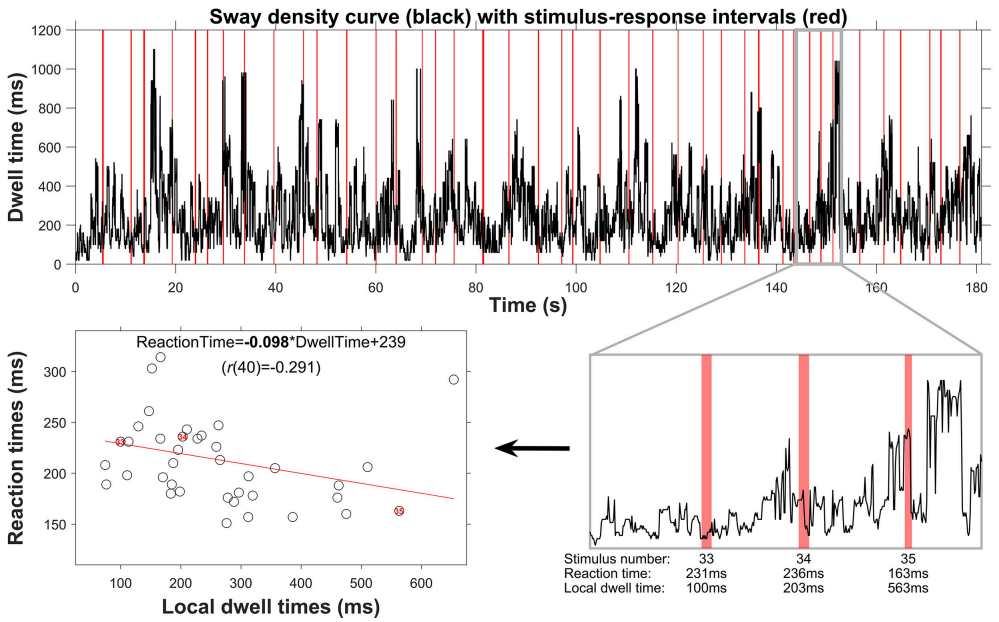


FIGURE 2 | Procedure outlining the posturographic analyses from global to local dwell-time estimation, and their relation to stimulus-response reaction times. The top panel displays the sway density curve, with in red the 41 episodes corresponding to stimulus-response intervals. Over the whole trial, the dwell time was on average 248 ms, but dwell times clearly fluctuate throughout the trial, with peaks up to 1,000 ms. In the lower-right panel, the sway-density curve is depicted for a period of about 10 s, containing three stimulus-response pairs (numbers 33, 34, and 35). As can be seen, the local dwell times taken over the stimulus-response intervals, as well as the reaction-time values, vary. This is confirmed by the negative correlation between local dwell times and reaction times, as depicted in the lower-left panel, with the linear fit (red line) and its regression equation yielding an overall negative slope (presented in bold font) for this trial.

foam) by 10 (radius: 0.25, …, 2.50 mm) repeated-measures ANOVA revealed shorter dwell times for foam (528 ms) than firm (1,063 ms) surfaces [main effect of Surface; $F_{(1,26)} = 89.77$, $p < 0.001$, ES = 0.775]. Dwell times increased with increasing radii [main effect of radius; $F_{(9,234)} = 225.74$, $p < 0.001$, ES = 0.897], with significant *post-hoc* differences between all radii (all p's < 0.001). The interaction between surface and radius was also significant [$F_{(9,234)} = 72.42$, $p < 0.001$, ES = 0.736], with significant between-surface differences growing with increasing radii (**Figure 3**, lower panel). Note that the average dwell times observed for a radius of 0.5 mm (198 ms) best corresponded to the average stimulus-response reaction times (209 ms), and hence to the time scale of interest. Consequently, we determined local dwell times based on a fixed radius value of 0.50 mm for the remainder of the analysis.

Relationships Among Local Posturographic Outcomes

Table 1 shows the correlations, slopes and statistics among the three local posturographic outcomes: local eccentricity, local velocity and local dwell times. As can be seen, there were consistent associations among all local posturographic outcomes (i.e., correlations and slopes differed significantly from zero), with higher velocity at greater eccentricity, shorter dwell times at greater eccentricity and particularly shorter dwell times at higher velocity, for firm and foam surfaces alike.

Relationships Between Local Posturographic Outcomes and Reaction Times

Table 2 shows the correlations, slopes, and statistics between the three local posturographic outcomes and RT. While the correlation and slope for the relationship between local eccentricity and RT was not significantly different from zero, and anecdotal (BF_{10} between 1/3 and 1), the values of the correlations and of the slopes between RT and local velocity, and between RT and local dwell times, differed significantly from zero. The correlations were overall weak and mostly not significant at the level of a single trial. Nevertheless, as predicted, the relationship between velocity and RT was consistently positive, implying longer RTs for sway episodes of greater velocity. In addition, the association between local dwell times and RT was consistently negative, implying longer RTs for episodes with lower local dwell times. This set of results is in agreement with the abovementioned strong negative correlation between local velocity and local dwell times (**Table 1**). The significant effects (in terms of both frequentist and Bayesian analyses) point to highly consistent behavior across participants, for firm and foam surfaces alike.

DISCUSSION

The aim of this study was to test a key prediction that could be derived from the intermittent control theory of quiet upright standing. Based on biomechanical measurements it has

TABLE 1 | Mean slopes (slope), Pearson correlation coefficients (*r*), and their standard deviations (SD) as well as the number of significant positive (+) and negative (-) correlations of all trials *n* among local eccentricity, local velocity and local dwell times, separately for firm and foam surfaces.

		Mean ± SD	$t_{(26)}$	*p*	*d*	BF_{10}
Eccentricity—velocity (firm)	slope	0.20 ± 0.30	3.496	0.002	0.673	21.3
	r	0.13 ± 0.17	3.935	<0.001	0.757	57.4
	+/−/*n*	14/0/53				
Eccentricity—velocity (foam)	slope	0.15 ± 0.23	3.465	0.002	0.667	19.8
	r	0.10 ± 0.12	4.164	<0.001	0.801	97.7
	+/−/*n*	7/0/54				
Eccentricity—dwell times (firm)	slope	−6.64 ± 8.46	−4.080	<0.001	−0.785	80.3
	r	−0.11 ± 0.14	−4.023	<0.001	−0.774	70.4
	+/−/*n*	1/7/53				
Eccentricity—dwell times (foam)	slope	−2.17 ± 3.01	−3.746	<0.001	−0.721	37.3
	r	−0.09 ± 0.10	−4.271	<0.001	−0.822	125.6
	+/−/*n*	0/3/54				
Velocity—dwell times (firm)	slope	−29.56 ± 11.71	−13.122	<0.001	−2.525	>1,000
	r	−0.68 ± 0.06	−55.078	<0.001	−10.600	>1,000
	+/−/*n*	0/53/53				
Velocity—dwell times (foam)	slope	−14.89 ± 7.65	−10.107	<0.001	−1.945	>1,000
	r	−0.72 ± 0.05	−82.504	<0.001	−15.878	>1,000
	+/−/*n*	0/54/54				

Statistics pertain to the one-sample t-tests against 0, with Cohen's d as effect size. BF_{10} represents the Bayes factor, with values > 10 quantifying strong evidence for the alternative hypothesis (slope differs from zero) relative to the null hypothesis (slope does not differ from zero).

been argued [e.g., (1)] that quiet standing is accomplished by a dual system, involving stiffness control, and feedforward control (based on anticipatory top-down regulation). Various papers (see Introduction) have emphasized that these control mechanisms seem to alternate in rapid succession, akin to eye movements consisting of saccades and fixations. We reasoned that passive stiffness control during quiet standing would be less computationally demanding than episodes involving "intermittent stabilization bursts" (9). In other words, the attentional load of maintaining stable upright stance was supposed to fluctuate during quiet standing, depending on which of the two control mechanisms happened to be at play. If this holds, then attentional load (as indexed using stimulus-response reaction time) should vary with local posturographic features reflecting active and passive control.

Our findings were as follows. First, we found that the mean reaction time did not differ between support surface conditions (i.e., firm vs. foam; **Figure 3**). A comparable study by Vuillerme and Nougier (12) found evidence for increased attentional requirements when standing on foam, but the effect (i.e., longer reaction times for foam than firm surfaces) was only found in a group of non-gymnasts, whereas gymnasts (with presumably superior balance abilities) showed no effect of standing on foam on RT. Our finding that RT did not differ between the two surface conditions suggests that our subjects had very good balance abilities, requiring very little attentional resources [as in (12)], and/or prioritized the reaction-time task over the balance task, focusing predominantly on RT performance, which is not unlikely given the observed posturographic changes when standing on foam (greater overall eccentricity, greater overall velocity and lower overall dwell time; **Figure 3**).

Second, when focusing exclusively on COP segments encompassing the stimulus-response intervals, we found a consistent statistical association among our three local posturographic features (**Table 1**). That is, we found that COP segments with relatively high local eccentricity (i.e., far removed from the center of the posturogram) also had relatively high local velocity and relatively low local dwell times. Although these correlations are relatively weak in magnitude and mostly not significant at the level of a single trial, the consistent positive and negative relationships over trials and participants reflect that the COP generally moves faster and dwells shorter, the further away it is from the origin, and vice versa. Such faster movements in more eccentric positions could signal an imminent loss of stability near the periphery (i.e., the onset of falling due to an accelerating center of mass) and/or postural adjustments to bring the eccentric center of mass back to the relative safety of the origin. Note that the negative correlation between local COP velocity and local dwell times was significant for all trials and quite strong in magnitude (**Table 1**), as it should be by definition.

Third, and this was the core finding of the study, we found consistent associations between attentional load (RT) and local velocity and local dwell times, but not between RT and postural eccentricity (**Table 2**). Participants generally took more time to respond to an auditory stimulus when their COP happened to move fast, and vice versa. Likewise, participants generally responded slower to the stimuli in COP episodes with lower dwell times (see also lower-left panel of **Figure 2**). In contrast, stimulus-response reaction times did not vary systematically

TABLE 2 | Mean slopes (slope), Pearson correlation coefficients (r), and their standard deviations (SD) as well as the number of significant positive (+) and negative (–) correlations of all trials *n* between the three local posturographic outcomes and reaction times (RT), separately for firm and foam surfaces.

		Mean ± SD	$t_{(26)}$	*P*	*d*	BF_{10}
Eccentricity—RT, firm	slope	1.04 ± 3.01	1.801	0.083	0.347	0.8
	r	0.04 ± 0.16	1.342	0.191	0.258	0.4
	+/−/*n*	5/1/53				
Eccentricity—RT, foam	slope	0.46 ± 1.87	1.267	0.216	0.244	0.4
	r	0.04 ± 0.12	1.790	0.085	0.344	0.8
	+/−/*n*	5/0/54				
Velocity—RT, firm	slope	2.03 ± 2.18	4.843	<0.001	0.932	487.9
	r	0.13 ± 0.12	5.516	<0.001	1.062	>1000
	+/−/*n*	8/0/53				
Velocity—RT, foam	slope	0.82 ± 0.95	4.470	<0.001	0.860	201.0
	r	0.11 ± 0.10	5.658	<0.001	1.089	>1000
	+/−/*n*	7/0/54				
Dwell times—RT, firm	slope	−0.051 ± 0.073	−3.656	0.001	−0.704	30.4
	r	−0.10 ± 0.12	−4.633	<0.001	−0.892	295.4
	+/−/*n*	1/4/53				
Dwell times—RT, foam	slope	−0.042 ± 0.050	−4.368	<0.001	−0.841	157.8
	r	−0.07 ± 0.09	−4.077	<0.001	−0.785	79.8
	+/−/*n*	0/3/54				

Statistics pertain to the one-sample t-test against 0, with Cohen's d as effect size. BF_{10} represents the Bayes factor, with values > 10 quantifying strong evidence for the alternative hypothesis (slope differs from zero) relative to the null hypothesis (slope does not differ from zero).

with how far away from the origin the COP was. These main findings have several implications. To start with, the increase in RT with lower local dwell times and faster COP velocity is in line with our main prediction. It suggests that phases in the COP trajectory with high velocity and low dwell times are associated with an elevated attentional cost, presumably because these posturographic features reflect instances of active control. Comparable findings have been reported in the literature on rhythmic arm movements [e.g., (13–15)], where it is found that RT is slowed down in certain phases in the movement cycle, possibly due to attentional engagement during "anchoring" [i.e., discrete instances in the continuous movement cycle during which control is exerted over the oscillator; see also (16, 17)]. In the context of locomotion, Lajoie et al. (18) found that reaction times to an auditory stimulus also varied systematically over the gait cycle; RTs were higher during the single-support phase compared to the double-support phase. These findings suggest that classical cognitive-motor dual-tasking effects [e.g., (19)] are visible not only across groups and conditions (e.g., comparing single task to dual-task performance), but also within a single continuous movement trajectory, such as a COP trace or cyclic movements. Classical dual-tasking studies typically compute average performance scores of the component tasks across the entire measurement, to assess the overall attentional requirements of the dual task at various difficulty levels. Our approach, in contrast, revealed that the attentional requirements of the continuous motor task of quiet standing exhibit an "ebb and flow", as evidenced by variations in reaction time that varied weakly but consistently with local posturographic features. This finding may help develop theorizing about the hypothesized dualistic nature of postural control, for example as regards the relative contribution of each mechanism and their respective time courses.

Two other implications follow from our main findings. First, the finding that local dwell times and local COP velocity are strongly interrelated (**Table 1**), while both correlate weakly but consistently with RT intervals (**Table 2**), implies that local COP velocity may yield the same information as local dwell times derived from sway density analysis. We would like to stress, however, that this redundancy only holds for our analysis approach where we correlated selected segments in the COP, and not necessarily applies to the entire time series. After all, several other parameters can be deduced from sway density curves (e.g., number of peaks, peak height, distance or time between peaks) that proved quite useful for between-task or between-group comparisons in the study of postural control [e.g., (7)]. If and when future studies find that, across different task conditions and populations, local COP velocity gives identical results as the local dwell times derived from sway density curves, then one might consider sticking to local COP velocity, as it is conceptually and computationally more straightforward. Second, our finding that RT was not associated with postural eccentricity in our sample of 27 young adults is in line with the original finding of Teasdale et al. (8), who found an effect only for older participants and not the young. It should be noted that their results were based on nine elderly and eight young, and that they did not employ Bayesian statistics to provide evidence in favor of the null. In combination with our results, it seems fair to conclude that the attentional demands of maintaining quiet upright standing in young adults are not related to eccentricity but instead to local

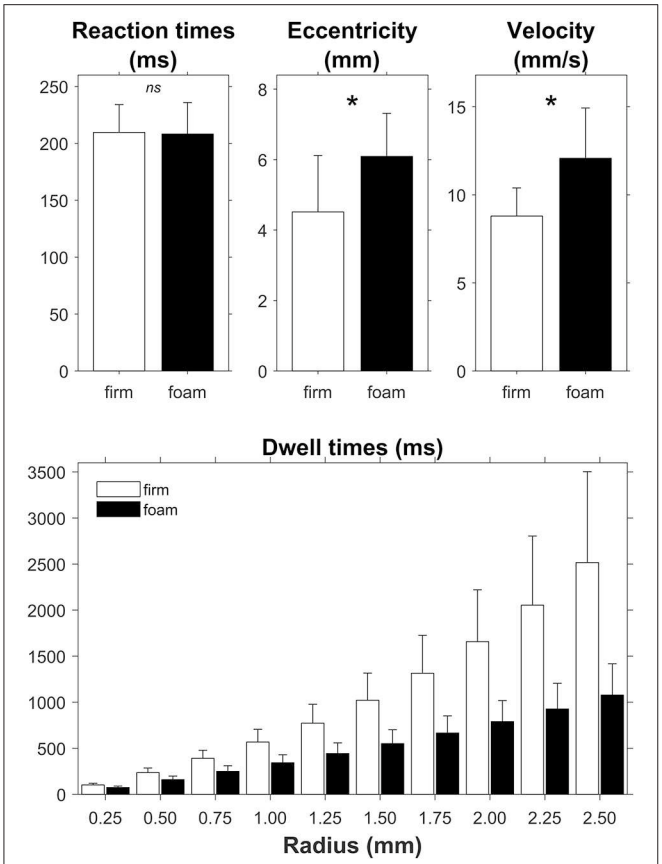


FIGURE 3 | Effect of support surface (firm, white bars and foam, black bars) on reaction times and the global posturographic outcomes eccentricity, velocity and dwell times, the latter presented for a range of radius values. Error bars represent standard deviations. Asterisks in the top panels denote a significant difference between firm and foam conditions. The difference between firm and foam was significant across all radii (bottom panel).

velocity and local dwell time, regardless of their position in the posturogram.

All in all, our results support a key prediction from the intermittent control theory of quiet standing by showing longer RTs for episodes containing local posturographic features indicative of active control (i.e., lower local dwell times, higher local velocity). Although the slopes and correlation coefficients of these associations were consistently and convincingly different from zero, it must be stressed that the correlation values were overall relatively low (roughly between 0.1 and 0.2) and mostly not significant at the level of a single trial (**Table 2**). These low correlations could partly be explained by the adopted approach for stimuli presentation. That is, we presented stimuli at random instances during a quiet standing trial, and we later correlated reaction times to local posturographic features that happened to be present at that moment in time. As can be appreciated from **Figure 2**, our stimuli generally missed the brief episodes with very high dwell times, that is, the episodes where the COP is relatively stationary and assumed to reflect passive control. We further noticed that episodes with high dwell time (peaks in the sway density curve) are typically quite short in duration, and notably shorter than the duration of a typical stimulus-response event. Looking again at the dwell times over a representative trial shown in the top panel of **Figure 2**, one can clearly see that the peaks (representing little COP movement) are shorter in duration than the intermediate episodes with lower dwell times (faster COP movement). As a consequence, most stimulus events will occur during such episodes of high postural activity. The typical short duration of episodes with high dwell times also implies that local dwell time estimates may reflect a mixture of passive and active control, such as for stimulus 34 in **Figure 2**. These three factors all reduce the explained variance of RT as a function of local dwell time and local velocity, and may hence explain why, despite the overall consistent directional trends, the magnitude of the correlations tends to be relatively low.

The observed slowing of reaction time with fast postural adjustments could point to the presence of a refractory period. This notion is quite common in the psychological literature and states that responding to a second event is slowed down if the event is in close temporal proximity to an immediately preceding stimulus-response event. Information processing of the first event takes some time to complete, which interferes with processing the following event, as demonstraded by delayed reaction times. The notion of refractoriness has recently been applied to the field of motor control by a study of van de Kamp et al. (20). In that study subjects had to manually control an unstable (virtual) inverted pendulum using a continuous joystick task. The pendulums varied in stability and system order. It was found that stabilization of the pendulum could be described by a series of brief ballistic control episodes, instead of continuous control. According to the authors, their data suggest a refractory period during which open loop control is not possible due to a hypothesized single-channel processing bottleneck. Moreover, continuous control was also unnecessary, since intermittent (serial ballistic) control was capable of stabilizing the unstable system. It could very well be that refractoriness is a general physiological mechanism that operates to control a wide range of homeostatic systems, including maintaining upright standing posture. We speculate that our observation of longer reaction times with shorter dwell times is compatible with the notion of such a general (cross-modal) bottleneck. More specifically, such an active intermittent postural control episode causes a brief temporal interference (i.e., refractoriness), blocking further response processing, such as responding to the auditory stimulus.

In conclusion, by mapping stimulus-response intervals to local posturographic features we demonstrated attentional fluctuations in the control of quiet upright standing, thereby validating core assumptions underlying the sway-density analysis and the theoretical notion of intermittent postural control. Future studies are recommended to control the presentation of the stimuli in a movement-dependent manner, such as successfully done in the context of cyclic tasks (15, 21, 22), in order to increase the likelihood of obtaining episodes with high dwell times. This may also be instrumental in identifying the method (i.e., local dwell times or some other local posturographic

parameter) that best parameterizes intermittent postural control, which seems relevant given the low magnitude of the correlations between local dwell times and reaction times. Furthermore, future studies are recommended to record EMG data of a set of muscles relevant to postural control. Complementing local posturographic features and associated stimulus-response intervals with recordings of neural activity could help unveil the neural circuitry driving the musculoskeletal control of posture (23–25). Moreover, when adopting an event-based approach, it could perhaps even pinpoint differences therein for the hitherto identified active and passive control regimes. To our knowledge, this has never been directly tested, despite offering a potentially informative window into the control processes underlying intermittency.

DATA AVAILABILITY STATEMENT

The raw data (Matlab struct containing all data) supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher. Processed data, i.e., means, are available as **Supplementary Material** to this paper.

ETHICS STATEMENT

The study was approved by the local ethics committee of the Vrije Universiteit of Amsterdam. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

JS developed the study concept and research plan and conducted the research. MR and JS conducted the data analysis. JS and MR wrote the paper.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2018.00850/full#supplementary-material

REFERENCES

1. Loram ID, Lakie M. Direct measurement of human ankle stiffness during quiet standing: The intrinsic mechanical stiffness is insufficient for stability. *J Physiol*. (2002) 545:1041–53. doi: 10.1113/jphysiol.2002.025049
2. Baratto L, Morasso P, Re C, Spada G. A new look at posturographic analysis in the clinical context: sway-density vs. other parameterization techniques. *Motor Control* (2002) 6:248–73. doi: 10.1123/mcj.6.3.246
3. Bottaro A, Yasutake Y, Nomura T, Casadio M, Morasso P. Bounded stability of the quiet standing posture: an intermittent control model. *Hum Mov Sci*. (2008) 27:473–95. doi: 10.1016/j.humov.2007.11.005
4. Villarrasa-Sapiña I, García-Massó X, Serra-Añó P, Garcia-Lucerga C, Gonzalez LM, Lurbe E. Differences in intermittent postural control between normal-weight and obese children. *Gait Posture* (2016) 49:1–6. doi: 10.1016/j.gaitpost.2016.06.012
5. Yamamoto T, Smith CE, Suzuki Y, Kiyono K, Tanahashi T, Sakoda S, et al. Universal and individual characteristics of postural sway during quiet standing in healthy young adults. *Physiol Rep*. (2015) 3:12329. doi: 10.14814/phy2.12329
6. Simoneau M, Mercier P, Blouin J, Allard P, Teasdale N. Altered sensory weighting mechanisms is observed in adolescents with idiopathic scoliosis. BMC *Neurosci*. (2006) 7:68. doi: 10.1186/1471-2202-7-68
7. Dutil M, Handrigan GA, Corbeil P, Cantin V, Simoneau M, Teasdale N, et al. The impact of obesity on balance control in community-dwelling older women. *Age* (2013) 35:883–90. doi: 10.1007/s11357-012-9386-x
8. Teasdale N, Bard C, LaRue J, Fleury M. On the cognitive penetrability of posture control. *Exp Ageing Res*. (1993) 19:1–13. doi: 10.1080/03610739308253919
9. Jacono M, Casadio M, Morasso PG, Sanguineti V. The sway-density curve and the underlying postural stabilization process. *Motor Control* (2004) 8:292–311. doi: 10.1123/mcj.8.3.292
10. Kruschke JK, Liddell TM. Bayesian data analysis for newcomers. *Psychon Bull Rev*. (2018) 25:155–77. doi: 10.3758/s13423-017-1272-1
11. Jeffreys H. *The Theory of Probability*. 3rd ed. Oxford, UK: Oxford University Press (1961).
12. Vuillerme N, Nougier V. Attentional demand for regulating postural sway: the effect of expertise in gymnastics. *Brain Res Bull*. (2004) 63:161–5. doi: 10.1016/j.brainresbull.2004.02.006
13. Latash M. Modulation of simple reaction time on the background of an oscillatory action implications for synergy organization. *Exp Brain Res*. (2000) 131:85–100. doi: 10.1007/s002219900284
14. Michaels CF, Bongers RM. The dependence of discrete movements on rhythmic movements: Simple RT during oscillatory tracking. *Human Movement Sci*. (1994) 13:473–93. doi: 10.1016/0167-9457(94)90050-7
15. Ridderikhoff A, Peper CE, Beek PJ. Attentional loads associated with interlimb interactions underlying rhythmic bimanual coordination. *Cognition* (2008) 109:372–88. doi: 10.1016/j.cognition.2008.10.002
16. Roerdink M, Bank PJ, Peper CE, Beek PJ. Anchoring in rhythmic in-phase and antiphase visuomotor tracking. *Motor Control* (2013) 17:176–89. doi: 10.1123/mcj.17.2.176
17. Roerdink M, Ridderikhoff A, Peper CE, Beek PJ. Informational and neuromuscular contributions to anchoring in rhythmic wrist cycling. *Ann Biomed Eng*. (2013) 41:1726–39. doi: 10.1007/s10439-012-0680-7
18. Lajoie Y, Teasdale N, Bard C, Fleury M. Attentional demands for static and dynamic equilibrium. *Exp Brain Res*. (1993) 97:139–44. doi: 10.1007/BF00228824
19. Fraizer EV, Mitra S. Methodological and interpretive issues in posture-cognition dual-tasking in upright stance. *Gait Posture* (2008) 27:271–9. doi: 10.1016/j.gaitpost.2007.04.002
20. van de Kamp C, Gawthrop PJ, Gollee H, Loram ID. Refractoriness in sustained visuo-manual control: is the refractory duration intrinsic or does it depend on external system properties? *PLoS Comput Biol*. (2013) 9:e1002843. doi: 10.1371/journal.pcbi.1002843
21. Peper CE, Oorthuizen JK, Roerdink M. Attentional demands of cued walking in healthy young and elderly adults. *Gait Posture* (2012) 36:378–82. doi: 10.1016/j.gaitpost.2012.03.032
22. Mazaheri M, Roerdink M, Bood RJ, Duysens J, Beek PJ, Peper CE. Attentional costs of visually guided walking: effects of age, executive function and stepping-task demands. *Gait Posture* (2014) 40:182–6. doi: 10.1016/j.gaitpost.2014.03.183

23. Boonstra TW, Danna-Dos-Santos A, Xie HB, Roerdink M, Stins JF, Breakspear M. Muscle networks: connectivity analysis of EMG activity during postural control. *Sci Rep*. (2015) 5:17830. doi: 10.1038/srep17830
24. Kerkman JN, Daffertshofer A, Gollo LL, Breakspear M, Boonstra TW. Network structure of the human musculoskeletal system shapes neural interactions on multiple time scales. *Sci Adv*. (2018) 4:eaat0497. doi: 10.1126/sciadv.aat0497
25. Loram I, Maganaris CN, Lakie M. Human postural sway results from frequent, ballistic bias impulses by soleus and gastrocnemius. *J Physiol*. (2005) 5641:295–311. doi: 10.1113/jphysiol.2004.076307

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

REVIEW
published: 26 October 2018
doi: 10.3389/fneur.2018.00899

Sensorimotor Manipulations of the Balance Control Loop–Beyond Imposed External Perturbations

Brandon G. Rasman[1,2], *Patrick A. Forbes*[1,3]*, *Romain Tisserand*[2] and *Jean-Sébastien Blouin*[2,4,5]

[1] Department of Neuroscience, Erasmus Medical Center, Rotterdam, Netherlands, [2] School of Kinesiology, University of British Columbia, Vancouver, BC, Canada, [3] Department of Biomechanical Engineering, Faculty of Mechanical, Maritime and Materials Engineering, Delft University of Technology, Delft, Netherlands, [4] Djavad Mowafaghian Center for Brain Health, University of British Columbia, Vancouver, BC, Canada, [5] Institute for Computing, Information and Cognitive Systems, University of British Columbia, Vancouver, BC, Canada

OPEN ACCESS

Edited by:
Emily Keshner,
Temple University, United States

Reviewed by:
Lorenz Assländer,
Universität Konstanz, Germany
Robert Peterka,
Oregon Health & Science University, United States
Pierre-Paul Vidal,
Université Paris Descartes, France

***Correspondence:**
Patrick A. Forbes
p.forbes@erasmusmc.nl

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: 29 June 2018
Accepted: 03 October 2018
Published: 26 October 2018

Citation:
Rasman BG, Forbes PA, Tisserand R and Blouin J-S (2018) Sensorimotor Manipulations of the Balance Control Loop–Beyond Imposed External Perturbations. Front. Neurol. 9:899. doi: 10.3389/fneur.2018.00899

Standing balance relies on the integration of multiple sensory inputs to generate the motor commands required to stand. Mechanical and sensory perturbations elicit compensatory postural responses that are interpreted as a window into the sensorimotor processing involved in balance control. Popular methods involve imposed external perturbations that disrupt the control of quiet stance. Although these approaches provide critical information on how the balance system responds to external disturbances, the control mechanisms involved in correcting for these errors may differ from those responsible for the regulation of quiet standing. Alternative approaches use manipulations of the balance control loop to alter the relationship between sensory and motor cues. Coupled with imposed perturbations, these manipulations of the balance control loop provide unique opportunities to reveal how sensory and motor signals are integrated to control the upright body. In this review, we first explore imposed perturbation approaches that have been used to investigate the neural control of standing balance. We emphasize imposed perturbations that only elicit balance responses when the disturbing stimuli are relevant to the balance task. Next, we highlight manipulations of the balance control loop that, when carefully implemented, replicate and/or alter the sensorimotor dynamics of quiet standing. We further describe how manipulations of the balance control loop can be used in combination with imposed perturbations to characterize mechanistic principles underlying the control of standing balance. We propose that recent developments in the use of robotics and sensory manipulations will continue to enable new possibilities for simulating and/or altering the sensorimotor control of standing beyond compensatory responses to imposed external perturbations.

Keywords: imposed perturbations, ongoing human in the loop manipulations, balance control, quiet standing, robotics, sensory stimulation

INTRODUCTION

Our ability to stand upright requires accurate estimation about the orientation of the body with respect to gravity as well as the relative relationships between body segments. These estimates are formed through multisensory integration of information arising from visual, vestibular, somatosensory and auditory sensory systems. Imposed perturbations of the sensory/motor systems and manipulations of the balance control loop provide methods of disrupting and/or modifying the balance controller. These approaches, however, differ. Imposed perturbations (transient or continuous) evoke external error signal inputs while manipulations of the balance control loop are designed to modify the sensorimotor relationships required to control quiet stance. Both approaches have proven critical in unraveling fundamental sensorimotor principles underlying standing balance. In this review, we explore perturbation and manipulation approaches used to probe the balance system. We first provide an overview of the sensorimotor and mechanical characteristics that are relevant for the control of standing balance. Then, we discuss imposed external perturbations that have enabled researchers to investigate how the balance system responds to these unexpected disturbances. Here, we operationally define imposed perturbations as methods which disrupt quiet standing behavior and represent external error signals for the balance system. As such, the parameters of the imposed external perturbations are designed exclusively by the experimenter. We subsequently present manipulations of the balance control loop that can be implemented to alter sensory feedback and/or their relationships with motor outputs during the ongoing control of quiet standing balance. Importantly, although these techniques can involve physical and/or sensory alterations, we define them as manipulations (rather than perturbations) as they are designed to modify relationships within the balance control loop such that their effects are a function of the action of the subject (i.e. human in the loop manipulations). Finally, we emphasize how manipulations of the balance control loop altering ongoing feedback can be combined with imposed perturbations to reveal sensorimotor principles of standing balance. Throughout this review, we prioritize information gained from experimental approaches applied to healthy human volunteers. Where appropriate, we relate these findings to observations gathered from clinical populations (e.g., persons with vestibular loss), whose behavior may complement our insight into the control of standing balance.

SENSORIMOTOR AND MECHANICAL ASPECTS OF STANDING BALANCE

The upright bipedal posture adopted for standing balance is mechanically unstable. When the vertical projection of the whole-body deviates from the ankle joint center of rotation, gravity acting on the body increases the magnitude of the toppling torque and must be compensated by active and passive forces. Consequently, although standing may be referred to as quiet stance or static balance, the acceleration of the whole-body center of mass is constantly varying in three-dimensional space. The mechanics of standing balance involve both large and fine adjustments used to stabilize the whole-body and the relative orientation of body segments (1–4). The mechanics of standing balance are often simplified by assuming that movement only occurs around a limited number of joints. In the anteroposterior direction, the standing body is commonly represented using a single-link inverted pendulum model where whole-body movements occur mainly around the ankle joints (5–8). In the mediolateral direction, an inverted pendulum with dual links (i.e., both limbs) has been proposed (9–11), with whole-body motion occurring around both the ankle and hip joints. The differential equation of an inverted pendulum is therefore used to describe the relationship between the net torque and whole-body angle when a person stands; explaining how body inertia mechanically filters muscle activation during standing, resulting in low frequency movements of the whole-body (typically below 0.5 Hz for quiet standing sway) (8, 12–14).

Given that forces are developed when musculoskeletal tissues are deformed, it has been proposed that tonic muscle activity may be sufficient to maintain standing balance passively (11, 15). For balancing along the anteroposterior direction, however, the toppling gravito-inertial torque associated with whole-body movements exceeds the intrinsic stabilizing torque developed by the viscoelastic forces during deformation of ankle tissues (16, 17). Consequently, active neural control of the ankle and hip muscles (as well as those acting at other joints) is required to stabilize the body and modulate the net forces and torques delivered through the feet onto the support surface (18–23). The active maintenance of standing balance involves a sensorimotor control loop that detects body orientation/motion and generates the stabilizing forces and torques required to remain upright (**Figure 1**). Information regarding the orientation of the body with respect to gravity and the relative relationship between body segments is provided by integrating multiple cues from sensors located throughout the body. In the following paragraphs, we describe briefly the balance-relevant sensory code provided by these sensors as they relate to the frequency characteristics of standing balance.

Balance-Relevant Sensory Code

Sensory inputs from the visual, vestibular, somatosensory and auditory systems all contribute to the control of standing balance. The information provided by individual sensory cues is shaped by the dynamics of each sensor and the coordinate system in which they are referenced [for a review of sensory dynamics related to standing balance, see (24)]. To be relevant for standing balance, a sensor must be capable of encoding frequencies up to and beyond those comprising the dynamics of the standing body; i.e., the dynamics of a sensor must be greater than the actuator, which must be greater than the mechanical system being controlled (25–27). Therefore, sensors that primarily encode low frequency (and static) information may be more likely to contribute to the low frequency control of quiet standing balance whereas those encoding higher frequencies may be more helpful in responding to imposed external perturbations.

The somatosensory system refers to a group of receptors found throughout the muscles, joints, and skin of the body. Several of these mechanoreceptors relay position and motion

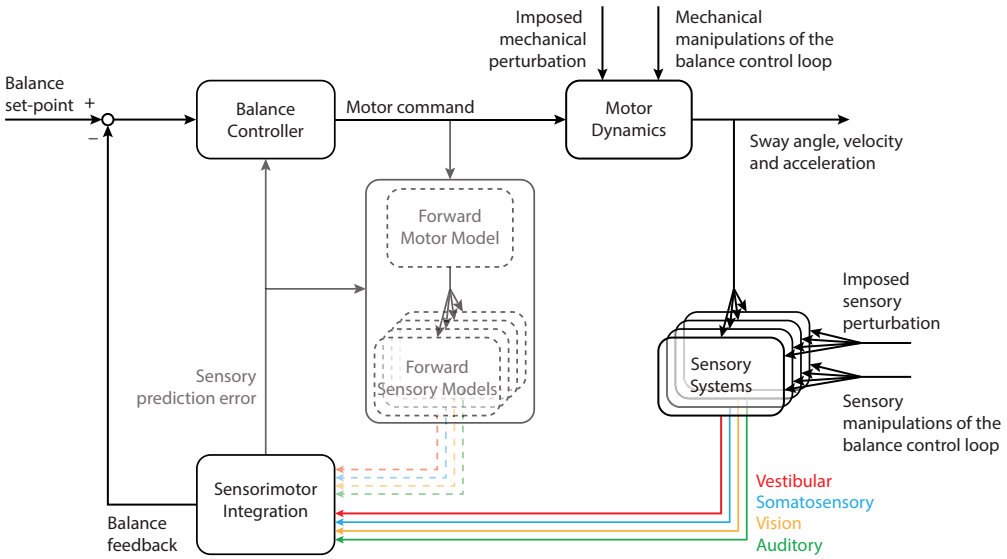


FIGURE 1 | Schematic of the balance control loop depicting the relationship between motor command, sensory feedback and multisensory integration. Sensory cues convey information about the external world and the body's orientation within it. This information is integrated with motor commands to estimate sensory prediction errors. Because these aspects of the balance control loop are not the focus of this review, they have been grayed out in the figure [see (24) for a more detailed exploration of these principles]. Mechanical and sensory inputs to the control loop illustrate a conceptual representation of imposed perturbations or manipulations of the balance control loop applied to understand the control of standing balance. Details on the implementation of imposed perturbations or manipulations of the balance control loop are presented in **Figure 2**. Portions of this figure were adapted from Forbes et al. (24).

cues referenced to the body and its different segments, also known as proprioception [(28–33); for a comprehensive review, see (34)]. Collectively, muscle and joint receptors encode static and dynamic joint angle and/or muscle force. Although cutaneous receptors may also encode joint angle (35), those located in the glabrous skin of the foot sole act as an interface between the external world and the body. They can sense contact forces and texture of the support surface that may be used for standing balance (36, 37). The visual system encodes cues referenced to the external world derived from our field of view. From visual inflow, motion signals of the surrounding world (object-motion) and of the body within the world (self-motion) are extracted and provide cues to stabilize the upright body (38). The accessory optic system (a series of nuclei in the midbrain with efferent connections to the brainstem and cerebellum) likely plays an important role for balance control given its preference for low frequency stimuli and interaction with vestibular inputs (39, 40). Visual signals further provide cues on the spatial orientation of objects in our surroundings that may be used for controlling posture and responding to disturbances (41, 42). The vestibular end organs, which are fixed within the inner ears, sense three dimensional orientation and inertial cues of the head-in-space (43). Two subtypes of end organs, the otoliths and the semicircular canals, allow the vestibular apparatus to encode translational and angular motion, respectively (44). Because otoliths also encode head orientation relative to gravity, the distinction between head orientation with respect to gravity and head acceleration signals can be achieved by the integration of otolith and canal cues along with visual and somatogravic ones (45–49). Hence, information derived from the peripheral vestibular apparatus provides important cues needed for the control of standing balance. The auditory system, often overlooked for its role in balance control, is situated alongside the vestibular apparatus in the inner ear. Auditory cues can be used for spatial localization of the head-in-space and produce illusions of self-motion (50, 51), most prominently in the absence of vision (52). When standing, stationary sound cues that are coherent with other sensory signals of balance allow subjects to construct spatial auditory maps that improve postural stability [see review by Campos et al. (53)].

Various imposed stimuli or sensory manipulations of the balance control loop can be used to investigate the role of sensory cues in balance control. In the following sections, we first describe imposed external perturbations that have been used to study the reactive control of standing balance. We emphasize that stimuli of this type evoke compensatory postural responses to external disturbances. Therefore, a particular focus is put on stimuli that specifically target balance control as opposed to methods that evoke responses irrespective of the need to balance upright (e.g., stretch reflexes). We subsequently present and propose methods that alter the ongoing control of quiet standing balance in order to assess the organization and potential adaptability of the neural control of standing balance.

IMPOSED EXTERNAL PERTURBATIONS TO CHARACTERIZE STANDING BALANCE

Imposed perturbations have been applied extensively to assess the control of standing balance. These perturbations are

often designed by experimenters to be similar to disturbances experienced during daily activities (e.g., standing on a bus that suddenly accelerates) and can have a range of amplitudes, velocities and/or accelerations. Carefully applied perturbations have been used to reveal important aspects of standing balance. For example, using imposed external perturbations researchers have estimated the passive and active mechanisms underlying standing balance and revealed how error signals are integrated and transformed to maintain upright stance (see subsections below). A point to consider, however, is that imposed perturbations represent an external error signal that is independent from the quiet standing balancing task (see **Figure 2A**). Quiet standing balance behaviors can be described using numerical models that also characterize responses to imposed perturbations (54, 55), but it cannot be assumed that the neural processes involved in these two scenarios are identical. Consequently, perturbations imposed on standing participants inform a researcher on how individuals respond to an external disturbance as opposed to how they integrate and combine multisensory cues to maintain quiet stance. Specifically, imposed perturbations may evoke responses originating from sensory cues activated by the perturbation that may not contribute to the control of quiet upright stance. Furthermore, it is currently not possible to estimate the contributions of ongoing sensory feedback involved in maintaining quiet standing balance by introducing additional sensory inputs through imposed perturbations [see (56) for locomotor analogy]. Nevertheless, there are certain imposed perturbations that only evoke whole-body responses when participants are engaged in standing balance and these may reveal fundamental principles underlying its control. We will discuss these different approaches in the following paragraphs but the reader is invited to consult (57–59) for comprehensive reviews of imposed perturbation approaches.

Mechanical Perturbations

A wide variety of mechanical perturbations have been used to study compensatory responses during standing balance. Popular approaches include rotating (60–63) or translating (64–67) the support surface of standing subjects, while others use forces or torques applied to specific points on the body (68–70). When applied as discrete physical perturbations to standing participants, mechanical perturbations evoke stereotypical transient muscle and whole-body responses (71–76). To align better with the continuous control of standing balance and to characterize muscle and whole-body responses to ongoing disturbances, other researchers have used prolonged mechanical oscillations to study standing balance (20, 77–79). Using specific perturbation frequencies and magnitudes, the relationship between oscillatory perturbations and muscle/postural responses can be estimated (80–82). Coupled with sensorimotor modeling, the input/output estimates from prolonged perturbations can reveal fundamental properties of upright stance such as stiffness, damping and time delays of the balance control loop. In animal models, mechanical support surface perturbation approaches have also led to the characterization of synergistic muscle responses in balance control (83–86). Coordinated patterns of muscle activity (i.e. "synergies" or "motor modules") are thought to be flexibly combined by the nervous system to facilitate functional motor control, and account for spatial, temporal and postural strategy variability in human responses to multidirectional imposed perturbations (87, 88). Mechanical perturbations can also be applied to perturb somatosensory cues of motion without physically moving the whole-body or its support surface. For instance, in "light touch" experiments, perturbations are provided through motion of an external reference that a subject is in contact with (often with a finger) that does not provide mechanical support (89–91). Recently, Asslander et al. (92) perturbed the touch surface that subjects contacted with a finger at different positions with respect to their body. The authors proposed that the brain transforms sensory information derived from light touch into a reference frame for standing balance by estimating the distance between the whole-body center of mass and the finger.

Mechanical stimuli can also be applied to activate cutaneous or muscle receptors. For example, vibration stimuli can be delivered at the foot soles or muscle tendons and adjusted (amplitude and frequency) to elicit responses in cutaneous (primarily fast-adapting) and muscle spindle (primarily Ia) afferents (93–95). When applied to standing participants, these stimuli evoke well-defined and direction-specific whole-body and muscle responses (96–99). Simultaneous vibration of cutaneous and muscle receptors elicits body tilts equal to the vector summation of individual responses (100), suggesting a linear combination of these specific stimuli. However, vibration and stretch stimuli are unspecific to balance control because they can elicit muscle responses in participants not maintaining standing balance (101–103). Consequently, it is not clear what (if any) principles specific to the control of quiet standing can be gained from mechanical vibrations targeting muscle(s) or cutaneous receptors.

Visual Perturbations

Visual perturbations can induce illusions of self-motion (i.e., vection) because retinal signals encode motion of the body and/or the environment. The brain must disambiguate these visual signals in order to control standing balance. For example, when standing on an idle train and viewing another train moving slowly, a perception that your train is moving may emerge. Researchers have exploited this ambiguity to investigate the role of visual cues on postural orientation and control of standing balance by imposing discrete translation or rotary visual perturbations (e.g., movements of the walls within a room or projected image). Standing participants exhibit well-defined compensatory balance responses (and illusions of self-motion) to discrete visual perturbations (104–109). The whole-body responses occur in the same direction as the visual motion (104, 110, 111). One explanation for this response is that the imposed visual stimuli are partially interpreted as a consequence of body motion. Hence, when the visual surround moves backwards (i.e., toward a subject), the balance system interprets the perturbation as self-motion in a forward direction which is corrected by leaning backwards. Consequently, visual perturbations provide a window into how visual signals of self-motion contribute to the control of standing balance.

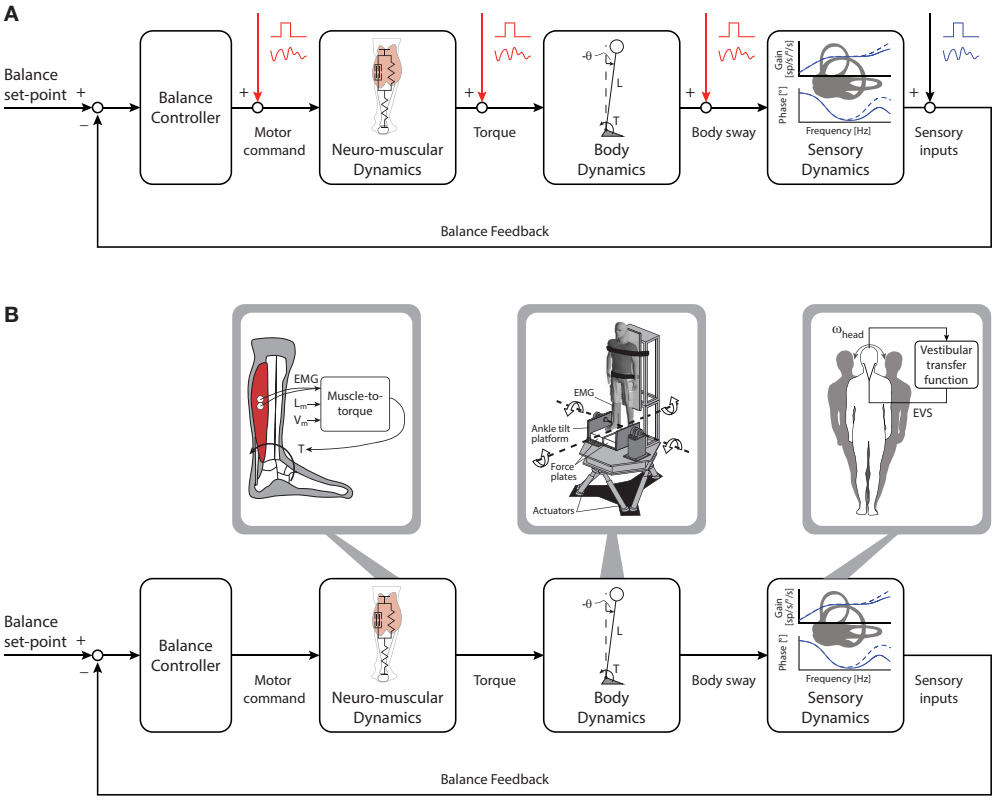


FIGURE 2 | Imposed perturbations and manipulations of the balance control loop. **(A)**: Mechanical and/or sensory perturbations can be imposed at the various stages of the control loop to produce external error signals independent from the ongoing control of quiet standing. Imposed perturbations can be delivered as discrete (e.g., square wave signal) or continuous (oscillatory signal) disturbances to evoke compensatory postural responses. **(B)** Manipulations of the balance control loop aim to simulate and/or modify the relationship between sensory and motor cues of ongoing balance control (i.e. human in the loop manipulations). These manipulations can be used to mimic or alter the dynamics of different components of the balance system through the use of robotic systems and sensory stimulation techniques. Transfer functions characterizing muscle contraction (electromyography [EMG], muscle length [L_m] and muscle velocity [V_m]) to torque output can be used to manipulate the ongoing effect of motor command (left). Similarly, a robotic balance simulator can be used to mimic and manipulate balance mechanics (middle). Torque delivered by the subject is used to control platform motion: this places the subject in-the-loop and allows for ongoing manipulation of standing balance. In addition, manipulations to sensor dynamics can be achieved, for example, by using instantaneous head velocity and transfer functions of the vestibular system to deliver an electrical vestibular stimulus that modulates the ongoing vestibular afferent firing rates (right). ω_{head}, head rotational velocity; EVS, electrical vestibular stimulation.

Visually-induced balance responses decrease as the amplitude of visual motion increases (20, 112–115). Dokka et al. (114) proposed that because slow visual signals of whole-body motion are more probable than faster motion, the slower visual signals are more likely to be interpreted as originating from self-motion. Day et al. (115) further reported a later visually-evoked balance response (∼0.7 s latency) that increases with stimulus velocity. They suggested that the later visually-evoked balance response is related to the alignment of the body to the erroneous estimate of gravity, an estimate that is biased by a prolonged stimulus of visual motion (107, 110, 115). This concept is reminiscent of the multisensory integration processes required to estimate the orientation of gravity from the otolith signals that can lead to an erroneous interpretation of translation (49, 116–119). It further highlights the usefulness of visual perturbations to explore and reveal physiological principles underlying the control of standing balance.

Vestibular Perturbations

Natural activation of the vestibular system requires movements of the head-in-space. Imposed head movements to examine the role of vestibular inputs on standing balance, however, have a limited use because head motion typically results in concomitant activation of other sensory signals. An isolated vestibular perturbation can be achieved by delivering electrical vestibular stimuli (EVS) through electrodes applied over the mastoid processes (assuming subjects keep their eyes closed). Application of such electrical stimuli modulates the activity of all vestibular afferents (increasing firing rates of all afferents under the cathodal electrode and decreasing under the anodal electrode), without having to move the head in space (120–124). Based on the anatomy and physiology of the vestibular system, bilateral binaural EVS is assumed to generate a vestibular error signal of head roll velocity around an axis pointing posterior and ∼18° up from Reid's plane (125–128). Although EVS represents a non-physiological stimulus (i.e., activation of all

vestibular afferents), responses elicited by EVS are only present in appendicular muscles when subjects are actively engaged in the task of balancing the whole-body (129–131). Hence, EVS can be used to investigate the vestibular control of balance and how vestibular signals are integrated, processed and relied upon for balance control [see reviews, (24, 125)]. We note, however, that this task dependency is not a ubiquitous feature because EVS evokes vestibulocollic reflexes in neck muscles even when the head and body are fully supported (132).

In standing participants, EVS evokes an unexpected vestibular error signal that requires a compensatory balance response to maintain an upright posture (125, 129, 133). The EVS-evoked error signal of head motion is head-referenced, such that its influence on standing balance depends on the orientation of the head with respect to the feet. Consequently, vestibular-evoked muscle and whole-body balance responses are spatially transformed based on head orientation with respect to the feet (134–137). This indicates that the whole-body responses evoked by an isolated vestibular perturbation (EVS) involve multisensory integration of information related to head-on-feet posture (e.g., via proprioceptive inputs) with vestibular cues of motion. Furthermore, the direction of the vestibular-evoked balance responses is influenced by body stability, whereby muscle and balance responses evoked by EVS are larger in the direction where postural stability is reduced (138, 139). This directional modulation of the vestibular-evoked balance responses based on balance stability without changes in sensory feedback may confound conclusions regarding sensory up-weighting of vestibular signals associated with experimental changes in sensory information (e.g., sway referencing or closing the eyes). This is because altering sensory information while balancing may decrease postural stability (i.e., increase sway), making it difficult to attribute the modulation of vestibular-evoked responses to changes in relative sensory information or changes in postural stability and upright position (140). Finally, the task-dependent characteristics of vestibular-evoked balance responses further suggest that they are not indicative of simple reflex arcs but instead reflect organized balance responses involving the integration of multiple sensory and motor cues (139, 141, 142).

SENSORIMOTOR MANIPULATIONS TARGETING THE ONGOING CONTROL OF STANDING BALANCE

As discussed in section Imposed External Perturbations to Characterize Standing Balance, imposed perturbations enable the identification and modeling of fundamental principles underlying standing balance. But these approaches must be interpreted within the framework of disturbances external to ongoing control of quiet standing. An alternative approach involves continuous sensory and/or mechanical manipulations of the balance control loop aimed at simulating or modifying the ongoing control of quiet standing balance (see **Figures 2B**, **3**). In other words, these manipulations are designed to modify feedback relationships within the balance control loop such that their effects are a function of the action of the subject (i.e. human in the loop manipulations). In addition, they must carefully match the dynamics of the sensory, motor and mechanical systems involved in standing balance, often requiring detailed knowledge of the neural code to be mimicked or elaborated by devices to induce these manipulations. Here, we review sensory and mechanical manipulations of the balance control loops that allow participants to experience controlled aspects of standing balance or altered sensorimotor conditions. Specifically, we discuss how replicating the sensors dynamics of standing balance can reveal how a specific cue is integrated and processed to maintain upright stability. In addition, we draw parallels between sensorimotor manipulations and specific clinical populations who can balance in the absence of specific sensory feedback cues (e.g., large-fiber sensor neuropathy or vestibular-loss). Where appropriate, we discuss limitations of sensorimotor manipulations and identify where additional work is needed.

Somatosensory Cues

The role of somatosensory cues in the control of standing balance can be partially investigated using ongoing mechanical manipulation of the support surface. Continuous manipulation of the support surface can be adjusted based on the participants' torque production and whole-body postural oscillations to minimize ankle plantar- and dorsi-flexor movements. This sway-referencing of the support surface reduces the contribution of lower limb receptors encoding ankle angle to the control of standing. The increase of whole-body oscillations observed under this condition has been interpreted as supporting the role of ankle somatoreceptors in the control of standing balance (144–147). Reports from the clinical literature add support to the importance of somatoreceptors in upright postural control: patients with large diameter afferent neuropathy (complete loss of proprioception) are unable to stand or walk without vision (148, 149). Sway-referencing the support surface to the postural oscillations, however, has mechanical consequences that must be taken into account when interpreting the standing balance behavior to this modified ankle somatosensory feedback. Because the ankle joint angle remains relatively constant as the body oscillates back and forth, minimal deformation of the ankle tissues (muscles, tendons, ligaments, skin) occurs. This prevents the development of length and velocity dependent passive forces that normally contribute to the stabilizing torque required to remain upright (17). Considering that passive forces are estimated to contribute between 10 and 90% of the net torque required to stand (16, 17, 20, 150), it is not clear what portion of the postural stability changes observed during sway-referencing are due to the contribution of ankle somatosensors versus the modulation of the active component of standing to compensate for a reduction in passive forces contributing to standing. A potential approach to explore these possibilities could involve simulating/altering the muscle activation to muscle torque transfer functions using robotic devices replicating the control of standing balance (13, 151, 152) (see **Figure 2B** and Mechanical and Sensory Approaches).

The isolated contribution of somatosensory cues to standing balance has been assessed using balance control of a body-equivalent load (8). Participants supported by a rigid frame with their head immobile (minimizing visual and vestibular cues) balanced a load with their feet that mimics the dynamics of an inverted pendulum (8, 130, 146, 153–155) (see **Figure 3B**). To distinguish contributions from muscle proprioceptors and foot sole cutaneous cues, skin receptors have been minimized by cooling or anesthetizing the feet (153, 156). The general consensus from these experiments is that ankle muscle receptors provide adequate inputs for maintaining standing balance. Although the range and variability of the body-equivalent load oscillations were larger than for natural standing balance (where all cues are available), participants could stabilize the load with only cues from the ankle muscle proprioceptors (153). The similar frequency characteristics of "whole-body" sway between these conditions further supported the conclusion that ankle muscle receptors are sufficient to maintain standing balance. Confirmatory findings by other groups provide additional validation regarding this conclusion (147, 157).

Additional somatosensory information may be incorporated within the balance control loop through the use of light touch. When subjects make light contact with a stationary external reference—typically with a finger—postural sway is reduced despite the negligible mechanical stabilizing effect of touch (158, 159). This suggests that cues encoded from low contact forces are incorporated as a sensory signal contributing to the balance control loop. Improved standing balance stability has also been observed when two standing subjects make light finger contact with one another (160–162). Using a simple modeling approach, Reynolds and Osler (162) suggested that interpersonal contact while standing is beneficial even if the balance controller does not distinguish self and partner motion. Taken together, these studies highlight the potential for light touch to alter sensory feedback within the balance control loop.

Visual Cues

A simple method to manipulate visual cues is to have subjects stand with the eyes closed or in the dark. Compared to eyes open, eyes closed (or darkness) increases quiet whole-body oscillations (9, 38, 163–165), but the low frequency components require long sampling durations of stance (>300s) to be captured accurately (14). The importance of visual information for standing has also been revealed by manipulating the number of fixation targets (166, 167), type of lighting (168) and depth cues (169–171). In a series of experiments, Paulus et al. (38) reported increases in postural stability under conditions with improved visual acuity, increased area of the central visual field and increased retinal displacement (caused by decreasing the eye-object distance). These observations emphasize that the influence of vision on standing balance is dependent on the features of the visual scene. An alternative approach is to keep visual signals constant on the retina (effectively sway-referencing vision) by having participants view a scene that moves according to the motion of the whole-body (144, 145, 154, 172). Under these conditions, balance was more unstable compared to when the eyes were closed (145, 173, 174). McCollum et al. (174) rationalized that this occurs because in the visual sway-referenced condition, there is a central integration conflict (or mismatch) between different sensory channels (i.e., vision-vestibular, vision-somatosensory). Collectively, these studies suggest that visual cues contribute to standing balance, and are likely fused with other signals encoding whole-body with postural oscillations.

An alternative approach to determine the role of visual cues in standing balance involves determining if these cues alone are sufficient to remain upright (see **Figure 3C**). Nagata et al. (157) devised a computer-controlled inverted pendulum allowing participants to apply forces and moments to the ground but experiencing only the visual consequences of their motion. Participants were stable in space while a motor replicated the visual signals of balance according to their motor actions—hence subjects attempted to balance an equivalent body load with sensory feedback limited mostly to visual cues (others included somatosensory cues of feet pressure changes and muscle contractions). Nagata et al. (157) reported that vision only contributed to the reduction of sway below 0.4 Hz. This aligns with previous suggestions that vision may primarily contribute to the low frequency (<1 Hz) control of standing balance (170, 175, 176). Although visual perturbations can evoke sway behavior as high as ∼2 Hz (20), responses tend to decline rapidly above 0.8 Hz. Nagata et al. (157) argued that the processing of visual information was too slow such that vision provided only a minor influence on the control of standing balance. A limiting factor of their approach, however, was that the rotational axis of the visual enclosure was not collinear with the ankle joints (154). Loram and colleagues, in contrast, have shown that participants standing braced can balance a real or virtual inverted pendulum with similar mechanics of the standing body using their hand to move a spring or a joystick with only visual cues of motion (155, 177, 178). To address this apparent discrepancy on the role of visual cues to maintain standing balance, we performed a simple experiment. Ten healthy subjects participated in this study after giving their written informed consent. The experiment protocol conformed to the Declaration of Helsinki and was approved by the University of British Columbia's Clinical Research Ethics Board. Similar to Fukuoka et al. (154), braced upright participants balanced with the expected visual cues of self-motion programmed to replicate the motion of an inverted pendulum in the antero-posterior direction (see **Figure 3C**). Initially, all participants ($n = 10$) exhibited difficulties in keeping the visual cues of motion within the balance limits (i.e., 6° anterior and 3° posterior). Sway variability was 5–6 times larger than when balancing a robotic simulator using all sensory cues (**Figure 4A**). After 5 days of training to balance with only visual cues of motion (∼20 min per day), their ability to balance within the programmed limits improved substantially (**Figure 4B**). Participants exhibited a ∼75% decrease in sway variability but this variability remained twice that observed when balancing with all sensory cues. These data show that although subjects exhibit initial difficulties in balancing with only visual cues of motion, they can adapt and use these cues to control standing balance with practice.

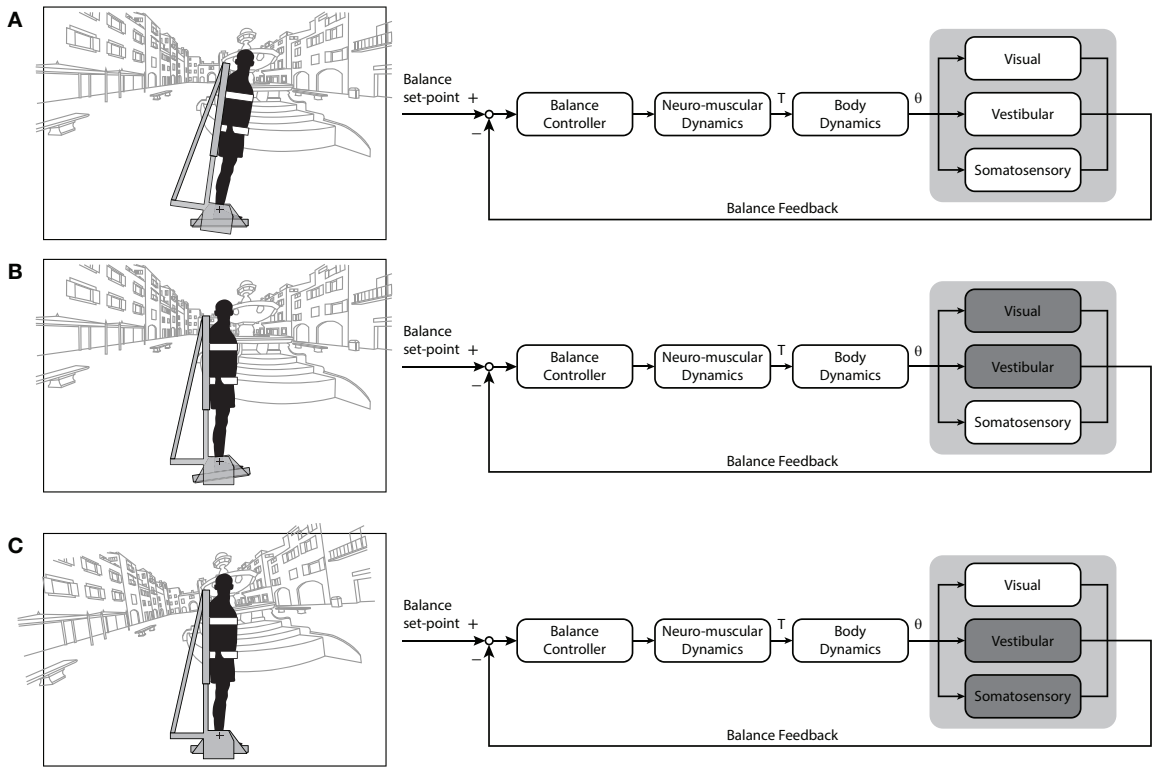


FIGURE 3 | Block diagrams of the varying sensory cue combinations that can be simulated using robotic balance platforms or mechanical devices. **(A)** Normal standing balance conditions where cues from visual, vestibular and somatosensory signals contribute to upright stance. Under these conditions, the foot is stationary, the whole-body moves and the head is moving relative to the visual scene. **(B)** A somatosensory-only balance condition. Subject's head and body are stationary in space in front of a stationary visual surround while the feet rotate, requiring subjects to balance a simulated inverted pendulum that mimics the body's mechanics with movement limited to their ankle joints. **(C)** A vision-only balance condition. Subjects are stationary in space while the visual scene is moving relative to the head, resulting in a balancing task that provides mostly balance-relevant visual cues. This condition was used here to re-examine the potential for standing subjects to use visual cues of motion (see **Figure 4**). Additional sensory cues (e.g. auditory) and other cue combinations could be considered. For example, by coupling simulated head motion with an electrical vestibular stimulus (see **Figure 2B**) it may be possible to provide dynamic vestibular cues of standing without actual motion. T, ankle torque; θ, inverted pendulum angle. Portions of this figure were adapted from Shepherd (143).

Vestibular Cues

The contribution of vestibular cues has been inferred by assessing the standing balance behavior while carefully controlling the available cues to remain upright. One approach involved characterizing postural oscillations while sway-referencing vision as well as the support surface (145, 174). By minimizing visual and ankle somatosensory cues, Nashner and colleagues were targeting the role of vestibular signals in maintaining upright stability. Participants exhibited difficulty in maintaining upright posture when vision and ankle proprioception were sway referenced, sometimes experiencing falls (145, 174). However, the limitation discussed above regarding the lack of passive forces contributing to upright stability under the sway-referencing of the support surface also applies to these experiments. A second approach consisted of comparing postural oscillations during normal upright stance (including vestibular cues) and during balancing a body-equivalent load while braced (excluding vestibular cues). When limiting whole-body movements to the ankle joints in both conditions, Fitzpatrick et al. (153) showed that balance stability was similar if vestibular cues contributed to the control of balance or not, irrespective of visual cues. Altogether, observations from these two distinct approaches suggest that vestibular cues provide limited benefit over visual and somatosensory cues to the control of standing balance. In support of this idea, vestibular loss patients can maintain upright stance with vision and somatosensory cues (even at the onset of the deficit), and over time, the instability is reduced due to compensation processes (179–182) and possibly from neural adaptation such as that observed in non-human primates (183–185).

Ongoing manipulation of vestibular cues according to postural oscillations was assessed in a different context by Héroux et al. (186). Participants were standing on foam with eyes closed while exposed to an electrical vestibular stimulus. The electrical stimulus was designed to replicate the general dynamics of primary semicircular afferents modulations during standing balance and coupled in real-time to the recorded movements of the head (see **Figure 2B**). Conceptually, this head-coupled vestibular stimulus increased or decreased vestibular gain depending on the polarity of the stimulus with respect to the

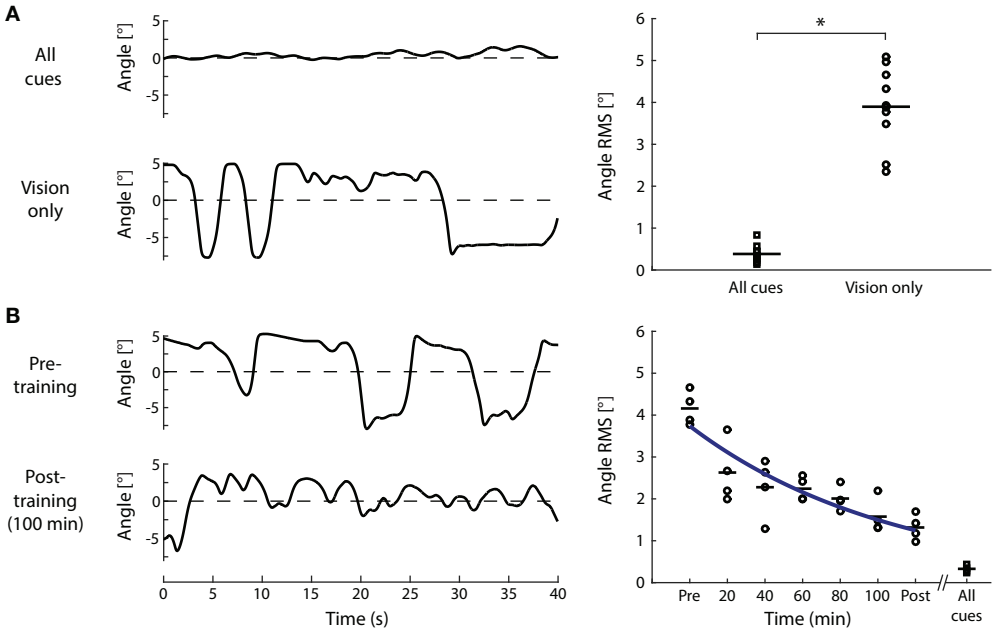


FIGURE 4 | Standing balance using only visual cues. **(A)** Subjects stood in a robotic balance simulator while either all sensory cues (see **Figure 3A**) or only visual cues of balance were provided (see **Figure 3C**). Angular oscillations of a representative subject (left) when balancing with all cues or only vision show an increase in angular sway when balancing with only vision. Mean removed root-mean-square (RMS) of angular oscillations of all subjects tested ($n = 10$, right) exhibited the same increase when using visual cues to balance (paired t-test; $t_9 = -13.2$, $P < 0.001$). Squares represent the "all cues" condition and circles represent the "vision only" condition. **(B)** Four of the original 10 subjects subsequently went through 5 days of training (∼20 min per day) under the vision only condition. Angular oscillations of a representative subject (left) show a decrease after 100 min (5 days) of training compared to the pre-training vision only condition. Mean-removed RMS of angular oscillations progressively decreased with each session of training (circles), but always remained above the all cues conditions (squares). For illustrative purposes, the blue line shows the fitting of mean angle RMS to an exponential function ($y = 4.4893\, e^{-0.1829\, x}$) using a least-square method. In both graphs, horizontal lines represent the mean of standard oscillation across all subjects and $^*P < 0.001$.

measured head motion. When the stimulus was applied, postural oscillations increased 4-fold. This finding bears some similarity to the decreased postural stability observed in acute unilateral vestibular loss patients (181, 187, 188) who are faced with asymmetric vestibular inputs. Although these results suggest that altering the gain of vestibular cues during standing influence the balance behavior, additional work is needed to determine if such vestibular cues of standing delivered in isolation (i.e., standing fixed to a rigid backboard) are sufficient to allow humans to balance upright.

COMBINING MANIPULATIONS TARGETING THE ONGOING CONTROL OF QUIET STANDING BALANCE WITH IMPOSED EXTERNAL PERTURBATIONS

Although manipulations targeting the ongoing control of standing balance can indicate limits of adaptability in the controller, there are limitations with interpreting standing behavior (forces, torques, sway) when sensory cues are manipulated in isolation. Specifically, while the combination of sensory cues can be well controlled, manipulations of the ongoing control of balance do not provide a known external perturbation signal. Van der Kooij et al. (57) compared different approaches to assess standing balance and showed that an external perturbation is needed to characterize the mechanisms governing balance. Applying imposed perturbations while controlling specific parameters of the ongoing control of standing combines the strengths of both approaches, affording a unique opportunity to reveal operating principles of the balance system and potentially revealing some of its inherent limitations. In the following section, we describe how imposed perturbations during well-controlled sensory manipulations have revealed fundamental features of standing balance such as inter-sensory interactions and re-calibration of sensory feedback loops. This includes the use of mechanical and robotic balance systems that allow for the replication of standing balance dynamics and provide users full control to virtualize parameters of the balance task. Finally, we briefly present an approach to alter the vestibular contribution to standing and discuss the resulting adaptation occurring in the control of standing balance.

Mechanical and Sensory Approaches

Pioneering work using a combination of perturbation approaches was conducted by Fitzpatrick et al. (130). The authors used their whole-body equivalent load device to explore how the vestibular control of standing balance—characterized with EVS-evoked muscle responses—was modulated by the sensory cues contributing to postural stability. Fitzpatrick et al. (130) revealed

strong context-dependency of the vestibular control of standing: vestibular-evoked muscle responses were absent when subjects balanced the body-equivalent load using only somatosensory cues. This suggests that although lower limb somatosensory cues are sufficient to maintain upright stance, balance-relevant vestibular feedback is required to engage the response to an external vestibular perturbation signal (130).

Cenciarini and Peterka (81) combined support surface perturbations (pseudorandom ankle tilt stimuli and sway-referenced conditions) with step EVS pulses to test predictions from their sensory re-weighting hypothesis (20). The authors showed that the amplitude of vestibular-evoked whole-body responses increased when concomitant perturbations were applied to the support surface and were largest when the ankle joint was sway-referenced. These observations corresponded well with predictions from their computational model and were interpreted as providing support for the sensory re-weighting hypothesis (79, 80, 189, 190). In this case, the limited balance feedback from the ankle proprioceptors during sway-referencing was interpreted as requiring an increased contribution of vestibular signals for standing balance as reflected by the larger EVS-evoked responses. Note that, as similarly discussed in section Vestibular Perturbations, support surface perturbations and sensorimotor manipulations may influence balance stability which in turn modulates vestibular-evoked balance responses (138, 139). Carefully designed experiments are needed to determine the relative contribution of standing balance state (i.e., angular position and angular velocity) and sensory re-weighting on the modulation of vestibular-evoked balance responses.

To take advantage of the possibilities enabled by manipulations of the balance control loop, our group developed a robotic system that can replicate and/or modify specific parameters of the sensorimotor control of standing balance (**Figure 2B**) (151). Upright participants are braced to a rigid backboard mounted atop a six-degree of freedom Stewart mechanism. Through a computer simulation in which the mechanics, sensory feedback and environment of standing can be simulated or altered, the robot rotates the whole-body about the ankle joints based on the real-time ground reaction forces and moments applied by the participants. Motion of the robot can be restricted to the anterior-posterior direction and the force plates are mounted to an ankle-tilt platform, allowing independent control of whole-body and ankle movements (191). When programmed to simulate an inverted pendulum, movement of the subjects actuating the robot replicates the torque-angle relationship of the whole-body during unrestricted standing balance (13). Under these subject-in-the-balance-loop conditions, a plantar-flexor torque is necessary to maintain the body in a forward leaning position.

Using this robotic balance simulator, Luu et al. (131) revisited the hypothesis that balance-relevant vestibular feedback is required to engage the response to an external vestibular perturbation signal. First, Luu et al. (131) showed that vestibular feedback (whole-body sway) independent from the balance task was not sufficient to elicit muscle responses to vestibular stimuli. Forbes et al. (139) complemented these findings by allowing participants to balance only along one plane (anteroposterior or mediolateral) while controlling the orientation of the head—and the direction of the vestibular-induced error signal. As the direction of balance and that of the vestibular error signal rotate orthogonally to one another, vestibular-evoked muscle responses are progressively suppressed even though subjects are engaged in balance. Hence, the vestibular contribution to balance muscle activity depends not only on the contribution of vestibular feedback to the ongoing muscle activity but also on the cross-product of the direction of balance instability and the direction of the induced vestibular error. Second, Luu et al. (131) addressed the possibility that balance-relevant vestibular signals must be temporally and spatially coupled to the motor commands to engage the vestibular control of standing. Participants stood atop the robotic balance system under two conditions: (1) with coupled sensory and motor signals, where subjects actively controlled the motion of their body in space by modulating their ankle torques (replicating normal standing), and (2) with decoupled sensory and motor signals, where the robot imperceptibly took control and imposed whole-body motion to the subjects following a pre-determined trajectory independent of their ankle torques. For the latter condition, subjects continued to actively modulate their ankle torques despite them not influencing the motion of their body, thus resulting in a discrepancy between predicted and actual sensory feedback associated with the standing balance task. Despite subjects demonstrating poor conscious awareness of the transitions between these two conditions (i.e., self vs. robot-controlled whole-body motion), vestibular-evoked muscle responses were attenuated when motor and sensory cues of balance were decoupled. These observations suggest that congruency between predicted and actual sensory signals is required to engage the vestibular control of standing balance. One caveat to these observations, however, is that the congruency of multiple balance feedback cues (visual, vestibular, somatosensory) was manipulated simultaneously (i.e., either all congruent or none were congruent). Hence, it remains unclear how individual sensory cues interact with the balance responses to vestibular error signals.

Forbes et al. (139) further used the robotic balance system to explore the adaptability of the control of standing balance. They modified the balance simulation by reversing the direction of whole-body motion produced by the measured ankle torques, effectively inverting the roles of the muscles controlling balance in the anteroposterior plane. Subjects were instructed to close their eyes and the ankle-torque relationship was maintained, mainly targeting the reversal to vestibular feedback. Under these reversed conditions, a dorsi-flexor torque is necessary to maintain the body in a forward leaning position. Participants adapted within 30–90 s to the reversed balance control. When EVS was applied, subjects swayed in the same direction for both the control and reversed balance conditions. To induce the same whole-body movement, the motor outputs from the balance controller (e.g., torque and muscle responses), however, were reversed and delayed. This indicates that the neural centers controlling standing balance can rapidly integrate the state of the relationship between motor commands and whole-body sensory

feedback, and generate appropriate muscle responses to correct for the induced vestibular error signals. Such swift re-associations of sensorimotor relationships may reflect our flexibility to maintain bipedal postures in varied settings, like when stepping from shore onto a stand-up paddle board. Similar reversals of vestibulomotor responses have been observed in the vestibulo-ocular reflex (VOR) during exposure to optical reversals of vision, although adaptation typically required days or weeks to fully invert vestibular-evoked eye movements (192–194). Despite the temporal differences in the balance and VOR adaptation to the reversals, the detailed characterization of the cellular mechanisms in the cerebellum and vestibular nuclei involved in the plasticity of the VOR [see review by Cullen and Mitchell (195)] may point toward similar neurophysiological processes playing a role in vestibulomotor adaptations for balance. In non-human primates, adaptations in neuronal recordings of vestibular nuclei and cerebellar neurons have been observed on a trial-by-trial basis (196). Over exposure to a novel relationship between motor commands and consequent head movement (altered head-neck dynamics), neuronal responses adapt from encoding head motion as externally generated to one that is self-generated. The multisensory convergence of sensory afferents at the vestibular nuclei and their projections to descending spinal tracts (197, 198) suggest that the vestibular nuclei contribute to the adaptive mechanisms observed in the vestibular control of balance.

Sensory and Sensory Approaches

Carefully manipulating the information from multiple sensory inputs further allows one to explore inter-sensory interactions in standing balance. Several groups have investigated how varying the availability and quality of visual cues interacts with the vestibular-evoked balance response to EVS (129, 130, 171, 199, 200). Day and Guerraz (171) manipulated the quality of visual cues providing information regarding whole-body oscillations during standing balance. Participants stood in a dark room while viewing nothing, a single light-emitting diode, a two-dimensional array of light-emitting diodes or a three-dimensional array of light-emitting diodes. The authors probed the vestibular control of balance using EVS under these different conditions to determine how the structure of visual cues related to standing balance influenced vestibular-evoked responses. In healthy controls, they showed that the early parts of vestibular-evoked responses vary when pre-stimulus visual information differs (i.e., light or dark), even when the post-stimulus feedback visual environments are equivalent. Feedback effects from the post-stimulus environment were also observed, affecting the later parts of the balance response ($> \sim$400 ms). This setting of the vestibular channel's gain can explain how vestibular responses evoked in healthy controls change with the amount of available visual cues.

Mian and Day (138) explored how sensory information derived from light touch can influence the direction of the vestibular-evoked balance response. Standing subjects were probed with EVS while lightly touching a stationary flat surface aligned laterally to the subjects. Despite light touch providing negligible mechanical stabilizing effects on the body, the response to EVS was biased toward the anteroposterior direction. As sensory cues from light touch are thought to be transformed into ongoing proprioceptive feedback for standing balance, this suggests that the gain of the vestibular-evoked balance response is spatially-modulated by the orientation (or direction) of balance-relevant proprioceptive feedback. Careful interpretation of these findings is warranted because light touch also reduced whole-body sway in the mediolateral plane.

As stated above, Héroux et al. (186) designed biologically-plausible head-coupled electrical vestibular stimuli to manipulate vestibular gain in healthy volunteers standing upright on foam with eyes closed. While balance oscillations increased four-fold when the electrical stimuli were applied (some subjects needed support to avoid a fall), the amplitude of the vestibular-evoked muscle responses (probed with an independent low-amplitude EVS signal) decreased. The authors further evaluated whether the participants could adapt to ongoing modulation of the vestibular cues associated with standing balance. The critical concept here was to determine if an imposed vestibular error signal that is coupled to the ongoing control of quiet standing balance can be calibrated and incorporated in the balance control loop. Participants were exposed to a re-calibration period of 240 s where the in-the-loop modified vestibular cues were provided with no foam and/or eyes open. Following this period, participants could maintain standing balance (on foam with eyes closed): postural sway and vestibulomotor response amplitudes returned to baseline. These results could not be explained by a down-regulation (or reweighting) of vestibular cues because matching levels of EVS that were uncoupled from head motion (hence remained an external imposed perturbation) did not yield any adaptation following a 240s re-calibration period. Instead, these observations indicate that the balance controller can integrate an external vestibular error signal into its control loop and likely interpret it as a self-generated signal as long as that signal follows the expected sensory dynamics encoding ongoing quiet standing balance. Consequently, a vestibular signal that was deemed an error signal before re-calibration was transformed into a meaningful signal that was used to maintain upright balance.

FUTURE DIRECTIONS

Sensorimotor manipulations of the balance control loop can target how muscle activation is related to the ground reaction forces and moments acting on the subject as well as the sensory feedback experienced (perceived or not) by participants maintaining standing balance. Critical questions to address include determining the influence of the state of standing balance stability [see (138, 139)] on imposed perturbations, how sensory signals are used to control standing balance under challenging conditions along with the limits of our capability to maintain upright stance. As a specific example, Luu et al. (131) proposed that a spatial and temporal relationship between sensory and motor signals is required to engage the vestibular control of standing balance. The factors underlying this spatio-temporal relationship need to be explored as well as their influence on our capability to remain upright. Future experiments should

also target how imposed visual perturbations are integrated in the control of standing balance under manipulations similar to those explored using imposed electrical vestibular stimuli (131, 138, 139) to determine if previous findings can be generalized and truly reflect fundamental mechanisms of the balance control loop. Building on the work from Héroux et al. (186), it is also conceivable to imagine innovative ways to characterize the unique contribution of sensory cues to the control of standing balance. As we learn more about the dynamics of standing and the resulting code from specific sensory afferents, artificial stimuli can be envisioned to replicate the neural code and assess its contribution to standing. For example, knowledge regarding the firing behavior of muscle spindle afferents during upright stance would permit the creation of a range of stimuli (intraneural electrical, mechanical or miniaturized robotics) to mimic it. The keys to such endeavors include a better understanding of the physiological code underlying standing balance and concerted efforts to replicate it during well-controlled balance-relevant experiments.

CONCLUSIONS

We have reviewed externally imposed perturbations and manipulations of the balance control loop that can be used to reveal the multisensory cue integration, task-dependent sensory processing and sensorimotor adaptation underlying the control of standing balance. We presented imposed external perturbations that elicit postural responses when the stimulus is related to the context of standing balance. These balance-specific approaches can provide important insight on the factors influencing the control of standing balance. We also described manipulations of the balance control loop which allow for the modification of mechanical and/or sensory dynamics to target the ongoing control of standing balance. Finally, we presented how combining imposed perturbations and manipulations of the balance control loop, including robotics and sensory manipulations, can reveal important principles underlying the maintenance of standing balance such as spatio-temporal congruency between sensory and motor signals, rapid re-association of sensorimotor relationships and re-calibration of vestibular signals in the balance control loop. We reason that by carefully considering the neural code of quiet standing, well-controlled experiments can utilize these combined imposed perturbations and manipulations of the balance control loop approaches to uncover the fundamental mechanisms of balance control.

AUTHOR CONTRIBUTIONS

BR, PAF, and J-SB contributed to conception and design of the review. RT collected and analyzed the data. BR and J-SB wrote the first draft of the manuscript. All authors contributed to manuscript revisions, and read and approved the submitted version.

FUNDING

The research leading to these results is supported by (1) the Netherlands Organization for Scientific Research (NWO #016.Veni.188.049, PAF), and (2) the Natural Sciences and Engineering Research Council of Canada (J-SB).

REFERENCES

1. Assaiante C, Amblard B. An ontogenetic model for the sensorimotor organization of balance control in humans. *Hum Movement Sci.* (1995) 14:13–43. doi: 10.1016/0167-9457(94)00048-J
2. Pozzo T, Levik Y, Berthoz A. Head and trunk movements in the frontal plane during complex dynamic equilibrium tasks in humans. *Exp Brain Res.* (1995) 106:327–38. doi: 10.1007/BF00241128
3. Gage WH, Winter DA, Frank JS, Adkin AL. Kinematic and kinetic validity of the inverted pendulum model in quiet standing. *Gait Post.* (2004) 19:124–32. doi: 10.1016/S0966-6362(03)00037-7
4. Pinter IJ, van Swigchem R, van Soest AJK, Rozendaal LA. The dynamics of postural sway cannot be captured using a one-segment inverted pendulum model: a PCA on segment rotations during unperturbed stance. *J Neurophysiol.* (2008) 100:3197–208. doi: 10.1152/jn.01312.2007
5. Smith JW. The forces operating at the human ankle joint during standing. *J Anat.* (1957) 91:545–64.
6. Gurfinkel VS, Osovets SM. Equilibrium dynamics of human vertical posture. *Biofizika* (1972) 17:478–86.
7. Nashner LM. Adapting reflexes controlling the human posture. *Exp Brain Res.* (1976) 26:59–72. doi: 10.1007/BF00235249
8. Fitzpatrick RC, Taylor JL, McCloskey DI. Ankle stiffness of standing humans in response to imperceptible perturbation: reflex and task-dependent components. *J Physiol.* (1992) 454:533–47. doi: 10.1113/jphysiol.1992.sp019278
9. Day BL, Steiger MJ, Thompson PD, Marsden CD. Effect of vision and stance width on human body motion when standing: implications for afferent control of lateral sway. *J Physiol.* (1993) 469:479–99. doi: 10.1113/jphysiol.1993.sp019824
10. Winter DA. Human balance and posture control during standing and walking. *Gait Post.* (1995) 3:193–214. doi: 10.1016/0966-6362(96)82849-9
11. Winter DA, Patla AE, Prince F, Ishac M, Gielo-Perczak K. Stiffness control of balance in quiet standing. *J Neurophysiol.* (1998) 80:1211–21. doi: 10.1152/jn.1998.80.3.1211
12. Rougier P, Farenc I. Adaptative effects of loss of vision on upright undisturbed stance. *Brain Res.* (2000) 871:165–74. doi: 10.1016/S0006-8993(00)02357-X
13. Luu BL, Huryn TP, Van der Loos HF, Croft EA, Blouin J-S. Validation of a robotic balance system for investigations in the control of human standing balance. *IEEE Trans Neural Syst Rehabil Eng.* (2011) 19:382–90. doi: 10.1109/TNSRE.2011.2140332
14. van der Kooij H, Campbell AH, Carpenter MG. Sampling duration effects on center of pressure descriptive measures. *Gait Post.* (2011) 34:19–24. doi: 10.1016/j.gaitpost.2011.02.025
15. Winter DA, Patla AE, Rietdyk S, Ishac MG. Ankle muscle stiffness in the control of balance during quiet standing. *J Neurophysiol.* (2001) 85:2630–3. doi: 10.1152/jn.2001.85.6.2630
16. Morasso PG, Sanguineti V. Ankle muscle stiffness alone cannot stabilize balance during quiet standing. *J Neurophysiol.* (2002) 88:2157–62. doi: 10.1152/jn.2002.88.4.2157
17. Loram ID, Lakie M. Direct measurement of human ankle stiffness during quiet standing: the intrinsic mechanical stiffness is insufficient for stability. *J Physiol.* (2002) 545:1041–53. doi: 10.1113/jphysiol.2002.025049

18. Morasso PG, Schieppati M. Can muscle stiffness alone stabilize upright standing? *J Neurophysiol*. (1999) 82:1622–6. doi: 10.1152/jn.1999.82.3.1622
19. Loram ID, Kelly S, Lakie M. Human balancing of an inverted pendulum: is sway size controlled by ankle impedance? *J Physiol*. (2001) 532:879–91. doi: 10.1111/j.1469-7793.2001.0879e.x
20. Peterka RJ. Sensorimotor integration in human postural control. *J Neurophysiol*. (2002) 88:1097–118. doi: 10.1152/jn.2002.88.3.1097
21. Kuo AD. An optimal state estimation model of sensory integration in human postural balance. *J Neural Eng*. (2005) 2:235–49. doi: 10.1088/1741-2560/2/3/S07
22. Loram ID, Maganaris CN, Lakie M. Active, non-spring-like muscle movements in human postural sway: how might paradoxical changes in muscle length be produced? *J Physiol*. (2005) 564:281–93. doi: 10.1113/jphysiol.2004.073437
23. Loram ID, Maganaris CN, Lakie M. Human postural sway results from frequent, ballistic bias impulses by soleus and gastrocnemius. *J Physiol*. (2005) 564:295–311. doi: 10.1113/jphysiol.2004.076307
24. Forbes PA, Chen A, Blouin J-S. Sensorimotor control of standing balance. In: Gait B, Day BL, Lord SR, editors. *Handbook of Clinical Neurology*. Vol. 159 (in press).
25. Franklin GF, Powell JD, Emami-Naeini A. *Feedback Control of Dynamic Systems*. Upper Saddle River, NJ: Prentice Hall (2009).
26. Forbes PA, Dakin CJ, Vardy AN, Happee R, Siegmund GP, Schouten AC, et al. Frequency response of vestibular reflexes in neck, back, and lower limb muscles. *J Neurophysiol*. (2013) 110:1869–81. doi: 10.1152/jn.00196.2013
27. Forbes PA, Siegmund GP, Schouten AC, Blouin J-S. Task, muscle and frequency dependent vestibular control of posture. *Front Integr Neurosci*. (2015) 8:94. doi: 10.3389/fnint.2014.00094
28. Goodwin GM, McCloskey DI, Matthews PB. The contribution of muscle afferents to kinaesthesia shown by vibration induced illusions of movement and by the effects of paralysing joint afferents. *Brain* (1972) 95:705–48. doi: 10.1093/brain/95.4.705
29. Roll JP, Vedel JP. Kinaesthetic role of muscle afferents in man, studied by tendon vibration and microneurography. *Exp Brain Res*. (1982) 47:177–90. doi: 10.1007/BF00239377
30. Clark FJ, Burgess RC, Chapin JW, Lipscomb WT. Role of intramuscular receptors in the awareness of limb position. *J Neurophysiol*. (1985) 54:1529–40. doi: 10.1152/jn.1985.54.6.1529
31. Edin BB. Quantitative analysis of static strain sensitivity in human mechanoreceptors from hairy skin. *J Neurophysiol*. (1992) 67:1105–13. doi: 10.1152/jn.1992.67.5.1105
32. Edin BB. Quantitative analyses of dynamic strain sensitivity in human skin mechanoreceptors. *J Neurophysiol*. (2004) 92:3233–43. doi: 10.1152/jn.00628.2004
33. Collins DF, Refshauge KM, Todd G, Gandevia SC. Cutaneous receptors contribute to kinesthesia at the index finger, elbow, and knee. *J Neurophysiol*. (2005) 94:1699–706. doi: 10.1152/jn.00191.2005
34. Proske U, Gandevia SC. The proprioceptive senses: their roles in signaling body shape, body position and movement, and muscle force. *Physiol Rev*. (2012) 92:1651–97. doi: 10.1152/physrev.00048.2011
35. Edin BB, Johansson N. Skin strain patterns provide kinaesthetic information to the human central nervous system. *J Physiol*. (1995) 487:243–51. doi: 10.1113/jphysiol.1995.sp020875
36. Kennedy PM, Inglis JT. Distribution and behavior of glabrous cutaneous receptors in the human foot sole. *J Physiol*. (2002) 538:995–1002. doi: 10.1113/jphysiol.2001.013087
37. Strzalkowski ND, Peters RM, Inglis JT, Bent LR. Cutaneous afferent innervation of the human foot sole: what can we learn from single unit recordings? *J Neurophsyiol*. (2018) 120:1233–46. doi: 10.1152/jn.00848.2017
38. Paulus WM, Straube A, Brandt T. Visual stabilization of posture. Physiological stimulus characteristics and clinical aspects. *Brain* (1984) 107:1143–63. doi: 10.1093/brain/107.4.1143
39. Simpson JI. The accessory optic system. *Ann Rev Neurosci*. (1984) 7:13–41. doi: 10.1146/annurev.ne.07.030184.000305
40. Giolli RA, Blanks RH, Lui F. The accessory optic system: basic organization with an update on connectivity, neurochemistry, and function. *Prog Brain Res*. (2006) 151:407–40. doi: 10.1016/S0079-6123(05)51013-6
41. Ghafouri M, McIlroy WE, Maki BE. Initiation of rapid reach-and-grasp balance reactions: is a pre-formed visuospatial map used in controlling the initial arm trajectory? *Exp Brain Res*. (2004) 155:532–6. doi: 10.1007/s00221-004-1855-8
42. Zettel JL, Holbeche A, McIlroy WE, Maki BE. Redirection of gaze and switching of attention during rapid stepping reactions evoked by unpredictable postural perturbation. *Exp Brain Res*. (2005) 165:392–401. doi: 10.1007/s00221-005-2310-1
43. Angelaki DE, Cullen KE. Vestibular system: the many facets of a multimodal sense. *Annu Rev Neurosci*. (2008) 31:125–50. doi: 10.1146/annurev.neuro.31.060407.125555
44. Goldberg JM. Afferent diversity and the organization of central vestibular pathways. *Exp Brain Res*. (2000) 130:277–97. doi: 10.1007/s002210050033
45. Fernández C, Goldberg JM. Physiology of peripheral neurons innervating otolith organs of the squirrel monkey. III. Response dynamics. *J Neurophysiol*. (1976) 39:996–1008. doi: 10.1152/jn.1976.39.5.996
46. Hess BJ, Angelaki DE. Inertial vestibular coding of motion: concepts and evidence. *Curr Opin Neurobiol*. (1997) 7:860–6. doi: 10.1016/S0959-4388(97)80147-X
47. Mergner T, Glasauer S. A simple model of vestibular canal-otolith signal fusion. *Ann N Y Acad Sci*. (1999) 871:430–4. doi: 10.1111/j.1749-6632.1999.tb09211.x
48. Green AM, Angelaki DE. An integrative neural network for detecting inertial motion and head orientation. *J Neurophysiol*. (2004) 92:905–25. doi: 10.1152/jn.01234.2003
49. Laurens J, Angelaki DE. The functional significance of velocity storage and its dependence on gravity. *Exp Brain Res*. (2011) 210:407–22. doi: 10.1007/s00221-011-2568-4
50. Urbantschitsch V. Über Störungen des Gleichgewichtes und Scheinbewegungen [On disturbances of the equilibrium and illusory motions]. *Zeitschrift Ohrenheilkunde* (1897) 31:234–94.
51. Clark B, Graybiel A. The effect of angular acceleration on sound displacement: the audiogyral illusion. *J Psychol*. (1949) 28:235–44. doi: 10.1080/00223980.1949.9916005
52. Lackner JR. Induction of illusory self-rotation and nystagmus by a rotating sound field. *Aviat Space Environ Med*. (1977) 48:129–31.
53. Campos J, Ramkhalawansingh R, Pichora-Fuller MK. Hearing, self-motion perception, mobility, and aging. *Hear Res*. (2018) 369:42–55. doi: 10.1016/j.heares.2018.03.025.
54. Peterka RJ. Postural control model interpretation of stabilogram diffusion analysis. *Biol Cybern*. (2000) 82:335–43. doi: 10.1007/s004220050587
55. Maurer C, Peterka RJ. A new interpretation of spontaneous sway measures based on a simple model of human postural control. *J Neurophysiol*. (2005) 93:189–200. doi: 10.1152/jn.00221.2004
56. Nielsen JB. Motoneuronal drive during human walking. *Brain Res Rev*. (2002) 40:192–201. doi: 10.1016/S0165-0173(02)00201-1
57. van der Kooij H, van Asseldonk E, van der Helm FCT. Comparison of different methods to identify and quantify balance control. *J Neurosci Methods* (2005) 145:175–203. doi: 10.1016/j.jneumeth.2005.01.003
58. Ting LH. Dimensional reduction in sensorimotor systems: a framework for understanding muscle coordination of posture. *Prog Brain Res*. (2007) 165:299–321. doi: 10.1016/S0079-6123(06)65019-X
59. Mergner T. A neurological view on reactive human stance control. *Annu Rev Control* (2010) 34:177–98. doi: 10.1016/j.arcontrol.2010.08.001
60. Diener HC, Bootz F, Dichgans J, Bruzek W. Variability of postural "reflexes" in humans. *Exp Brain Res*. (1983) 52:423–8.
61. Keshner EA, Allum JHJ, Pfaltz CR. Postural coactivation and adaptation in the sway stabilizing responses of normals and patients with bilateral vestibular deficit. *Exp Brain Res*. (1987) 69:77–92. doi: 10.1007/BF00247031

62. Keshner EA, Allum JH, Honegger F. Predictors of less stable postural responses to support surface rotations in healthy human elderly. *J Vestib Res.* (1993) 3:419–29.
63. Allum JHJ, Honegger F. Interactions between vestibular and proprioceptive inputs triggering and modulating human balance-correcting responses differ across muscles. *Exp Brain Res.* (1998) 121:478–94. doi: 10.1007/s002210050484
64. Nashner LM. Fixed patterns of rapid postural responses among leg muscles during stance. *Exp Brain Res.* (1977) 30:13–24. doi: 10.1007/BF00237855
65. McIlroy WE, Maki BE. Changes in early 'automatic' postural responses associated with the prior-planning and execution of a compensatory step. *Brain Res.* (1993) 631:203–11.
66. Huang QM, Hodges PW, Thorstensson A. Postural control of the trunk in response to lateral support surface translations during trunk movement and loading. *Exp Brain Res.* (2001) 141:552–9. doi: 10.1007/s00221-001-0896-5
67. Carpenter MG, Thorstensson A, Cresswell AG. Deceleration affects anticipatory and reactive components of triggered postural responses. *Exp Brain Res.* (2005) 167:433–45. doi: 10.1007/s00221-005-0049-3
68. Cresswell AG, Oddsson L, Thorstensson A. The influence of sudden perturbations on trunk muscle activity and intraabdominal pressure while standing. *Exp Brain Res.* (1994) 98:336–41. doi: 10.1007/BF00228421
69. Aruin AS, Latash ML. The role of motor action in anticipatory postural adjustments studied with self-induced and externally triggered perturbations. *Exp Brain Res.* (1995) 106:291–300. doi: 10.1007/BF00241125
70. Gilles M, Wing AM, Kirker SG. Lateral balance organisation in human stance in response to a random or predictable perturbation. *Exp Brain Res.* (1999) 124:137–44. doi: 10.1007/s002210050607
71. Nashner LM. A model describing vestibular detection of body sway motion. *Acta Otolaryngol.* (1971) 72:429–36. doi: 10.3109/00016487109122504
72. Allum JHJ. Organization of stabilizing reflex responses in tibialis anterior muscles following ankle flexion perturbations of standing man. *Brain Res.* (1983) 264:297–301. doi: 10.1016/0006-8993(83)90828-4
73. Horak FB, Nashner LM. Central programming of postural movements: adaptation to altered support-surface configurations. *J Neurophysiol.* (1986) 55:1369–81. doi: 10.1152/jn.1986.55.6.1369
74. Carpenter MG, Allum JH, Honegger F. Directional sensitivity of stretch reflexes and balance corrections for normal subjects in the roll and pitch planes. *Exp Brain Res.* (1999) 129:93–113. doi: 10.1007/s002210050940
75. Allum JHJ, Carpenter MG, Adkin AL. Balance control analysis as a method for screening and identifying balance deficits. *Ann N Y Acad Sci.* (2001) 942:413–27. doi: 10.1111/j.1749-6632.2001.tb03763.x
76. Torres-Oviedo G, Macpherson JM, Ting LH. Muscle synergy organization is robust across a variety of postural perturbations. *J Neurophysiol.* (2006) 96:1530–46. doi: 10.1152/jn.00810.2005
77. Maki BE, Holliday PJ, Fernie GR. A posture control model and balance test for the prediction of relative postural stability. *IEEE Trans Biomed Eng.* (1987) 34:797–810. doi: 10.1109/TBME.1987.325922
78. Johansson R, Magnusson M, Akesson M. Identification of human postural dynamics. *IEEE Trans Biomed Eng.* (1988) 35:858–69. doi: 10.1109/10.7293
79. Maurer C, Mergner T, Peterka RJ. Multisensory control of human upright stance. *Exp Brain Res.* (2006) 171:231–50. doi: 10.1007/s00221-005-0256-y
80. van der Kooij H, Jacobs R, Koopman B, van der Helm F. An adaptive model of sensory integration in a dynamic environment applied to human stance control. *Biol Cybern.* (2001) 84:103–15. doi: 10.1007/s004220000196
81. Cenciarini M, Peterka RJ. Stimulus-dependent changes in the vestibular contribution to human postural control. *J Neurophysiol.* (2006) 95:2733–50. doi: 10.1152/jn.00856.2004
82. Goodworth AD, Peterka RJ. Identifying mechanisms of stance control: a single stimulus multiple output model-fit approach. *J Neurosci Methods* (2018) 296:44–56. doi: 10.1016/j.jneumeth.2017.12.015
83. Tresch MC, Saltiel P, Bizzi E. The construction of movement by the spinal cord. *Nat Neurosci.* (1999) 2:162–7. doi: 10.1038/5721
84. d'Avella A, Saltiel P, Bizzi E. Combinations of muscle synergies in the construction of a natural motor behavior. *Nat. Neurosci.* (2003) 6:300–8. doi: 10.1038/nn1010
85. Ting LH, Macpherson JM. A limited set of muscle synergies for force control during a postural task. *J Neurophysiol.* (2005) 93:609–13. doi: 10.1152/jn.00681.2004
86. Lockhart DB, Ting LH. Optimal sensorimotor transformations for balance. *Nat Neurosci.* (2007) 10:1329–36. doi: 10.1038/nn1986
87. Torres-Oviedo G, Ting LH. Muscle synergies characterizing human postural responses. *J Neurophysiol.* (2007) 98:2144–56. doi: 10.1152/jn.01360.2006
88. Ting LH, Chiel HJ, Trumbower RD, Allen JL, McKay JL, Hackney ME, et al. Neuromechanical principles underlying movement modularity and their implications for rehabilitation. *Neuron* (2015) 86:38–54. doi: 10.1016/j.neuron.2015.02.042
89. Jeka JJ, Schoner G, Dijkstra T, Ribeiro P, Lackner JR. Coupling of fingertip somatosensory information to head and body sway. *Exp Brain Res.* (1997) 113:475–83. doi: 10.1007/PL00005600
90. Rogers MW, Wardman DL, Lord SR, Fitzpatrick RC. Passive tactile sensory input improves stability during standing. *Exp Brain Res.* (2001) 136:514–22. doi: 10.1007/s002210000615
91. Wing AM, Johannsen L, Endo S. Light touch for balance: influence of a time-varying external driving signal. *Phil Trans R Soc B* (2011) 366:3133–41. doi: 10.1098/rstb.2011.0169
92. Asslander L, Smith CP, Reynolds RF. Sensory integration of a light touch reference in human standing balance. *PLoS ONE* (2018) 13:e0197316. doi: 10.1371/journal.pone.0197316
93. Burke D, Hagbarth KE, Lofstedt L, Wallin BG. The responses of human muscle spindle endings to vibration of non-contracting muscles. *J Physiol.* (1976) 261:673–93. doi: 10.1113/jphysiol.1976.sp011580
94. Vedel JP, Roll JP. Response to pressure and vibration of slowly adapting cutaneous mechanoreceptors in the human foot. *Neurosci Lett.* (1982) 34:289–94. doi: 10.1016/0304-3940(82)90190-2
95. Ribot-Ciscar E, Vedel JP, Roll JP. Vibration sensitivity of slowly and rapidly adapting cutaneous mechanoreceptors in the human foot and leg. *Neurosci Lett.* (1989) 104:130–5. doi: 10.1016/0304-3940(89)90342-X
96. Eklund G. General features of vibration-induced effects on balance. *Ups J MedSci.* (1972) 77:112–24. doi: 10.1517/03009734000000016
97. Kavounoudias A, Roll R, Roll JP. Specific whole-body shifts induced by frequency-modulated vibrations of human plantar soles. *Neurosci Lett.* (1999) 266:181–4. doi: 10.1016/S0304-3940(99)00302-X
98. Thompson C, Bélanger M, Fung J. Effects of bilateral achilles tendon vibration on postural orientation and balance during standing. *Clin Neurophysiol.* (2007) 118:2456–67. doi: 10.1016/j.clinph.2007.08.013
99. Thompson C, Bélanger M, Fung J. Effects of plantar cutaneo-muscular and tendon vibration on posture and balance during quiet and perturbed stance. *Hum Movement Sci.* (2011) 30:153–71. doi: 10.1016/j.humov.2010.04.002
100. Kavounoudias A, Roll R, Roll JP. Foot sole and ankle muscle inputs contribute jointly to human erect posture regulation. *J Physiol.* (2001) 532 (Pt 3):869–78. doi: 10.1111/j.1469-7793.2001.0869e.x
101. Eklund G, Hagbarth KE. Normal variability of tonic vibration reflexes in man. *Exp Neurol.* (1966) 16:80–92. doi: 10.1016/0014-4886(66)90088-4
102. Stam J, Tan KM. Tendon reflex variability and method of stimulation. *Electroencephalogr Clin Neurophysiol.* (1987) 67:463–7. doi: 10.1016/0013-4694(87)90010-1
103. Chung SG, Van Rey EM, Bai Z, Rogers MW, Roth EJ, Zhang L. Aging-related neuromuscular changes characterized by tendon reflex system properties. *Arch Phys Med Rehabil.* (2005) 86:318–27. doi: 10.1016/j.apmr.2004.04.048
104. Lishman JR, Lee DN. The autonomy of visual kinaesthesis. *Perception* (1973) 2:287–94. doi: 10.1068/p020287
105. Brandt T, Dichgans J, Koenig E. Differential effects of central versus peripheral vision on egocentric and exocentric motion perception. *Exp Brain Res.* (1973) 16:476–91. doi: 10.1007/BF00234474

106. Lee DN, Lishman JR. Visual proprioceptive control of stance. *J Hum Move Stud.* (1975) 1:87–95.
107. Dichgans J, Held R, Young LR, Brandt T. Moving visual scenes influence the apparent direction of gravity. *Science* (1972) 178:1217–9. doi: 10.1126/science.178.4066.1217
108. Held R, Dichgans J, Bauer J. Characteristics of moving visual scenes influencing spatial orientation. *Vis Res.* (1975) 15:357–65. doi: 10.1016/0042-6989(75)90083-8
109. Dichgans J, Brandt T. Visual-vestibular interaction: effects on self-motion perception and postural control. In: Held R, Leibowitz HW, Teuber HL, editors. *Handbook of Sensory Physiology: Perception*. Berlin, Heidelberg: Springer Berlin Heidelberg (1978). p. 755–804.
110. Lestienne F, Soechting JF, Berthoz A. Postural readjustment induced by linear motion of visual scenes. *Exp Brain Res.* (1977) 45:363–84. doi: 10.1007/BF00235717
111. Dijkstra TMH, Gielen CCAM, Melis BJM. Postural responses to stationary and moving scenes as a function of distance to the scene. *Hum Movement Sci.* (1992) 11:195–203. doi: 10.1016/0167-9457(92)90060-O
112. Peterka RJ, Benolken MS. Role of somatosensory and vestibular cues in attenuating visually induced human postural sway. *Exp Brain Res.* (1995) 105:101–10. doi: 10.1007/BF00242186
113. Mergner T, Schweigart G, Maurer C, Blumle A. Human postural responses to motion of real and virtual visual environments under different support base conditions. *Exp Brain Res.* (2005) 167:535–56. doi: 10.1007/s00221-005-0065-3
114. Dokka K, Kenyon RV, Keshner EA, Kording KP. Self versus environment motion in postural control. *PLoS Comput Biol.* (2010) 6:e1000680. doi: 10.1371/journal.pcbi.1000680
115. Day BL, Muller T, Offord J, Di Giulio I. Dual processing of visual rotation for bipedal stance control. *J Physiol.* (2016) 594:5661–71. doi: 10.1113/JP271813
116. Hess BJ, Angelaki DE. Oculomotor control of primary eye position discriminates between translation and tilt. *J Neurophysiol.* (1999) 81:394–8. doi: 10.1152/jn.1999.81.1.394
117. Merfeld DM, Zupan L, Peterka RJ. Humans use internal models to estimate gravity and linear acceleration. *Nature* (1999) 398:615–8. doi: 10.1038/19303
118. Angelaki DE, Shaikh AG, Green AM, Dickman JD. Neurons compute internal models of the physical laws of motion. *Nature* (2004) 430:560–4. doi: 10.1038/nature02754
119. Dakin CJ, Rosenberg AS. Models and mechanisms of gravity estimation and verticality perception. In: Gait B, Day BL, Lord SR, editors. *Handbook of Clinical Neurology*. Vol. 159 (2018).
120. Goldberg JM, Fernández C, Smith CE. Responses of vestibular-nerve afferents in the squirrel monkey to externally applied galvanic currents. *Brain Res.* (1982) 252:156–60. doi: 10.1016/0006-8993(82)90990-8
121. Goldberg JM, Smith CE, Fernandez C. Relation between discharge regularity and responses to externally applied galvanic currents in vestibular nerve afferents of the squirrel monkey. *J Neurophysiol.* (1984) 51:1236–56. doi: 10.1152/jn.1984.51.6.1236
122. Kim J, Curthoys IS. Responses of primary vestibular neurons to galvanic vestibular stimulation (GVS) in the anaesthetised guinea pig. *Brain Res Bull.* (2004) 64:265–71. doi: 10.1016/j.brainresbull.2004.07.008
123. Kim K, Minor LB, Della Santina CC, Lasker DM. Variation in response dynamics for regular and irregular vestibular-nerve afferents during sinusoidal head rotations and currents in the chinchilla. *Exp Brain Res.* (2011) 210:643–9. doi: 10.1007/s00221-011-2600-8
124. Kwan A, Mitchell DE, Forbes PA, Blouin JS, Cullen KE. Neural correlates of transmastoid galvanic vestibular stimulation in alert primates: linking vestibular afferent activation to perceptual, ocular and postural responses. Program No. 802.06. *2016 Neuroscience Meeting Planner*. San Diego, CA: Society for Neuroscience (2016).
125. Fitzpatrick RC, Day BL. Probing the human vestibular system with galvanic stimulation. *J Appl Physiol.* (2004) 96:2301–16. doi: 10.1152/japplphysiol.00008.2004
126. Mian OS, Dakin CJ, Blouin JS, Fitzpatrick RC, Day BL. Lack of otolith involvement in balance responses evoked by mastoid electrical stimulation. *J Physiol.* (2010) 588:4441–51. doi: 10.1113/jphysiol.2010.195222
127. Day BL, Marsden JF, Ramsay E, Mian OS, Fitzpatrick RC. Non-linear vector summation of left and right vestibular signals for human balance. *J Physiol.* (2010) 588:671–82. doi: 10.1113/jphysiol.2009.181768
128. Peters RM, Rasman BG, Inglis JT, Blouin J-S. Gain and phase of perceived virtual rotation evoked by electrical vestibular stimuli. *J Neurophysiol.* (2015) 114:264–73. doi: 10.1152/jn.00114.2015
129. Britton TC, Day BL, Brown P, Rothwell JC, Thompson PD, Marsden CD. Postural electromyographic responses in the arm and leg following galvanic vestibular stimulation in man. *Exp Brain Res.* (1993) 94:143–51. doi: 10.1007/BF00230477
130. Fitzpatrick R, Burke D, Gandevia SC. Task-dependent reflex responses and movement illusions evoked by galvanic vestibular stimulation in standing humans. *J Physiol.* (1994) 478:363–72. doi: 10.1113/jphysiol.1994.sp020257
131. Luu BL, Inglis JT, Huryn TP, Van der Loos HF, Croft EA, Blouin J-S. Human standing is modified by an unconscious integration of congruent sensory and motor signals. *J Physiol.* (2012) 590:5783–94. doi: 10.1113/jphysiol.2012.230334
132. Forbes PA, Seigmund GP, Happee R, Schouten AC, Blouin J.-S. Vestibulocollic reflexes in the absence of head postural control. *J Neurophysiol.* (2014) 112:1692–702. doi: 10.1152/jn.00343.2014
133. Day BL, Cauquil AS, Bartolomei L, Pastor MA, Lyon IN. Human body-segment tilts induced by galvanic stimulation: a vestibularly driven balance protection mechanism. *J Physiol.* (1997) 500:661–72. doi: 10.1113/jphysiol.1997.sp022051
134. Nashner LM, Wolfson P. Influence of head position and proprioceptive cues on short latency postural reflexes evoked by galvanic stimulation of the human labyrinth. *Brain Res.* (1974) 67:255–68. doi: 10.1016/0006-8993(74)90276-5
135. Lund S, Broberg C. Effects of different head positions on postural sway in man induced by a reproducible vestibular error signal. *Acta Physiol Scand.* (1983) 117:307–9. doi: 10.1111/j.1748-1716.1983.tb07212.x
136. Dakin CJ, Son GML, Inglis JT, Blouin J-S. Frequency response of human vestibular reflexes characterized by stochastic stimuli. *J Physiol.* (2007) 583:1117–27. doi: 10.1113/jphysiol.2007.133264
137. Reynolds RF. Vertical torque responses to vestibular stimulation in standing humans. *J Physiol (Lond)* (2011) 589:3943–53. doi: 10.1113/jphysiol.2011.209163
138. Mian OS, Day BL. Violation of the craniocentricity principle for vestibularly evoked balance responses under conditions of anisotropic stability. *J Neurosci.* (2014) 34:7696–703. doi: 10.1523/JNEUROSCI.0733-14.2014
139. Forbes PA, Luu BL, Van der Loos HF, Croft EA, Inglis JT, Blouin J-S. Transformation of vestibular signals for the control of standing in humans. *J Neurosci.* (2016) 36:11510–20. doi: 10.1523/JNEUROSCI.1902-16.2016
140. Son GM, Blouin J-S, Inglis JT. Short-duration galvanic vestibular stimulation evokes prolonged balance responses. *J Appl Physiol.* (2008) 105:1210–7. doi: 10.1152/japplphysiol.01398.2006
141. Dakin CJ, Héroux ME, Luu BL, Blouin J-S. Vestibular contribution to balance control in the medial gastrocnemius and soleus. *J Neurophysiol.* (2016) 115:1289–97. doi: 10.1152/jn.00512.2015
142. Dalton BH, Rasman BG, Inglis JT, Blouin J-S. The internal representation of head orientation differs for conscious perception and balance control. *J Physiol.* (2017) 595:2731–49. doi: 10.1113/JP272998
143. Shepherd M. *Intersensory Vestibular Control of Standing Balance*. Master's thesis, Vancouver: University of British Columbia (2014).
144. Nashner LM, Black FO, Wall C. Adaptation to altered support and visual conditions during stance: patients with vestibular deficits. *J Neurosci.* (1982) 2:536–44. doi: 10.1523/JNEUROSCI.02-05-00536.1982
145. Black FO, Nashner LM. Vestibulospinal control differs in patients with reduced versus distorted vestibular function. *Acta Otolaryngol.* (1984) 406:110–4.
146. Ishida A, Imai S, Fukuoka Y. Analysis of the posture control system under fixed and sway-referenced support conditions. *IEEE Trans Biomed Eng.* (1997) 44:331–6. doi: 10.1109/10.568908

147. Fukuoka Y, Nagata T, Ishida A, Minamitani H. Characteristics of somatosensory feedback in postural control during standing. *IEEE Trans Neural Syst Rehabil Eng.* (2001) 9:145–53. doi: 10.1109/7333.928574
148. Cole J. *Pride and a Daily Marathon.* Boston: MIT Press (1995).
149. Cole J. Large-fiber sensor neuropathy. In: Binder MD, Hirokawa N, Windhorst U, editors. *Encyclopedia of Neuroscience*, Berlin: Spinger (2009). p. 2102–7.
150. Casadio M, Morasso PG, Sanguineti V. Direct measurement of ankle stiffness during quiet standing: implications for control modelling and clinical application. *Gait Post.* (2005) 21:410–24. doi: 10.1016/j.gaitpost.2004.05.005
151. Huryn TP, Luu BL, Van der Loos HFM. (2010). Investigating human balance using a robotic motion platform. *IEEE International Conference on Robotics and Automation*. Anchorage, AK: IEEE. p. 5090–5.
152. Huryn TP, Blouin J-S, Croft EA, Koehle MS, Van der Loos HF. Experimental performance evaluation of human balance control models. *IEEE Trans Neural Syst Rehabil Eng.* (2014) 22:1115–27. doi: 10.1109/TNSRE.2014.2318351
153. Fitzpatrick R, Rogers DK, McCloskey DI. Stable human standing with lower-limb muscle afferents providing the only sensory input. *J Physiol.* (1994) 480:395–403. doi: 10.1113/jphysiol.1994.sp020369
154. Fukuoka Y, Tanaka K, Ishida A, Minamitani H. Characteristics visual feedback in postural control during standing. *IEEE Trans. Rehab. Eng.* (1999) 7:427–34. doi: 10.1109/86.808946
155. Lakie M, Loram ID. Manually controlled human balancing using visual, vestibular and proprioceptive senses involves a common, low frequency neural process. *J Physiol.* (2006) 577:403–16. doi: 10.1113/jphysiol.2006.116772
156. Magnusson M, Enbom H, Johansson R, Pyykoo I. Significance of pressor input from the human feet in anterior-posterior postural control. *Acta Otolaryngol.* (1990) 110:182–8. doi: 10.3109/00016489009122535
157. Nagata T, Fukuoka Y, Ishida A, Minamitani H. Analysis of role of vision in human upright posture control. *Eng Med Biol Soc Proc.* (2001) 2:1155–8. doi: 10.1109/IEMBS.2001.1020396
158. Holden M, Ventura J, Lackner JR. Stabilization of posture by precision contact of the index finger. *J Vestib Res.* (1994) 4:285–301.
159. Jeka JJ, Lackner JR. Fingertip contact influences human postural control. *Exp Brain Res.* (1994) 100:495–502. doi: 10.1007/BF02738408
160. Johannsen L, Guzman-Garcia A, Wing AM. Interpersonal light touch assists balance in the elderly. *J Mot Behav.* (2009) 41:397–9. doi: 10.3200/35-09-001
161. Johannsen L, Wing AM, Hatzitaki V. Contrasting effects of finger and shoulder interpersonal light touch on standing balance. *J Neurophysiol.* (2012) 107:216–25. doi: 10.1152/jn.00149.2011
162. Reynolds RF, Osler CJ. Mechanisms of interpersonal sway synchrony and stability. *J R Soc Interface* (2014) 11:20140751. doi: 10.1098/rsif.2014.0751
163. Travis RC. An experimental analysis of dynamic and static equilibrium. *J Exp Psychol.* (1945) 35:216–34. doi: 10.1037/h0059788
164. Edwards AS. Body sway and vision. *J Exp Psychol.* (1946) 36:526–35. doi: 10.1037/h0059909
165. Teasdale N, Stelmach GE, Breunig A. Postural sway characteristics of the elderly under normal and altered visual and support surface conditions. *J Gerontol.* (1991) 46:B238–B244. doi: 10.1093/geronj/46.6.B238
166. Bles W, Kapteyn TS, Brandt T, Arnold F. Mechanism of physiological height vertigo. *II Posturography Acta Otolaryngol.* (1980) 89:534–40. doi: 10.3109/00016488009127171
167. Brandt T, Arnold F, Bles W, Kapteyn T. Mechanism of physiological height vertigo. I. Theoretical approach and psychophysics. *Acta Otolaryngol.* (1980) 89:512–23. doi: 10.3109/00016488009127169
168. Amblar B, Cremieux J, Marchand AR, Carblanc A. Lateral orientation and stabilization of human stance: static versus dynamic visual cues. *Exp Brain Res.* (1985) 61:21–37.
169. Guerraz M, Sakellari V, Burchill P, Bronstein AM. Influence of motion parallax in the control of spontaneous body sway. *Exp Brain Res.* (2000) 131:244–52. doi: 10.1007/s002219900307
170. Guerraz M, Gianna C, Burchill P, Gresty MA, Bronstein AM. Effect of visual surrounding motion on body sway in a 3D environment. *Percept Psychophys.* (2001) 63:47–58. doi: 10.3758/BF03200502
171. Day BL, Guerraz M. Feedforward versus feedback modulation of human vestibular-evoked balance responses by visual self-motion information. *J Physiol.* (2007) 582:153–61. doi: 10.1113/jphysiol.2007.132092
172. Berthoz A, Soechting JF, Lacour M, Vidal PP. The role of vision in the control of posture during linear motion. *Progress Brain Res.* (1979) 50:197–209. doi: 10.1016/S0079-6123(08)60820-1
173. Nashner LM, McCollum G. The organization of human postural movements: a formal basis and experimental synthesis. *Behav Brain Sci.* (1985) 8:135–50. doi: 10.1017/S0140525X00020008
174. McCollum G, Shupert CL, Nashner LM. Organizing sensory information for postural control in altered sensory environments. *J Theor Biol.* (1996) 180:257–70. doi: 10.1006/jtbi.1996.0101
175. Vidal PP, Berthoz A, Millanvoye M. Difference between eye closure and visual stabilization in the control of posture in man. *Aviat Space Environ Med.* (1982) 53:166–70.
176. Bronstein AM, Buckwell D. Automatic control of postural sway by visual motion parallax. *Exp Brain Res.* (1997) 113:243–8. doi: 10.1007/BF02450322
177. Loram ID, Lakie M, Gawthrop PJ. Visual control of stable and unstable loads: what is the feedback delay and extent of linear time-invariant control? *J Physiol.* (2009) 587:1343–65. doi: 10.1113/jphysiol.2008.166173
178. Loram ID, Gollee H, Lakie M, Gawthrop PJ. Human control of an inverted pendulum: is continuous control necessary? Is intermittent control effective? Is intermittent control physiological? *J Physiol.* (2011) 589:307–24. doi: 10.1113/jphysiol.2010.194712
179. Fetter M, Diener HC, Dichgans J. Recovery of postural control after an acute unilateral vestibular lesion in humans. *J Vestib Res.* (1991) 1:373–83.
180. Furman JM. Role of posturography in the management of vestibular patients. *Otolaryngol Head Neck Surg.* (1995) 112:8–15. doi: 10.1016/S0194-5998(95)70300-4
181. Peterka RJ, Statler KD, Wrisley DM, Horak FB. Postural compensation for unilateral vestibular loss. *Front Neurol.* (2011) 2:57. doi: 10.3389/fneur.2011.00057
182. Gauchard GC, Parietti-Winkler C, Lion A, Simon C, Perrin PP. Impact of pre-operative regular physical activity on balance control compensation after vestibular schwannoma surgery. *Gait Post.* (2013) 37:82–7. doi: 10.1016/j.gaitpost.2012.06.011
183. Sadeghi SG, Minor LB, Cullen KE. Neural correlates of motor learning in the vestibulo-ocular reflex: dynamic regulation of multimodal integration in the macaque vestibular system. *J Neurosci.* (2010) 30:10158–68. doi: 10.1523/JNEUROSCI.1368-10.2010
184. Sadeghi SG, Minor LB, Cullen KE. Multimodal integration after unilateral labyrinthine lesion: single vestibular nuclei neuron responses and implications for postural compensation. *J Neurophysiol.* (2011) 105:661–73. doi: 10.1152/jn.00788.2010
185. Sadeghi SG, Minor LB, Cullen KE. Neural correlates of sensory substitution in vestibular pathways following complete vestibular loss. *J Neurosci.* (2012) 32:14685–95. doi: 10.1523/JNEUROSCI.2493-12.2012
186. Héroux ME, Law TC, Fitzpatrick RC, Blouin J-S. Cross-Modal Calibration of Vestibular Afference for Human Balance. *PLoS ONE* 10:e0124532. doi: 10.1371/journal.pone.0124532
187. Mbongo F, Patko T, Vidal PP, Vibert N, Tran Ba Huy P, de Waele C. Postural control in patients with unilateral vestibular lesions is more impaired in the roll than in the pitch plane: a static and dynamic posturography study. *Audiol Neurotol.* (2005) 10:291–302. doi: 10.1159/000086081
188. Mbongo F, Quhen C, Vidal P, Tran Ba Huy P, de Waele C. Role of vestibular input in triggering and modulating postural responses in unilateral and bilateral vestibular loss patients. *Audiol Neurotol.* (2009) 14:130–8. doi: 10.1159/000162665
189. Kiemel T, Oie KS, Jeka JJ. Multisensory fusion and the stochastic structure of postural sway. *Biol Cybern.* (2002) 87:262–77. doi: 10.1007/s00422-002-0333-2
190. Peterka RJ, Loughlin PJ. Dynamic regulation of sensorimotor integration in human postural control. *J Neurophysiol.* (2004) 91:410–23. doi: 10.1152/jn.00516.2003

191. Pospisil ER, Luu BL, Blouin JS, Van der Loos HF, Croft EA. (2012). Independent ankle motion control improves robotic balance simulator. *2012 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*. San Diego, CA: IEEE. p. 6487–91.
192. Gonshor A, Jones GM. Extreme vestibulo-ocular adaptation induced by prolonged optical reversal of vision. *J Physiol.* (1976) 256:381–414. doi: 10.1113/jphysiol.1976.sp011330
193. Jones GM, Barlow HB, Gaze RM. Plasticity in the adult vestibulo-ocular refelx arc. *Philos Trans R Roc Lond B Biol Sci.* (1977) 278:319–34. doi: 10.1098/rstb.1977.0045
194. Berthoz A, Jones GM, Bégué AE. Differential visual-adaptation of vertical canal-dependent vestibulo-ocular reflexes. *Exp Brain Res.* (1981) 44:19–26.
195. Cullen KE, Mitchell DE. Procedural learning: VOR. In: Eichenbaum H, editor. *Memory Sytems*. Byrne JH, editor. *Vol. 3 of Learning and Memory: A Comprehensive Reference*, 2nd ed. Oxford: Academic Press (2017). p. 357–4.
196. Brooks JX, Carriot J, Cullen KE. Learning to expect the unexpected: rapid updating in primate cerebellum during voluntary self-motion. *Nat Neurosci.* (2015) 18:1310–7. doi: 10.1038/nn.4077
197. Abzug C, Maeda M, Peterson BW, Wilson VJ. Cervical branching of lumbar vestibulospinal axons. *J. Physiol.* (1974) 243:499–522. doi: 10.1113/jphysiol.1974.sp010764
198. Carleton SC, Carpenter MB. Afferent and efferent connections of the medial, inferior and lateral vestibular nuclei in the cat and monkey. *Brain Res.* (1983) 278:29–51. doi: 10.1016/0006-8993(83)90223-8
199. Smetanin BN, Popov KE, Shlykov VY. Changes in vestibular postural response determined by information content of visual feedback. *Neurophysiology* (1990) 22:66–72. doi: 10.1007/BF01052057
200. Asslander L, Peterka RJ. Sensory reweighting dynamics following removal and addition of visual and proprioceptive cues. *J Neurophysiol* (2016) 116 272–85. doi: 10.1152/jn.01145.2015

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

REVIEW
published: 29 October 2018
doi: 10.3389/fneur.2018.00913

Cognitive Involvement in Balance, Gait and Dual-Tasking in Aging: A Focused Review From a Neuroscience of Aging Perspective

Karen Z. H. Li[1,2,3]*, *Louis Bherer*[3,4,5,6], *Anat Mirelman*[7,8], *Inbal Maidan*[7,8] and *Jeffrey M. Hausdorff*[7,9,10]

[1] Department of Psychology, Concordia University, Montreal, QC, Canada, [2] Centre for Research in Human Development, Concordia University, Montreal, QC, Canada, [3] PERFORM Centre, Concordia University, Montreal, QC, Canada, [4] Department of Medicine, Université de Montréal, Montreal, QC, Canada, [5] Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, Montreal, QC, Canada, [6] Research Center, Montreal Heart Institute, Montreal, QC, Canada, [7] Center for the Study of Movement, Cognition and Mobility, Neurological Institute, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [8] Department of Neurology, Sackler Faculty of Medicine and Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel, [9] Department of Physical Therapy, Sackler Faculty of Medicine and Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel, [10] Rush Alzheimer's Disease Center and Department of Orthopaedic Surgery, Rush University Medical Center, Chicago, IL, United States

OPEN ACCESS

Edited by:
Joyce Fung,
McGill University, Canada

Reviewed by:
Francesca Morgante,
Università degli Studi di Messina, Italy
Maayan Agmon,
University of Haifa, Israel

***Correspondence:**
Karen Z. H. Li
karen.li@concordia.ca

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *12 July 2018*
Accepted: *09 October 2018*
Published: *29 October 2018*

Citation:
Li KZH, Bherer L, Mirelman A, Maidan I and Hausdorff JM (2018) Cognitive Involvement in Balance, Gait and Dual-Tasking in Aging: A Focused Review From a Neuroscience of Aging Perspective. Front. Neurol. 9:913. doi: 10.3389/fneur.2018.00913

A substantial corpus of evidence suggests that the cognitive involvement in postural control and gait increases with aging. A large portion of such studies were based on dual-task experimental designs, which typically use the simultaneous performance of a motor task (e.g., static or dynamic balancing, walking) and a continuous cognitive task (e.g., mental arithmetic, tone detection). This focused review takes a cognitive neuroscience of aging perspective in interpreting cognitive motor dual-task findings. Specifically, we consider the importance of identifying the neural circuits that are engaged by the cognitive task in relation to those that are engaged during motor task performance. Following the principle of neural overlap, dual-task interference should be greatest when the cognitive and motor tasks engage the same neural circuits. Moreover, the literature on brain aging in general, and models of dedifferentiation and compensation, in particular, suggest that in cognitive motor dual-task performance, the cognitive task engages different neural substrates in young as compared to older adults. Also considered is the concept of multisensory aging, and the degree to which the age-related decline of other systems (e.g., vision, hearing) contribute to cognitive load. Finally, we discuss recent work on focused cognitive training, exercise and multimodal training of older adults and their effects on postural and gait outcomes. In keeping with the principle of neural overlap, the available cognitive training research suggests that targeting processes such as dividing attention and inhibition lead to improved balance and gait in older adults. However, more studies are needed that include functional neuroimaging during actual, upright performance of gait and balance tasks, in order to directly test the principle of neural overlap, and to better optimize the design of intervention studies to improve gait and posture.

Keywords: gait, balance, aging, cognitive training, dual task, cognition, motor-cognitive interference

INTRODUCTION

Approximately 30% of individuals over age 65 experience one or more falls each year (1, 2), leading to significant health care costs worldwide (3). Accumulating behavioral, neuropsychological, and neuroimaging evidence shows that slow gait, postural instability, and fall risk are associated with cognitive capacity. More specifically, poor mobility in aging has been associated with exaggerated effects of cognitive-motor dual tasking, cognitive impairment, and degeneration of gray and white matter in anterior brain regions that subserve executive functions (EFs) and link to motor regions (4–8). Substantial progress has been made in understanding the cortical control of gait and balance, with several comprehensive reviews on this topic (9, 10).

Inasmuch as cognitive contributions to posture and gait are well-acknowledged in the movement sciences, there is less consideration of the basic literature on age differences in patterns of neural activity during cognitive performance, and the potential for cognitive and neural plasticity through training in old age to ameliorate the age-associated declines. These basic aging findings suggest that older adults commonly activate additional brain regions when performing cognitive tasks, compared to young adults, suggesting that cognitive involvement in motor behaviors may have different implications for older adults than for younger adults. Nonetheless, we suggest that a greater consideration of findings from the cognitive neuroscience of aging can enhance the interpretation of two major experimental paradigms: (1) the cognitive-motor dual-task paradigm, which aims to restrict or occupy the available cognitive capacity hypothesized to support motor functioning in old age and assess the impact on performance; (2) the cognitive remediation or training paradigm, which aims to enhance available cognitive capacity and/or increase neural efficiency, and thereby free up cognitive resources to support motor functioning.

Accordingly, in this review, we first describe current findings in neurocognitive aging, with an emphasis on empirical evidence of cognitive processes that have been related to postural control and gait. We then discuss major models that link neural aging with plasticity and compensatory patterns of neural activity, such as the Scaffolding Theory of Aging and Cognition [STAC: (11)] and Hemispheric Asymmetry Reduction in Older Adults [HAROLD: (12)]. We then summarize the research on cognitive plasticity in an effort to contextualize the recent application of cognitive training or dual-task training to improve gait and posture. We then review recent empirical work on cognitive-motor dual-tasking (CMDT), and on cognitive training and associated mobility gains. Finally, we consider the implications from the cognitive neuroscience of aging work as applied to the study of gait and posture. **Figure 1** illustrates the proposed joint influences of neurocognitive aging and compensation on cognitive capacity, the implications for cognitive, perceptual and motor performance, and the potential for cognitive enrichment to improve these performances.

Abbreviations: ACC, Anterior cingulate cortex; BDNF, Brain derived neurotrophic factor; CMDT, Cognitive-motor dual-tasking; DLPFC, Dorsolateral prefrontal cortex; DT, Dual task; DTC, Dual-task cost; DTI, Diffusion tensor imaging; EEG, Electroencephalography; EF, Executive function; FA, Fractional anisotropy; HAROLD, Hemispheric asymmetry reduction in older adults; HbO_2, Oxy-hemoglobin; HbR, Deoxy-hemoglobin; IGF, Insulin-like growth factor; MRI, Magnetic resonance imaging; NIRS, Near-infrared spectroscopy; PD, Parkinson's disease; PET, Positron emission tomography; PFC, Prefrontal cortex; SMA, Supplementary motor area; STAC, Scaffolding theory of cognitive aging; TUG, Timed-up-and-go; VEGF, Vascular endothelial growth factor; VLPFC, Ventrolateral prefrontal cortex; VR, Virtual reality; WMH, White matter hyperintensities.

NEUROCOGNITIVE AGING

Brain aging has been well-described in terms of both structural and functional dimensions (13), multiple chapters; (9). Briefly, longitudinal studies indicate that cortical gray matter volumes decrease linearly across adulthood (from the 20s to 80s) in frontal and temporal regions, whereas other regions such as primary visual, parietal, and entorhinal cortex remain relatively stable across adulthood (14). Regions such as the dorsolateral prefrontal cortex (DLPFC) and the orbitofrontal cortex appear to be most age-sensitive (15), and are associated with concomitant behavioral declines in cognitive functions such as working memory, episodic memory encoding, and divided attention (13). Other regions with accelerated decline in aging include the cerebellar hemispheres and the hippocampus (16). Diffusion tensor imaging (DTI) reveals normative changes in white matter volume and integrity with aging, such that anterior white matter tracts show greater age-related declines as compared to more posterior tracts [e.g., (17)].

In the adult lifespan, these white matter changes precede gray matter volumetric declines, thus compromising the efficiency of communication between regions (11). White matter hyperintensities (WMH), an index of lesion burden, explain more of the age-related variance in cognitive performance than total brain volumes (11). Recent work suggests a negative relationship between white matter integrity and functional activation, as if to compensate for the white matter decline, coined the "less wiring more firing" principle (18, 19).

COMPENSATION

Functional neuroimaging studies of cognitive aging, using primarily MRI or PET, commonly reveal age-related increases in frontal activation bilaterality during tests of memory, which are associated with better cognitive performance [e.g., (20, 21)]. Another notable pattern, observed in older compared to younger adults, is prefrontal up-regulation during memory encoding, coupled with reduced parahippocampal activation, suggesting a compensatory function for the extra neural recruitment in response to decreased activity in the task-relevant brain regions (22). Similarly, in auditory tasks such as speech perception in the presence of noise, older adults exhibit greater activity in frontal regions and less activity in auditory cortex (23), possibly reflecting the recruitment of intact cognitive functions such as

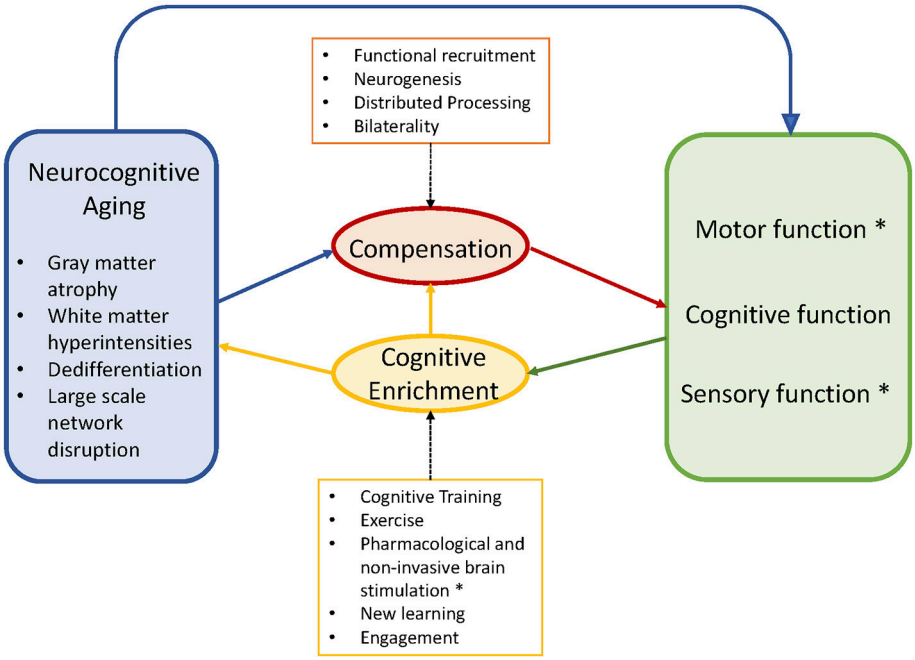


FIGURE 1 | Conceptual diagram adapted from Park and Reuter-Lorenz (11). Asterisks indicate our modifications and extensions, particularly the inclusion of motor and sensory functioning. The schematic shows the negative aspects of neurocognitive aging (blue) that trigger compensation via functional recruitment in older adults (red). These maladaptive and adaptive factors jointly contribute to observed motor, cognitive, sensory functions (green). Cognitive enrichment (yellow) can ameliorate aspects of brain aging and facilitate compensatory efficiency if there is neural overlap between the improved and targeted outcomes. Motor, cognitive, and sensory functions benefit from, and compete for, common capacity (e.g., prefrontal cortex), particularly during complex behaviors such as cognitive-motor dual-tasking. Copyright permission not required.

verbal ability and semantic memory (24). Notably, the observed increase in neural recruitment among older adults may only be effective in mitigating the negative effects of neural aging to a point. In a study of aging and *n*-back working memory performance, older adults performed as well as younger adults (1-back) and showed greater bilateral prefrontal activity (BA 9) during that condition. However, with greater levels of memory load (2- and 3-back), older adults performed worse than younger adults and did not exhibit increased prefrontal activity (25), suggesting that a functional limit of compensatory recruitment had been reached.

Notably, not all extra activations are considered adaptive. Dedifferentiation, or loss of neural specificity, has been observed in the visual cortex where activations are more diffuse in older than younger adults [e.g., (26)]. These functional imaging observations are mirrored in behavioral observational studies of sensory and sensorimotor abilities, which appear to share increasing variance with many cognitive functions in older age (27, 28). Similarly, older adults exhibit ability dedifferentiation (29) within EF measures (inhibition, updating, switching) that are identified in young adulthood as relatively distinct factors (30).

Finally, studies of functional connectivity suggest that the dynamic coordination of large-scale networks is disrupted with aging, potentially leading to the observed cognitive decline [e.g., (31, 32)]. It appears that older adults recruit the fronto-parietal and salience networks less consistently than young adults (33), resulting in diminished frequency of switching between large-scale networks and reduced flexibility in performance (34). Age-related decline in white matter integrity and gray matter volume are correlated with activity in prefrontal nodes of the salience and fronto-parietal network, possibly a consequence of compensatory mechanisms (33).

Together, these negative attributes of brain aging (e.g., gray and white matter changes, dedifferentiation, and large scale network disruption) have been conceptualized as complementary to the observed compensatory patterns of brain activity (e.g., frontal recruitment, bilaterality) in models of cognitive aging such as the STAC model [(11); STAC-R: (35)], and HAROLD model (12). Both models propose that upregulation of additional brain regions occurs in response to age-related neurodegeneration, and that older adults who do not exhibit such upregulation tend to exhibit lower levels of cognitive performance than those who do. Notably, the potentially positive, compensatory patterns of neural recruitment take place in the same regions that show the greatest degeneration with aging. However, the research on cognitive enrichment (36, 37) offers encouragement in terms of potential for the improvement of EFs. In the STAC models, the capacity to engage in compensatory scaffolding is enhanced through cognitive training, social stimulation, and exercise (11, 35).

COGNITIVE ENRICHMENT

While a detailed review of the topic of cognitive enrichment in aging research is beyond the scope of the present review [see (36, 37)], we highlight a few key issues that are of relevance for the involvement of cognitive aging in balance and gait. A central issue in this research domain is the extent to which older adults can improve through cognitive training, and if the trained skill(s) transfer to untrained skills. Process-based cognitive training studies, in which targeted cognitive mechanisms are trained via computer programs, commonly show that healthy older adults exhibit robust gains in the trained cognitive processes or skills (37, 38). However, older adults do not exhibit significant transfer beyond the trained tasks unless there is an overlap in underlying processes [e.g., (39)]. By contrast, greater transferability of trained skills is observed in studies that target EFs such as divided attention, working memory, and task switching (40–43).

The question of when to expect broader transfer of training can be addressed with the Principle of Neural Overlap (36, 42, 44). This principle proposes that the degree of common neural activation between trained and untrained cognitive tasks should correspond to the degree of training-related transfer observed. This is illustrated well in Dahlin's study of EF training and transfer (42). Young and older adults were trained for 5 weeks on a memory updating task engaging the striatum, as shown in pre-training fMRI scans. The researchers also assessed an array of transfer tasks that showed varying levels of functional and neural overlap with the trained updating task. In the young adults, behavioral evidence of transfer was greatest for another updating task (*n*-back) associated with striatial activation, and less evident for those outcomes engaging other neural structures. In contrast, older adults showed no training-related transfer to the *n*-back task, nor was there any striatal activation during this task.

Kramer's early studies of dual-task training (45) showed greater training-related transfer to other variants of dual-task performance when a variable priority procedure (emphasis on two cognitive tasks; Task A vs. B changed across blocks) was used, compared to a fixed priority procedure involving equal attention allocation between tasks [see also (46, 47)]. Importantly, although older adults can be trained to divide attention accurately between two tasks when instructed, the allocation of attention between tasks of differing priority (48) or difficulty level (49) in more ecological contexts may differ from that observed in the laboratory.

The extant evidence on cognitive and neural plasticity appears promising [see (36, 50) for reviews] and relevant to mobility. Lövden et al. (51) compared young and older adults after roughly 100 h of training using multiple cognitive tasks (working memory, episodic memory, processing speed), reporting significant white matter improvement (FA) in the older adults, particularly in the anterior portion of the anterior cingulate cortex (ACC). Behavioral changes were observed in working memory, perceptual speed and episodic memory, although the degree of improvement was differentially greater in younger adults only for perceptual speed and episodic memory. In an fMRI study (52), using Bherer's dual-task training protocol, young adults showed significant pre-to-post increases in bilateral DLPFC activity while performing the trained task, and the degree of activation change correlated with the degree of improvement in behavioral reaction time data for the dual-task condition. In follow-up work, older adults showed a training-related increase in left VLPFC and a decrease in DLPFC bilaterally, suggesting a shift to using articulatory rehearsal (i.e., subvocal repetition of task-relevant information) as a control strategy (53). Finally, functional neural changes appear to precede structural changes, occurring after as little as 9 h of multimodal cognitive training in older adults (54).

A second major strategy of cognitive enrichment is exercise training. As reviewed elsewhere (55, 56), training studies have abundantly demonstrated that moderate aerobic exercise such as walking, swimming, or cycling, improves attentional control and executive functioning in older adults, compared to non-aerobic protocols such as stretching or toning (57–59). Strength or resistance training can also benefit cognitive ability and brain health (55, 60), but evidence for its impact on multiple EFs is presently limited in comparison to the aerobic training findings. Neuroplastic changes after aerobic training echo the behavioral cognitive findings in showing increased efficiency in brain regions associated with executive control processes. For example, (61) compared older adults assigned to an aerobic exercise versus a stretch control condition on fMRI during flanker task selective attention performance. The aerobic group showed improved attentional control, and increased task-related activity in right middle frontal gyrus and superior parietal regions. The aerobic group also showed greater volumetric increases in anterior white matter, gray matter in left inferior frontal gyrus, anterior cingulate, and superior temporal gyrus (62). Using DTI, (63) found increases in the white matter integrity (fractional anisotropy: FA) of prefrontal and temporal regions in older adults and associated improvements in short-term memory after aerobic exercise (walking) but not toning. Aerobic training appears to trigger global neuroplastic effects by increasing the production of neurotrophic factors (e.g., BDNF, IGF-1, VEGF) that are able to cross the blood-brain barrier and support neurogenesis, vascularization, axonal repair, and synaptogenesis, particularly in frontal, prefrontal, and hippocampal regions [Erickson (64)]. Notably, levels of these neurotrophic factors were positively associated with exercise-induced increases in temporal lobe functional connectivity (65).

A recent meta-analysis examined combined, multi-modality training protocols and cognitive outcomes (66). Compared to exercise training alone, combined exercise and cognitive training appears superior in the majority of aging studies [e.g., (67)], whereas multi-modal training is not consistently superior to cognitive training alone [e.g., (68)].

Together, the extant findings on neurocognitive aging and cognitive enrichment reveal a number of observations that are relevant for our understanding of postural control and gait in aging. First, neuroimaging findings suggest that the health of white matter tracts and functional connectivity between brain regions may be more age-sensitive than volumetric or functional assessments of discrete brain regions. We note that while many earlier studies focused on the relationships between changes in the structure of specific brain regions and their

impact on behavioral outcomes like CMDT, more recent work emphasizes the connections across networks; structural changes in the PFC, for example, may reverberate across a relatively large attention network that extends beyond the PFC. Second, age-related dedifferentiation, coupled with compensatory scaffolding, suggests that there may be qualitative differences in neural activation and behavioral strategies exhibited in young versus older adults. Third, cognitive training research suggests that targeting specific EFs, and including a flexibility or variable-priority component, yields the broadest transfer to untrained cognitive skills. However, an important qualification is that, following the principle of neural overlap, training efficacy apparently depends on the degree of neural similarity between trained and untrained skills. Similarly, the degree of interference observed during dual-tasking should depend on the degree of competition for common neural structures.

We turn next to recent findings in cognitive-motor dual-tasking and aging, focusing on the neural underpinnings of single-task gait and balance as well as CMDT. The fact that CMDT induces activation of cognitive and motor networks simultaneously, both networks that share common pathways as well as very specific pathways, enables the examination of their vulnerability during cognitive-motor interference and the compensatory mechanisms that are called into play with aging.

COGNITIVE REDUCTION: COGNITIVE-MOTOR DUAL-TASKING (CMDT)

The ability to divide attention between cognitive and motor activity has been examined in efforts to quantify the amount of cognitive capacity recruited for motor functioning (8, 69). CMDT designs typically contrast a balance or walking task performed alone (single task), versus the same motor task performed with a concurrent cognitive task (e.g., talking, mental arithmetic). This comparison forms the basis for the calculation of dual-task costs (DTCs: [single - dual task]/single), which indicate the degree of performance decline or cognitive recruitment that is prompted by the secondary task. Cognitive recruitment to aid motor performance is presumed to reduce the already limited cognitive capacity that can be devoted to a concurrent cognitive task in old age (28, 48).

Briefly, the behavioral CMDT research on postural control shows that age-related DTCs are exacerbated by a variety of factors such as postural threat (70), reduced sensory inputs (71), platform perturbations (72), and concurrent visual imagery (73). Similarly, in studies of gait, age-related increases in DTCs are observed when walking over obstacles (74), and with increased complexity of walking (75). Simple cognitive loads may elicit dual-task motor facilitation relative to no-load conditions, while more complex cognitive loads elicit proportionately greater costs in postural stability (76) and in an array of spatiotemporal gait parameters (77). In light of the known frontal recruitment associated with age-related sensory decline, it is perhaps not surprising that additional competition for cognitive capacity is observed when auditory challenges are experimentally imposed on dual-task walking (78) and dual-task balance (79), or when older adults with hearing impairment undergo CMDT (80).

Structural Brain Changes Associated With Gait, Balance, and CMDT

Studies of brain structure and mobility provide convergent evidence for the cognition-mobility link in older adults. For example, gray matter volumes in the left DLPFC were correlated with usual gait speed in healthy older adults, whereas reduced volumes in putamen and superior posterior parietal lobule were associated with balance difficulty during semi-tandem stance (81). Interestingly, the association between prefrontal volumes and gait speed was mediated by cognitive processing speed (82). In Parkinson's disease (PD), which has been viewed to some degree as a model of "unsuccessful" aging, structural and functional MRI were used to compare PD fallers and non-fallers (83). The fallers, as compared to non-fallers, showed reduced volumes in the caudate head region of the basal ganglia, coupled with increased resting state connectivity in posterior parietal regions of the central executive network. In general, the DTCs that occur in aging are more exaggerated in the presence of neurodegenerative disease, like PD [see (84) for a recent review]. This pattern of reduced structural integrity in task-specific brain regions, coupled with increased neural recruitment in other areas, is consistent with the STAC model, in that prefrontal recruitment is considered a compensatory response to neural degeneration of conventionally relevant networks.

Age-related changes in white matter integrity have also been implicated in mobility status. Moscufo et al. (85) observed associations in healthy older adults between gait speed and WMH burden in the anterior corpus callosum (splenium), attributing the reduction of mobility to a disruption of interhemispheric transfer of visual and somatosensory information. Similarly, Srikanth et al. (86) reported that bilateral frontal periventricular white matter lesion volumes correlated with a composite gait score, and attributed this association to a disconnection from frontal motor cortical areas with subcortical regions (e.g., basal ganglia). Similar to Rosano et al. (82) gray matter results, Bolandzadeh et al. (87) found that the relationship between WMHs in frontal corpus callosum and gait speed was mediated by cognitive processing speed. Everyday levels of physical activity also appear to moderate the relationship between global WMH burden and mobility (88), similar to the cognitive findings (63). Ezzati et al. (89) reported significant associations between cortical gray matter volumes and usual gait speed, but not with total white matter or ventricular volumes. In contrast, in the LADIS study of patients presenting with mild memory complaints (90, 91), the severity of age-related white matter changes was associated with the severity of gait and functional decline. Using DTI methods (FA), Bruijn et al. (92) reported significant associations in older adults between parameters of gait quality during treadmill walking and the diffusivity of the left anterior thalamic radiation (connecting the thalamus to frontal regions).

Functional Imaging of Gait and Balance

There is a growing number of functional brain imaging studies during walking [for reviews: (93, 94)]. Imagined walking

and dual-task walking during fMRI scans elicit activations in supplementary motor (SMA) and prefrontal regions in older adults, but show less activity in the same brain regions than what is observed during actual walking as measured using portable neuroimaging methods (95). Using fMRI and motor imagery during imagined walking, compared to watching a film, PD patients had greater activation in inferior frontal gyrus and precuneus than healthy controls [Maidan (96)]. These findings suggest that there is increased recruitment of frontal regions in PD even during imagined walking; perhaps this is an ineffective compensatory attempt. In a study of healthy older adults, resting state functional connectivity in sensorimotor, visual, vestibular, and left fronto-parietal regions was associated with off-line gait velocity under single-task and walking while talking CMDT conditions (reciting alternating letters of the alphabet), and supplementary motor and prefrontal regions were associated with only with CMDT (97).

The development of portable functional near-infrared spectroscopy [fNIRS: (98)] allows brain activity to be measured during active, upright (not just imagined) walking. Like fMRI, fNIRS directly measures the hemodynamic response (oxy- & deoxygenated hemoglobin: HbO_2, HbR), and is more tolerant of motion artifacts (99). In early studies of fNIRS and dual-task walking, Holtzer et al. (100, 101) reported greater prefrontal activation overall (HbO_2) in younger versus older adults, and increased HbO_2 during dual-task walking while talking compared to walking alone in young adults. By contrast, older adults showed less of a dual-task change, and their HbO_2 levels did not correlate with walking speed, suggesting that older adults show less efficient or effective frontal recruitment compared to young adults. In a recent study of young adults, a graded positive association between rostral frontal cortex HbO_2 levels (Brodmann's area 10) and increasingly complex dual-task contexts (walking alone, with counting forward, and with serial 7s subtraction) was observed (see **Figure 2**) (102). Others recently reported that activity in bilateral prefrontal cortices increased with cognitive load (*n*-back auditory working memory) during walking (103). Further, younger adults showed more left lateralization whereas older adults showed more bilateral activity (see **Figure 3**), consistent with the HAROLD model (12). In contrast, (104) found decreased activation of the prefrontal cortex under CMDT conditions (walking + visual checking) relative to single-task walking, and this downregulation was associated with greater dual-task costs in walking. The authors surmise that older adults were recruiting other posterior regions during complex CMDT as an alternative to prefrontal cortex, although their fNIRS array did not permit empirical confirmation. Using a dynamic balance protocol with varying sensory inputs (somatosensory, visual, vestibular) and fNIRS, others have shown that both middle-aged and older adults increase their frontal-lateral blood oxygenation during dynamic balance tasks (105).

Another recent development in the gait literature is the assessment of walking using electroencephalography [EEG: (10, 106)]. Notably, spectral power analyses have revealed that the gamma band is sensitive to manipulations of attentional load during walking in older adults and in neurological patients. More gamma band activity (30–100 Hz), which is associated with attention, learning, and memory (107), was observed in neurological patients than in healthy older adults (106), providing convergent evidence for increased cognitive compensation. Functional neuroimaging studies of balance, reviewed elsewhere (10) and in this special issue, reveal a similar pattern. For example, in EEG studies using postural evoked potentials and platform translations, the N100 amplitude, associated with attentional orienting responses, commonly shows attenuation in response to perturbations and cognitive loads such as visuomotor tracking or visual memory [e.g., (108, 109)].

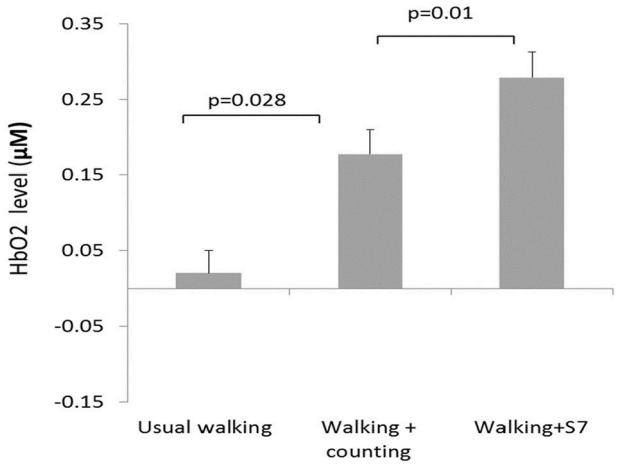


FIGURE 2 | *fNIRS* results (102) showing significant increases in blood oxygenation (HbO_2) as a function of walking complexity, i.e., the greater the cognitive load, the greater the increase in frontal activation during walking. Copyright permission not required.

In sum, the extant findings on neuroimaging, aging, and mobility suggest that many of the age-normative brain changes associated with declining cognitive control are associated with diminished gait and postural control. The literature on online neuroimaging of gait implicates prefrontal, premotor, and SMA regions (93). Under more challenging conditions involving CMDT, younger adults appear to recruit left prefrontal regions whose activity is related to better performance, whereas older adults show more bilateral recruitment that is not as well-linked to performance.

COGNITIVE ENHANCEMENT

Interventions designed to improve CMDT performance have focused largely on practicing the targeted motor function alone, termed "specific single-task training," or when combined with a cognitive load, termed "specific dual-task training" (110). This is contrasted with training on related but non-matching motor tasks, termed "general single- or dual-task training." The latter is recommended to strengthen attentional flexibility and dual-task management [e.g., (47, 111–113)]. The present focus, however, is to review training studies that more directly evaluate the cognitive contributions to balance and gait improvements.

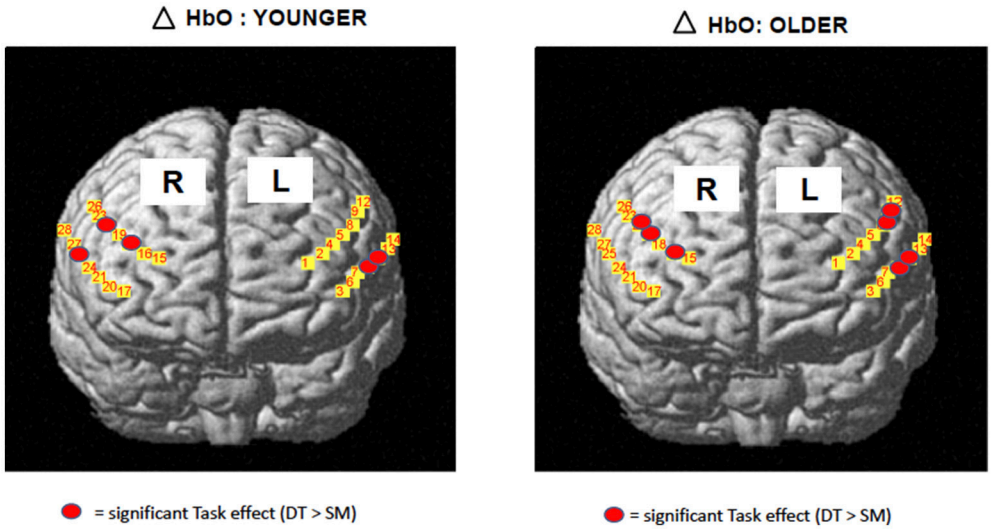


FIGURE 3 | *fNIRS data* [adapted from (103)] 19 young, 14 older adults during treadmill walking alone or with *n*-back cognitive load. Both age groups showed greater bilateral HbO_2 change from single motor to dual task conditions, OA had greater bilateral activations. Copyright permission not required.

The most clear-cut approach is therefore to selectively enhance cognitive capacity using seated computerized cognitive training.

Computerized Cognitive Training

An early computerized training study examined the effects of dual-task training on single and dual-task postural control (114). Healthy older adults completed five sessions of seated dual-task training involving two visual-manual reaction time tasks (40). The trained group showed pre-to-post improvements in static and dynamic balance measures given singly and with a concurrent *n*-back cognitive load, whereas the no-treatment control group showed negligible change (see **Figure 4**). The degree of learning in the trained cognitive task, particularly in dual-task trials, was correlated with the magnitude of improvement in postural stability, suggesting that the "active ingredient" of the training was dual-task coordination and not general processing speed. As mentioned earlier, the same DT training protocol led to increased left VLPFC activity in older adults, and reduced DLPFC activity while performing the trained task after training compared to before training (52). Future research comparing brain activity at pre- and post-training during motor and CMDT performance is needed to directly evaluate the neural overlap hypothesis, however the extant evidence of neuroplasticity is aligned with the upregulation observed in fronto-lateral brain regions during dynamic balance (105).

Others have examined commercially available cognitive training programs targeting multiple cognitive and EF processes such as attention, visual working memory, and speed of processing, and observed greater improvements in Timed-Up-and-Go (TUG), gait velocity, and dual-task gait, compared with untrained controls (115, 116). In older fallers, cognitive training was more beneficial for TUG performance than in non-fallers (116). In low to moderate-severity patients with PD, significant improvements were found on TUG and global cognition after 36 sessions of EF training [(117), see **Figure 5**].

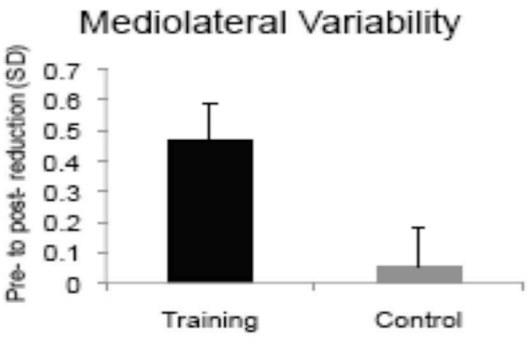


FIGURE 4 | Bars show magnitude of training-related improvements in postural sway during single support balancing after computerized dual-task training vs. no-treatment [adapted from (114)]. Copyright permission not required.

Pharmacological and Non-pharmacological Stimulation

Another approach to enhancing cognitive function in order to improve mobility and CMDT is to leverage the cognitive enhancing effects of certain pharmacologic agents. For example, methylphenidate and rivastigmine apparently improve cognition and mobility and, at least among people with PD, a reduction in fall risk may be related to the effects of the drug on cognition and CMDT (118–121). While the mechanisms are likely different from that of cognitive remediation training, these studies further highlight the idea that "cognitive" interventions can enhance mobility. Similarly, recent work using non-invasive brain stimulation that targets cognitive areas also supports

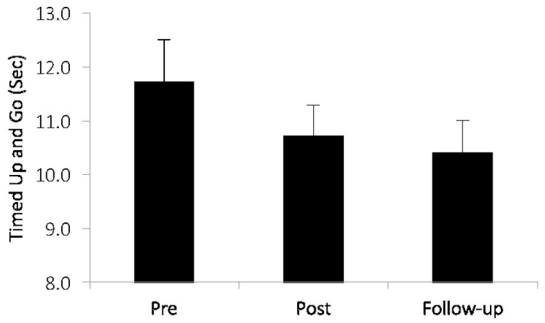


FIGURE 5 | In patients with mild to moderate Parkinson's disease after executive function training [adapted from (117)]. Training-related changes over time ($p = 035$) in a clinical index of mobility: the Timed-Up-and-Go (TUG). Copyright permission not required.

this idea. Indeed, a number of studies have reported that stimulation of the DLPFC either using repetitive trans-cranial magnetic (rTMS) or transcranial direct current stimulation (tDCS) enhances cogntion and reduces dual-tasks costs of balance and gait in older adults and patient groups [e.g., (122–125)].

Exercise Training

Beyond the non-motor cognitive training approach, more recent studies have added aerobic exercise training, again to enhance cognitive capacity in frontal regions and thereby free up more capacity to support motor control. Synergistic effects of combined cognitive and aerobic training were examined in a study of healthy older adults, randomized to one of four training conditions: aerobic plus EF training, aerobic plus computer lessons (cognitive placebo), EF training plus stretching (physical placebo), or cognitive placebo plus physical placebo (68, 126). Each group completed two exercise sessions and a separate computer session per week for 12 weeks. Across an array of cognitive and physical outcome measures, including CMDT gait and balance, the first three training formats yielded equivalent benefits, suggesting the absence of synergistic benefits with combined training. Similarly, cognitive training showed equivalent benefits to aerobic exercise on spontaneous walking speed (127). Using similar training tasks (aerobic cycling, computerized DT training), subsequent research with healthy older adults has examined whether delivery format (sequential versus simultaneous) yields differential benefits to CMDT. The sequentially trained group showed greater gains in working memory outcomes than the simultaneously trained group (128), whereas both groups showed similar CMDT Sit-to-Stand improvements [(129); see also (130)].

A final category of multi-modal training that contains a cognitive component is exergaming or virtual reality treadmill training. In contrast to the foregoing DT training approaches, this category reflects training activities in which the cognitive processing is integral to the motor task. For example, a randomized controlled study of older adults with a history of falls based on largely motor (i.e., PD patients), cognitive (i.e., people with mild cognitive impairment) and a mixed background (i.e., idiopathic fallers), compared the impact of treadmill training to the impact of treadmill training augmented with non-immersive virtual reality (VR) for 6 weeks (3 times per week), that targeted both cognitive aspects of safe ambulation (e.g., EF) and mobility (131). Falls, a problem presumably related to motor and cognitive function and to CMDT, were significantly reduced in the group who trained with treadmill training that included the targeting of cognitive aspects. More specifically, 6 months after the end of training, the incident rate of falls was significantly lower in the treadmill training plus VR group than in the treadmill training group (incident rate ratio 0.58, 95% CI 0.36–0.96; $p = 0.033$). Moreover, although usual single task walking improved similarly in both groups, walking under challenging conditions (e.g., obstacle negotiation variability and clearance) improved more in those who also received the cognitive training. Interestingly, in a subset of subjects with PD who underwent imaging before and after the training, fMRI and fNIRS results supported the added value of the cognitive component (see **Figure 6**). For example, among the subjects who underwent treadmill training alone, prefrontal activation during dual-task walking and obstacle negotiation increased after training, while in the combined training arm, activation decreased (132, 133). These findings support the idea that cognitive-motor training can reduce the need for cognitive compensation and the impact of CMDT, improve performance (more than motor training alone), and lead to changes in brain function and activation patterns.

CONCLUSIONS AND RECOMMENDATIONS

In the foregoing review, we have discussed aspects of the cognitive neuroscience of aging that are pertinent to the study of gait and balance in aging. Accordingly, we highlight several key points that might inform future studies of CMDT. First, the research on brain aging suggests a more accelerated age-related decline of gray and white matter in anterior structures than posterior structures, with white matter changes preceding gray matter atrophy, both leading to alterations within and across brain networks. Models of cognitive and brain aging suggest that compensatory prefrontal activity, or neural recruitment, may occur in the face of structural and functional declines in response to task demands that exceed available resources. However, the same prefrontal regions are also implicated in supporting age-related declines in sensory, cognitive, and motor domains. Thus, the aging of multiple systems implies competition for common neural structures and potential tradeoffs when older adults multi-task or when any one domain of functioning becomes more challenging (e.g., with sensory or cognitive impairment, with reduced mobility). We add that the same patterns of interference and tradeoff may occur in young adults, given sufficiently challenging task demands.

The principle of neural overlap applies both to the issue of dual-task interference, and to the issue of training-related transfer. In the case of CMDT performance, we argue that consideration of the neural underpinnings of single-task

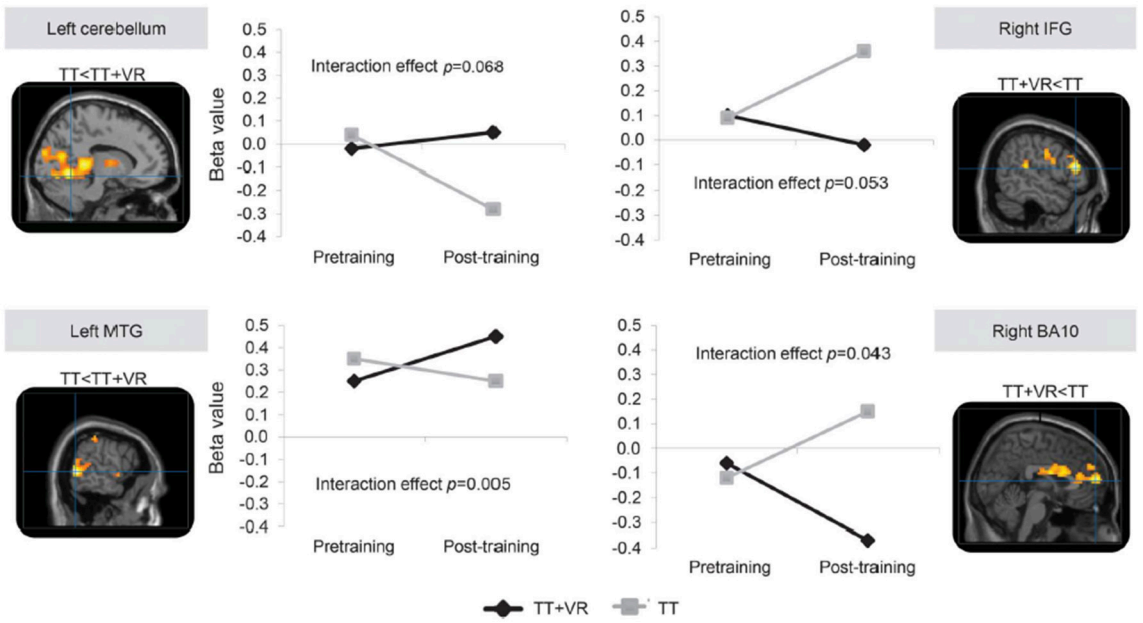


FIGURE 6 | fMRI data adapted from Maidan et al. (132). Training-specific differences in brain activation during obstacle negotiation after two interventions. The images present the 4 brain areas with different patterns of activation after training between the 2 training arms, while the corresponding graphs show the changes in mean β values for voxels in each of these 4 brain areas before and after training. *P*-values are from mixed model analyzes and represent the interaction between time (pre- vs. post-training) and training arm (treadmill training, TT vs. treadmill training with virtual reality, TT + VR). BA, Brodmann area; IFG, inferior frontal gyrus; MTG, middle temporal gyrus. Figure reproduced by permission of Wolters Kluwer Health Inc. (4386371208392).

cognitive and motor conditions, compared to the CMDT condition, can elucidate patterns of dual-task costs and facilitation. Similarly, consideration of the neural underpinnings of cognitive training or combined multimodal training should provide more direct evidence for the type of cognitive scaffolding and scaffolding enhancement that, to date, has been examined primarily in the realm of cognitive outcomes. Again, following the principle of neural overlap, it would be expected that training protocols that target discrete cognitive processes are likely to benefit related cognitive performance, either tested singly or in the context of CMDT performance. In contrast, the same cognitive training protocols might also indirectly benefit single- and dual-task motor performance by enhancing the capacity for compensatory cognitive or neural recruitment. Future studies should include neural outcome measures at pre- and post-training if feasible, in addition to independent behavioral indices of the targeted cognitive processes to be trained. Associating the magnitude of cognitive and neural plasticity to the magnitude of improvement in motor and CMDT performances would provide a more detailed understanding of the "active ingredients" underlying cognitive training effects.

Returning to the question posed in the introductory section, the extant research on neurocognitive aging and plasticity suggests that we cannot assume that the nature of cognitive involvement in postural control and gait is the same in younger and older adults. The available studies that combine age-comparisons, behavioral and functional neuroimaging measures of single-task cognitive, single-task motor, and dual-task performance, are few, and even more scant if one includes cognitive training and pre- and post-training imaging data.

AUTHOR CONTRIBUTIONS

KL and JH wrote the original draft of the manuscript. AM, IM, and LB contributed additional material. All co-authors contributed to the conceptualization of the manuscript.

FUNDING

Manuscript preparation was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC: RGPIN/6662-2016) awarded to KL.

REFERENCES

1. Hausdorff JM, Rios DA, Edelberg HK. Gait variability and fall risk in community-living older adults: a 1-year prospective study. *Arch Phys Med Rehabil.* (2001) 82:1050–6. doi: 10.1053/apmr.2001.24893
2. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *NEJM* (1988) 319:1701–7. doi: 10.1056/NEJM198812293192604
3. Davis JC, Robertson MC, Ashe MC, Liu-Ambrose T, Khan KM, Marra CA. International comparison of cost of falls in older adults living in

the community: a systematic review. *Osteoporos Int*. (2009) 8:1295–306. doi: 10.1007/s00198-009-1162-0
4. Hausdorff G, Yogev S, Springer S, Simon ES, Giladi N. Walking is more like catching than tapping: gait in the elderly as a complex cognitive task. *Exp Brain Res*. (2005) 164:541–8. doi: 10.1007/s00221-005-2280-3
5. Holtzer R, Verghese J, Xue X, Lipton RB. Cognitive processes related to gait velocity: results from the Einstein aging study. *Neuropsychology* 20:215–23. doi: 10.1037/0894-4105.20.2.215
6. Montero-Odasso M, Verghese J, Beauchet O, Hausdorff JM. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. *J Am Geriatr Soc*. (2012) 60:2127–36. doi: 10.1111/j.1532-5415.2012.04209.x
7. Van Iersel MB, Kessels RP, Bloem BR, Verbeek AL, Olde Rikkert MG. Executive functions are associated with gait and balance in community-living elderly people. *J Geront Biol Med Sci*. (2008) 63:1344–9. doi: 10.1093/gerona/63.12.1344
8. Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. *Mov Dis*. (2008) 23:329–42. doi: 10.1002/mds.21720
9. Seidler RD, Bernard JA, Burutolu TB, Fling BW, Gordon MT, Gwin JT, et al. Motor control and aging: links to age-related brain structural, functional, and biochemical effects. *Neurosci Biobehav Rev*. (2010) 34:721–33. doi: 10.1016/j.neubiorev.2009.10.005
10. Wittenberg E, Thompson J, Nam CS, Franz JR. Neuroimaging of human balance control: a systematic review. *Front Hum Neurosci*. (2017) 11:170. doi: 10.3389/fnhum.2017.00170
11. Park DC, Reuter-Lorenz P. The adaptive brain: aging and neurocognitive scaffolding. *Ann Rev Psychol*. (2009) 60:173–96. doi: 10.1146/annurev.psych.59.103006.093656
12. Cabeza R. Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychol Aging* (2002) 1:85–100. doi: 10.1037/0882-7974.17.1.85
13. Cabeza R, Nyberg L, Park D. *Cognitive Neuroscience of Aging: Linking Cognitive and Cerebral Aging*. New York, NY: Oxford University Press (2005).
14. Raz N, Rodrigue KM, Haacke EM. Brain aging and its modifiers. *Ann N Y Acad Sci*. (2007) 1097:84–93. doi: 10.1196/annals.1379.018
15. Raz N, Gunning FM, Head D, Dupuis JH, McQuain J, Briggs SD, et al. Selective aging of the human cerebral cortex observed *in vivo:* differential vulnerability of the prefrontal gray matter. *Cereb Cortex* (1997) 7:268–82.
16. Raz N, Lindenberger U, Rodrigue KM, Kennedy KM, Head D, Williamson A, et al. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cereb Cortex* (2005) 15:1676–89. doi: 10.1093/cercor/bhi044
17. Davis SW, Dennis NA, Buchler NG, White LE, Madden DJ, Cabeza R. Assessing the effects of age on long white matter tracts using diffusion tensor tractography. *Neuroimage* (2009) 46:530–41. doi: 10.1016/j.neuroimage.2009.01.068
18. Daselaar SM, Iyengar V, Davis SW, Eklund K, Hayes SM, Cabeza RE. Less wiring, more firing: low-performing older adults compensate for impaired white matter with greater neutral activity. *Cereb Cortex* (2015) 25:983–90. doi: 10.1093/cercor/bht289
19. Davis SW, Kragel JE, Madden DJ, Cabeza R. The architecture of cross-hemispheric communication in the aging brain: linking behavior to functional and structural connectivity. *Cereb Cortex* (2012) 22:232–42. doi: 10.1093/cercor/bhr123
20. Cabeza R, Grady CL, Nyberg L, McIntosh AR, Tulving E, Kapur S, et al. Age-related differences in neural activity during memory encoding and retrieval: a positron emission tomography study. *J Neurosci*. (1997) 17:391–400.
21. Gutchess AH, Welsh RC, Hedden T, Bangert A, Minear M, Liu LL, et al. Aging and the neural correlates of successful picture encoding: frontal activations compensate for decreased medial-temporal activity. *J Cogn Neurosci*. (2005) 17:84–96. doi: 10.1162/0898929052880048
22. Cabeza R, Daselaar SM, Dolcos F, Prince SE, Budde M, Nyberg L. Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. *Cereb Cortex* (2004) 14:364–75. doi: 10.1093/cercor/bhg133
23. Wong PCM, Jin JX, Gunasekera GM, Abel R, Lee ER, Dhar S. Aging and cortical mechanisms of speech perception in noise. *Neuropsychologia* (2009) 47:693–703. doi: 10.1016/j.neuropsychologia.2008.11.032
24. Schneider BA, Pichora-Fuller MK. Implications of perceptual deterioration for cognitive aging research. In: Craik FIM, Salthouse TA, editors. *The Handbook of Aging and Cognition 2nd Edn*. Mahwah, NJ: Erlbaum. (2000). p. 155–219.
25. Mattay VS, Fera F, Tessitore A, Hariri AR, Berman KF, Weinberger DR. Neurophysiological correlates of age-related changes in working memory capacity. *Neurosci Lett*. (2006) 392:32–7. doi: 10.1016/j.neulet.2005.09.025
26. Park DC, Polk TA, Park R, Minear M, Savage A, Smith MR. Aging reduces neural specialization in ventral visual cortex. *Proc Natl Acad Sci USA*. (2004) 101:13091–5. doi: 10.1073/pnas.0405148101
27. Baltes PB, Lindenberger U. Emergence of a powerful connection between sensory and cognitive functions across the adult life span: a new window to the study of cognitive aging? *Psychol Aging* (1997) 12:12–21. doi: 10.1037/0882-7974.12.1.12
28. Li KZH, Lindenberger U. Relations between aging sensory/sensorimotor and cognitive functions. *Neurosci Biobehav Rev*. (2002) 26:777–83. doi: 10.1016/S0149-7634(02)00073-8
29. de Frias CM, Dixon RA, Strauss E. Structure of four executive functioning tests in healthy older adults. *Neuropsychology* (2006) 20:206–14. doi: 10.1037/0894-4105.20.2.206
30. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wagner T. The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: a latent variable analysis. *Cogn Psychol*. (2000) 41:49–100. doi: 10.1006/cogp.1999.0734
31. Andrews-Hanna JR, Snyder AZ, Vincent JL, Lustig C, Head D, Raichle ME, et al. Disruption of large-scale brain systems in advanced aging. *Neuron* (2007) 56:924–235. doi: 10.1016/j.neuron.2007.10.038
32. Sambataro F, Murty VP, Callicott JH, Tan H-Y, Das S, Weinberger DR, et al. Age-related alterations in default mode network: impact on working memory performance. *Neurobiol Aging* 31:839–52. doi: 10.1016/j.neurobiolaging.2008.05.022
33. Marstaller L, Williams M, Rich A, Savage G, Burianová H. Aging and large-scale functional networks: white matter integrity, gray matter volume, and functional connectivity in the resting state. *Neuroscience* (2015) 290:369–78. doi: 10.1016/j.neuroscience.2015.01.049
34. Grady C. The cognitive neuroscience of aging. *Nat Rev Neurosci*. (2012) 13:491–505. doi: 10.1038/nrn3256
35. Reuter-Lorenz PA, Park DC. How does it STAC up? Revisiting the scaffolding theory of aging and cognition. *Neuropsychol Rev*. (2014) 24:355–70. doi: 10.1007/s11065-014-9270-9
36. Lustig C, Shah P, Seidler R, Reuter-Lorenz PA. Aging, training, and the brain: a review and future directions. *Neuropsychol Rev*. (2009) 19:504–22. doi: 10.1007/s11065-009-9119-9
37. Hertzog C, Kramer AF, Wilson RS, Lindenberger U. Enrichment effects on adult cognitive development can the functional capacity of older adults be preserved and enhanced? *Psychol Sci Public Interest* (2008) 9:1–65. doi: 10.1111/j.1539-6053.2009.01034.x
38. Karbach J, Verhaeghen P. Making working memory work: a meta-analysis of executive-control and working memory training in older adults. *Psychol Sci*. (2014) 25:2027–37. doi: 10.1177/0956797614548725
39. Ball K, Berch DB, Helmers KF, Jobe JB, Leveck MD, Marsiske M, et al. Effects of cognitive training interventions with older adults—a randomized controlled trial. *J Am Med Assoc*. (2002) 288:2271–81. doi: 10.1001/jama.288.18.2271
40. Bherer L, Kramer AF, Peterson MS, Colcombe S, Erickson K, Becic E. Training effects on dual-task performance: Are there age-related differences in plasticity of attentional control? *Psychol Aging* 20:695–709. doi: 10.1037/0882-7974.20.4.695
41. Bherer L, Kramer AF, Peterson MS, Colcombe S, Erickson K, Becic E. Testing the limits of cognitive plasticity in older adults: application to attentional control. *Acta Psychol*. (2006) 123:261–78. doi: 10.1016/j.actpsy.2006.01.005
42. Dahlin E, Neely AS, Larsson A, Backman L, Nyberg L. Transfer of learning after updating training mediated by the striatum. *Science* (2008) 320:1510–2. doi: 10.1126/science.1155466
43. Karbach J, Kray J. How useful is executive control training: age differences in near and far transfer of task-switching training? *Dev Sci*. (2009) 12:978–90. doi: 10.1111/j.1467-7687.2009.00846.x

44. Persson J, Reuter-Lorenz PA. Gaining control training executive function and far transfer of the ability to resolve interference. *Psychol Sci*. (2008) 19:881–8. doi: 10.1111/j.1467-9280.2008.02172.x
45. Kramer AF, Larish JF, Strayer DL. Training for attentional control in dual task settings: a comparison of young and old adults. *J Exp Psychol Appl*. (1995) 1:50–76.
46. Lussier M, Bugaiska A, Bherer L. Specific transfer effects following variable priority dual-task training in older adults. *Restor Neurol Neurosci*. 35:237–50. doi: 10.3233/RNN-150581
47. Silsupadol P, Siu KC, Shumway-Cook A, Woollacott MH. Training of balance under single- and dual-task conditions in older adults with balance impairment. *Phys Ther*. (2006) 86:269–81. doi: 10.1093/ptj/86.2.269
48. Li KZH, Krampe RT, Bondar A. An ecological approach to studying aging and dual-task performance. In: Engle RW, Sedek G, Von hecker U, McIntosh DN, editors. *Cognitive Limitations in Aging and Psychopathology: Attention, Working Memory, and Executive Functions*. Cambridge: Cambridge University Press (2005). p. 190–218. doi: 10.1017/CBO9780511720413.009
49. Salthouse TA, Hambrick DZ, Lukas KE, Dell TC. Determinants of adult age differences on synthetic work performance. *J Exp Psychol Appl*. (1996) 2:305–29.
50. Belleville S, Bherer L. Biomarkers of cognitive training effects in aging. *Curr. Transl. Geriatr. Exp. Gerontol. Rep*. 1:104–10. doi: 10.1007/s13670-012-0014-5
51. Lövden M, Bodammer NC, Kühn S, Kaufmann J, Schutze H, Tempelmann C, et al. Experience-dependent plasticity of white-matter microstructure extends into old age. *Neuropsychologica* (2010) 48:3878–83. doi: 10.1016/j.neuropsychologia.2010.08.026
52. Erickson KI, Colcombe SJ, Wadhwa R, Bherer L, Peterson MS, Scalf PE, et al. Training-induced functional activation changes in dual-task processing: an fMRI study. *Cereb Cortex* (2007) 17:192–204. doi: 10.1093/cercor/bhj137
53. Erickson KI, Colcombe SJ, Wadhwa R, Bherer L, Peterson MS, Scalf PE, et al. Training-induced plasticity in older adults: effects of training on hemispheric asymmetry. *Neurobiol. Aging* (2007) 28:272–83. doi: 10.1016/j.neurobiolaging.2005.12.012
54. Lampit A, Hallock H, Suo C, Naismith SL, Valenzuela M. Cognitive training-induced short-term functional and long-term structural plastic change is related to gains in global cognition in healthy older adults: a pilot study. *Front Aging Neurosci.* (2015) 7:14. doi: 10.3389/fnagi.2015.00014
55. Bherer L, Erickson KI, Liu-Ambrose T. Physical exercise and brain functions in older adults. *J Aging Res*. 2013:197326. doi: 10.1155/2013/197326
56. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol Sci*. (2003) 14:125–30. doi: 10.1111/1467-9280.t01-1-01430
57. Albinet CT, Boucard G, Bouquet CA, Audiffren M. Increased heart rate variability and executive performance after aerobic training in the elderly. *Eur J Appl Physiol*. (2010) 109:617–24. doi: 10.1007/s00421-010-1393-y
58. Dustman RE, Ruhling RO, Russell EM, Shearer DE, Bonekat HW, Shigeoka JW, et al. Aerobic exercise training and improved neuropsychological function of older individuals. *Neurobiol. Aging*. (1984) 5:35–42.
59. Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR, et al. Ageing, fitness and neurocognitive function. *Nature* (1999) 400:418–9. doi: 10.1038/22682
60. Singh MAF, Gates N, Saigal N, Wilson GC, Meiklejohn J, Valenzuela M. The Study of Mental and Resistance Training (SMART) study – resistance training and/or cognitive training in mild cognitive impairment: a randomized, double-blind, double-sham controlled trial. *J Am Med Direc Assn*. (2014) 15:873–80. doi: 10.1016/j.jamda.2014.09.010
61. Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, Cohen NJ, et al. Cardiovascular fitness, cortical plasticity, and aging. *Proc Natl Acad Sci USA*. (2004) 101:3316–21. doi: 10.1073/pnas.0400266101
62. Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E, et al. Aerobic exercise training increases brain volume in aging humans. *J Gerontol A Biol Sci Med Sci*. (2006) 61:1166–70. doi: 10.1093/gerona/61.11.1166
63. Voss MW, Heo S, Prakash RS, Erickson KI, Alves H, Chaddock L, et al. The influence of aerobic fitness on cerebral white matter integrity and cognitive function in older adults: results of a one-year exercise intervention. *Hum Brain Mapp*. (2013) 34:2972–85. doi: 10.1002/hbm.22119
64. Erickson KI, Hillman CH, Kramer AF. Physical activity, brain, and cognition. *Curr Opin Behav Sci.* (2015) 4:27–32. doi: 10.1016/j.cobeha.2015.01.005
65. Voss MW, Erickson KI, Prakash RS, Chaddock L, Kim JS, Alves H, et al. Neurobiological markers of exercise-related brain plasticity in older adults. *Brain Behav Immun*. (2013) 28:90–9. doi: 10.1016/j.bbi.2012.10.021
66. Zhu X, Yin S, Lang M, He R, Li J. The more the better? A meta-analysis on effects of combined cognitive and physical intervention on cognition in healthy older adults. *Ageing Res Rev*. (2016) 31:67–79. doi: 10.1016/j.arr.2016.07.003
67. Rahe J, Petrelli A, Kaesberg S, Fink GR, Kessler J, Kalbe E. Effects of cognitive training with additional physical activity compared to pure cognitive training in healthy older adults. *Clin Interv Aging* (2015) 10:297–310. doi: 10.2147/CIA.S74071
68. Desjardins-Crépeau L, Berryman N, Fraser SA, Vu TTM, Kergoat M-J, Li KZH, et al. Effects of combined physical and cognitive training on fitness and neuropsychological outcomes in healthy older adults. *Clin Interv Aging* (2016) 11:1287–99. doi: 10.2147/CIA.S115711
69. Woollacott M, Shumway-Cook A. Attention and the control of posture and gait: a review of an emerging area of research. *Gait Posture* (2002) 16:1–14. doi: 10.1016/S0966-6362(01)00156-4
70. Brown LA, Sleik RJ, Polych MA, Gage WH. Is the prioritization of postural control altered in conditions of postural threat in younger and older adults? *J Gerontol Med Sci*. (2002) 57:M785–92. doi: 10.1093/gerona/57.12.M785
71. Brown LA, Shumway-Cook A, Woollacott MH. Attentional demands and postural recovery: the effects of aging. *J Gerontol Med Sci.* (1999) 54A:165–71.
72. Redfern MS, Müller MLTM, Jennings JR, Furman JM. Attentional dynamics in postural control during perturbations in young and older adults. *J Gerontol Biol Sci.* (2002) 57:B298–303. doi: 10.1093/gerona/57.8.B298
73. Maylor EA, Wing AM. Age differences in postural stability are increased by additional cognitive demands. *J Gerontol Psychol Sci*. (1996) 51B:P143–54.
74. Li KZH, Lindenberger U, Freund AM, Baltes PB. Walking while memorizing: age-related differences in compensatory behavior. *Psychol Sci*. (2001) 12:230–7. doi: 10.1111/1467-9280.00341
75. Lindenberger U, Marsiske M, Baltes PB. Memorizing while walking: increase in dual-task costs from young adulthood to old age. *Psychol Aging* (2000) 15:417–36. doi: 10.1037/0882-7974.15.3.417
76. Huxhold O, Li SC, Schmiedek F, Lindenberger U. Dual-tasking postural control: aging and the effects of cognitive demand in conjunction with focus of attention. *Brain Res Bull.* (2006) 69:294–305. doi: 10.1016/j.brainresbull.2006.01.002
77. Lövdén M, Schaefer S, Pohlmeyer AA, Lindenberger U. Walking variability and working-memory load in aging: a dual-process account relating cognitive control to motor control performance. *J Gerontol Series B Psychol Sci Soc Sci*. (2008) 63:P121–8. doi: 10.1093/geronb/63.3.P121
78. Nieborowska V, Lau ST, Campos J, Pichora-Fuller MK, Novak A, Li KZH. Effects of age on dual-task walking while listening. *J Motor Behav*. (2018). doi: 10.1080/00222895.2018.1498318
79. Bruce H, Aponte D, St-Onge N, Phillips N, Gagné J-P, Li KZH. The effects of age and hearing loss on dual-task balance and listening. *J Gerontol Psychol Sci B* (2017). doi: 10.1093/geronb/gbx047. [Epub ahead of print].
80. Lau ST, Pichora-Fuller MK, Li KZH, Singh G, Campos J. Effects of hearing loss on dual-task performance in an audiovisual virtual reality simulation of listening while walking. *J Am Acad Audiol*. 27:567–87. doi: 10.3766/jaaa.15115
81. Rosano C, Aizenstein HJ, Studenski S, Newman AB. A regions-of-interest volumetric analysis of mobility limitations in community-dwelling older adults. *J Gerontol Med Sci*. (2007) 62:1048–55. doi: 10.1093/gerona/62.9.1048
82. Rosano C, Bennett DA, Newman AB, Venkatraman V, Yaffe K, Harris T, et al. Patterns of focal gray matter atrophy are associated with bradykinesia and gait disturbances in older adults. *J Gerontol Series A* (2012) 67:957–62. doi: 10.1093/gerona/glr262
83. Rosenberg-Katz K, Herman T, Jacob Y, Mirelman A, Giladi N, Hendler T, et al. Fall risk is associated with amplified functional connectivity of the central executive network in patients with Parkinson's disease. *J Neurol*. (2015) 262:2448–56. doi: 10.1007/s00415-015-7865-6
84. Wajda DA, Mirelman A, Hausdorff JM, Sosnoff JJ. Intervention modalities for targeting cognitive-motor interference in individuals

with neurodegenerative disease: a systematic review. *Expert Rev Neurother*. (2017) 17:251–61. doi: 10.1080/14737175.2016.1227704
85. Moscufo N, Guttmann CR, Meier D, Csapo I, Hildenbrand PG, Healy BC, et al. Brain regional lesion burden and impaired mobility in the elderly. *Neurobiol Aging* (2009) 32:646–54. doi: 10.1016/j.neurobiolaging.2009.04.010
86. Srikanth V, Phan TG, Chen J, Beare R, Stapleton JM, Reutens DC. The location of white matter lesions and gait-a voxel-based study. *Ann Neurol*. (2010) 67:265–9. doi: 10.1002/ana.21826
87. Bolandzadeh N, Liu-Ambrose T, Aizenstein H, Harris T, Launer L, Yaffe K, et al. Pathways linking regional hyperintensities in the brain and slower gait. *NeuroImage* (2014) 99:7–13. doi: 10.1016/j.neuroimage.2014.05.017
88. Fleischman DA, Yang J, Arfanakis K, Arvanitakis Z, Leurgans SE, Turner AD, et al. Physical activity, motor function, and white matter hyperintensity burden in healthy older adults. *Neurology* 84:1294–300. doi: 10.1212/WNL.0000000000001417
89. Ezzati A, Katz MJ, Lipton ML, Lipton RB, Verghese J. The association of brain structure with gait velocity in older adults: a quantitative volumetric analysis of brain MRI. *Neuroradiology* (2015) 57:851–61. doi: 10.1007/s00234-015-1536-2
90. Baezner H, Blahak C, Poggesi A, Pantoni L, Inzitari D, Chabriat H, et al. Association of gait and balance disorders with age-related white matter changes: the LADIS study. *Neurology* 70:935–42. doi: 10.1212/01.wnl.0000305959.46197.e6
91. Inzitari D, Simoni M, Pracucci G, Poggesi A, Chabriat H, Langhorne P. Risk of rapid global functional decline in elderly patients with severe cerebral age-related white matter changes. *Arch Intern Med*. (2007) 167:81–8. doi: 10.1001/archinte.167.1.81
92. Bruijn SM, Impe AV, Duysens J, Swinnen SP. White matter microstructural organization and gait stability in older adults. *Front Aging Neurosci.* (2014) 6:104. doi: 10.3389/fnagi.2014.00104
93. Holtzer R, Epstein N, Mahoney JR, Izzetoglu M, Blumen HM. Neuroimaging of mobility in aging: a targeted review. *J Gerontol Series A Biol Sci Med Sci*. (2014) 69:1375–88. doi: 10.1093/gerona/glu052
94. Leone C, Feys P, Moumdjian L, D'Amico E, Zappia M, Patti F. Cognitive-motor dual-task interference. A systematic review of neural correlates. *Neurosci Biobeh Rev*. (2017) 75:348–60. doi: 10.1016/j.neubiorev.2017.01.010
95. Miyai I, Tanabe HC, Sase I, Eda H, Oda I, Konishi I, et al. Cortical mapping of gait in humans: a near-infrared spectroscopic topography study. *Neuroimage* (2001) 14:1186–92. doi: 10.1006/nimg.2001.0905
96. Maidan I, Rosenberg-Katz K, Jacob Y, Giladi N, Deutsch JE, Hausdorff JM, et al. Altered brain activation in complex walking conditions in patients with Parkinson's disease. *Parkinsonims Relat Disord*. (2016) 25:91–6. doi: 10.1016/j.parkreldis.2016.01.025
97. Yuan J, Blumen HM, Verghese J, Holtzer R. Functional connectivity associated with gait velocity during walking and walking-while-talking in aging: a resting-state fMRI study. *Hum Brain Mapp*. (2015) 36:1484–93. doi: 10.1002/hbm.22717
98. Arenth PM, Ricker JH, Schultheis MT. Applications of functional near-infrared spectroscopy (fNIRS) to neurorehabilitation of cognitive disabilities. *Clin Neuropsychol*. 21:38–57. doi: 10.1080/13854040600878785
99. Huppert TJ, Hoge RD, Diamond SG, Franceschini MA, Boas DA. A temporal comparison of BOLD, ASL, and NIRS hemodynamic responses to motor stimuli in adult humans. *Neuroimage* 29:368–82. doi: 10.1016/j.neuroimage.2005.08.065
100. Holtzer R, Mahoney JR, Izzetoglu M, Onaral B, Verghese J. fNIRS study of walking and walking while talking in young and old individuals. *J Gerontol Med Sci.* (2011) 66:879–87. doi: 10.1093/gerona/glr068
101. Holtzer R, Mahoney JR, Izzetoglu M, Wang C, England S, Verghese J. Online fronto-cortical control of simple and attention-demanding locomotion in humans. *Neuroimage* (2015) 112:152–9. doi: 10.1016/j.neuroimage.2015.03.002
102. Mirelman A, Maidan I, Bernard-Elazari H, Nieuwhof F, Reelick M, Giladi N, et al. Increased frontal brain activation during walking while dual-tasking: an fNIRS study in healthy young adults. *J NeuroEng Rehab*. (2014) 11:1–7. doi: 10.1186/1743-0003-11-85
103. Fraser SA, Dupuy O, Pouliot P, Lesage F, Bherer L. Comparable cerebral oxygenation patterns in younger and older adults during dual-task walking with increasing load. *Front Aging Neurosci*. (2016) 8:204. doi: 10.3389/fnagi.2016.00240
104. Beurskens R, Helmich I, Rein R, Bock O. Age-related changes in prefrontal activity during walking in dual-task situations: a fNIRS study. *Int J Psychophysiol*. (2014) 92:122–8. doi: 10.1016/j.ijpsycho.2014.03.005
105. Lin CC, Barker JW, Sparto PJ, Furman JM, Huppert TJ. Functional near-infrared spectroscopy (fNIRS) brain imaging of multi-sensory integration during computerized dynamic posturography in middle-aged and older adults. *Exp Brain Res*. (2017) 235:1247–56. doi: 10.1007/s00221-017-4893-8
106. Costa A, Ianez E, Ubeda A, Hortal E, Del-Ama AJ, Gil-Agudo A, et al. Decoding the attentional demands of gait through EEG Gamma band features. *PLoS ONE* 11:e0154136. doi: 10.1371/journal.pone.0154136
107. Kaiser J, Lutzenberger W. Human gamma-band activity: a window to cognitive processing. *Neuroreport* (2005) 16:207–11. doi: 10.1097/00001756-200502280-00001
108. Little CE, Woollacott M. EEG measures reveal dual-task interference in postural performance in young adults. *Exp Brain Res*. 233:27–37. doi: 10.1007/s00221-014-4111-x
109. Quant S, Adkin AL, Staines WR, Maki BE, McIlroy WE. The effect of a concurrent cognitive task on cortical potentials evoked by unpredictable balance perturbations. *BMC Neurosci.* 5:18. doi: 10.1186/1471-2202-5-18
110. Wollesen B, Voelcker-Rehage C. Training effects on motor-cognitive dual-task performance in older adults. *Eur Rev Aging Phys Act*. 11:5–24. doi: 10.1007/s11556-013-0122-z
111. Silsupadol P, Lugade V, Shumway-Cook A, Van Donkelaar P, Chou L-S, Mayr U, et al. Training-related changes in dual-task walking performance of elderly persons with balance impairment: a double-blind, randomized controlled trial. *Gait Posture* (2009) 29:634–9. doi: 10.1016/j.gaitpost.2009.01.006
112. Wollesen B, Mattes K, Schulz S, Bischoff LL, Seydell L, Bell JW, et al. Effects of dual-task management and resistance training on gait performance in older individuals: a randomized controlled trial. *Front Aging Neurosci.* (2017) 9:415. doi: 10.3389/fnagi.2017.00415
113. Wongcharoen S, Sungkarat S, Munkhetvit P, Lugade V, Silsupadol P. Home-based interventions improve trained, but not novel, dual-task balance performance in older adults: a randomized controlled trial. *Gait Posture* (2017) 52:147–52. doi: 10.1016/j.gaitpost.2016.11.036
114. Li KZH, Roudaia E, Lussier M, Bherer L, Leroux A, McKinley P. Benefits of cognitive dual-task training on balance performance in healthy older adults. *J Gerontol Series A Biol Sci Med Sci*. (2010) 65:1344–52. doi: 10.1093/gerona/glq151
115. Verghese J, Mahoney J, Ambrose A, Wang C, Holtzer R. Effect of cognitive remediation on gait in sedentary seniors. *J Gerontol Series A Biol Sci Med Sci*. (2010) 65A:1338–43. doi: 10.1093/gerona/glq127
116. Smith-Ray RL, Hughes SL, Prohaska TR, Little DM, Jurivich DA, Hedeker D. Impact of cognitive training on balance and gait in older adults. *J Gerontol B Psychol Sci Soc Sci*. (2015) 70:357–66. doi: 10.1093/geronb/gbt097
117. Milman U, Atias H, Weiss A, Mirelman A, Hausdorff JM. Can cognitive remediation improve mobility in patients with Parkinson's disease? findings from a 12 week pilot study. *J. Parkinsons. Dis.* (2014) 4:37–44. doi: 10.3233/JPD-130321
118. Auriel E, Hausdorff JM, Herman T, Simon ES, Giladi N. Effects of methylphenidate on cognitive function and gait in patients with Parkinson's disease: a pilot study. *Clin Neuropharmacol.* (2006) 29:15–7. doi: 10.1097/00002826-200601000-00005
119. Ben-Itzhak R, Giladi N, Guendlinger L, Hausdorff JM. Can methylphenidate reduce fall risk in community living older adults? A double blind, single-dose cross-over study. *J Am Ger Soc*. (2008) 56:695–700. doi: 10.1111/j.1532-5415.2007.01623.x
120. Henderson EJ, Lord SR, Brodie MA, Gaunt DM, Lawrence AD, Ben-Shlomo Y. Rivastigmine for gait stability in patients with parkinson's disease (ReSPonD): a randomized, double-blind, placebo-controlled, phase 2 trial. *Lancet Neurol.* (2016) 15:249–58. doi: 10.1016/S1474-4422(15)00389-0
121. Segev-Jacubovski O, Herman T, Yogev-Seligmann G, Mirelman A, Giladi N, Hausdorff JM. The interplay between gait, falls and cognition: can cognitive therapy reduce fall risk? *Exp Rev Neurother*. (2011) 11:1057–75. doi: 10.1586/ern.11.69

122. Dagan M, Herman T, Harrison R, Zhou J, Giladi N, Ruffini G, et al. Multitarget transcranial direct current stimulation for freezing of gait in Parkinson's disease. *Mov Dis*. (2018) 33:642–6. doi: 10.1002/mds.27300
123. Manor B, Zhou J, Jordan A, Zhang J, Fang J, Pascual-Leone A. Reduction of dual-task costs by noninvasive modulation of prefrontal activity in healthy elders. *J Cogn Neurosci.* (2016) 28:275–81. doi: 10.1162/jocn_a_00897
124. Manor B, Zhou J, Harrison R, Lo O-Y, Travison TG, Hausdorff JM, et al. Transcranial direct current stimulation may improve cognitive-motor function in functionally limited older adults. *Neurorehabil Neural Repair* (2018) 32:788–98. doi: 10.1177/1545968318792616
125. Zhou J, Hao Y, Wang Y, Jordan A, Pascual-Leone A, Zhang J, et al. Transcranial direct current stimulation (tDCS) reduces the cost of performing a cognitive task on gait and postural control. *Eur J Neurosci.* (2014) 39:1343–8. doi: 10.1111/ejn.12492
126. Fraser SA, Li KZH, Berryman N, Desjardins-Crépeau L, Lussier M, Vadaga K, et al. Does combined physical and cognitive training improve dual-task balance and gait outcomes in sedentary older adults? *Front Hum Neurosci.* (2017) 10:688. doi: 10.3389/fnhum.2016.00688
127. Pothier K, Gagnon C, Fraser SA, Lussier M, Desjardins-Crépeau L, Berryman N, et al. A comparison of the impact of physical exercise, cognitive training and combined intervention on spontaneous walking speed in older adults. *Aging Clin Exp Res*. (2018) 30:921–5. doi: 10.1007/s40520-017-0878-5
128. Lai L, Bruce H, Bherer L, Lussier M, Li KZH. Comparing the transfer effects of simultaneous and sequential combined aerobic exercise and cognitive training in older adults. *J Cogn Enhan.* (2017) 1:478–90. doi: 10.1007/s41465-017-0052-1
129. Bruce H, Lai L, Bherer L, Lussier M, St-Onge N, Li KZH. The effect of simultaneously and sequentially delivered cognitive and aerobic training on mobility among older adults with hearing loss. *Gait Posture* (in press).
130. Jehu D, Paquet N, Lajoie Y. Balance and mobility training with or without concurrent cognitive training does not improve posture, but improves reaction time in healthy older adults. *Gait Posture* (2017) 52:227–32. doi: 10.1016/j.gaitpost.2016.12.006
131. Mirelman A, Rochester L, Maidan I, Del Din S, Nieuwhof F, Abbruzzese G. Addition of a non-immersive virtual reality component to treadmill training to reduce fall risk in older adults (V-TIME): a randomised controlled trial. *Lancet* (2016) 388:1170–82. doi: 10.1016/S0140-6736(16)31325-3
132. Maidan I, Rosenberg-Katz K, Jacob Y, Giladi N, Deutsch JE, Hausdorff JM, et al. Disparate effects of training on brain activation in Parkinson's disease. *Neurology*. (2017) 89:1804–10. doi: 10.1212/WNL.0000000000004576
133. Maidan I, Nieuwhof F, Bernad-Elazari H, Bloem B, Giladi N, Hausdorff JM, et al. Evidence of differential effects of 2 forms of exercise on prefrontal plasticity during walking in parkinson's disease. *Neruorehab Neural Repair* (2018) 32:200–8. doi: 10.1177/1545968318763750

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

REVIEW
published: 30 October 2018
doi: 10.3389/fneur.2018.00924

Forecast or Fall: Prediction's Importance to Postural Control

Christopher J. Dakin and David A. E. Bolton*

Department of Kinesiology and Health Science, Utah State University, Logan, UT, United States

To interact successfully with an uncertain environment, organisms must be able to respond to both unanticipated and anticipated events. For unanticipated events, organisms have evolved stereotyped motor behaviors mapped to the statistical regularities of the environment, which can be trigged by specific sensory stimuli. These "reflexive" responses are more or less hardwired to prevent falls and represent, maybe, the best available solution to maintaining posture given limited available time and information. With the gift of foresight, however, motor behaviors can be tuned or prepared in advance, improving the ability of the organism to compensate for, and interact with, the changing environment. Indeed, foresight's improvement of our interactive capacity occurs through several means, such as better action selection, processing, and conduction delay compensation and by providing a prediction with which to compare our actual behaviors to, thereby facilitating error identification and learning. Here we review the various roles foresight (prediction) plays in maintaining our postural equilibrium. We start by describing some of the more recent findings related to the prediction of instability. Specifically, we cover recent advancements in the understanding of anticipatory postural behaviors that are used broadly to stabilize volitional movement and compensate for impending postural disturbances. We also describe anticipatory changes in the state, or set, of the nervous system that may facilitate anticipatory behaviors. From changes in central set, we briefly discuss prediction of postural instability online before moving into a discussion of how predictive mechanisms, such as internal models, permit us to tune, perhaps our highest level predictive behaviors, namely the priming associated with motor affordances. Lastly, we explore methods best suited to expose the contribution of prediction to postural equilibrium control across a variety of contexts.

Keywords: fall, balance, posture, prediction, anticipation, postural control

OPEN ACCESS

Edited by:
Emily Keshner,
Temple University, United States

Reviewed by:
Roberto Esposti,
Università degli Studi di Milano, Italy
Eric Yiou,
Université Paris-Sud, France

****Correspondence:***
Christopher J. Dakin
chris.dakin@usu.edu

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *26 July 2018*
Accepted: *11 October 2018*
Published: *30 October 2018*

Citation:
Dakin CJ and Bolton DAE (2018) Forecast or Fall: Prediction's Importance to Postural Control. Front. Neurol. 9:924. doi: 10.3389/fneur.2018.00924

INTRODUCTION

The world is full of obstacles, opportunities and distractions with which we must interact. Some of these interactions are simple, permitting a reliable stereotyped response with each occurrence, while others are more complicated, requiring more refined pattern recognition, and decision making mechanisms. All of these interactions operate under the constraint of time. Traditionally, balance (the act of maintaining postural equilibrium) studies have favored simple (i.e., unobstructed) environments, where cues can be controlled, and where response settings are purposely unadorned in an attempt to isolate putatively pure elements of balance control. In many of these types of study, the central nervous system can maintain postural equilibrium using relatively simple righting mechanisms embedded within the most basic levels of the neural hierarchy (e.g., spinal cord and

brainstem) thereby minimizing processing delays. However, many real-life falls occur in complex environments that require flexible decision-making mechanisms (**Figure 1**). Here, a much more distributed neural network must play a role, but this comes at a cost. Processing information in a more expansive network can render a "better" decision but one that is too late to be effective. The solution to this problem is to predict and prepare for our future interactions.

Accumulating evidence indicates that a broad network of high-level neural structures with known adaptive and predictive functions, including the cerebellum, basal ganglia and cerebral cortex, contribute to maintaining postural equilibrium. Given the capacity of these "cognitive" networks to process current and historical information, they are ideally suited to recognize current context in the light of previous experience for the purpose of dynamically anticipating and preparing for action. Such flexibility is important as we move through the world because the actions that are ideal for maintaining postural equilibrium will change with the constraints and opportunities afforded by a particular environment. The additional need to select the most appropriate response from an array of options, while simultaneously suppressing unsuitable, yet potentially automated actions, implies a need for higher-level supervision. It also raises the question of how we combine the utility of rapid, stereotyped compensatory reactions with the need to match our actions to what is permitted by a given environment at a particular moment in time? Insight into this question may arrive from fields of study not traditionally associated with postural control, such as cognitive psychology and even artificial intelligence. This cross pollination of ideas across multiple fields broadens how we view the neural control of balance (1, 2). Specific cross-discipline concepts such as predictive modeling (internals models), affordances for action, and associative learning each have important implications for adapting our movements to maintain postural equilibrium in challenging environments, and provide a way to overcome conflicting demands for goal-directed action at high speed.

FIGURE 1 | Dealing with complex environments often requires behavioral flexibility to maintain postural equilibrium. For example, in cluttered environments it is often necessary to grasp a nearby object to establish a new base of support, while suppressing a highly automatic stepping reaction if an obstacle blocks the foot. The speed and complexity of such sophisticated, goal-directed behaviors necessitates a higher level of control, and implicates a role for advanced preparation based on environmental cues in the control of balance.

Qualifying Statements

Before we begin to examine these concepts, we would like to make clear that the aim of this review is to highlight the many means by which prediction can contribute to postural, and by extension, movement control. Additional compensatory mechanisms are also crucial to the maintenance of our stability, and their omission here is not meant to minimize their importance, but to highlight the oft-neglected contribution prediction plays in these behaviors. In addition, throughout this exploration of prediction we have avoided categorizing predictions based on whether it contributes to a volitionally driven events or to the compensation of externally induced events. Instead, we would like the reader to focus on the importance of certainty in a prediction's utility.

PREDICTING INSTABILITY

Anticipatory Postural Adjustments

To prevent destabilization of the body during volitional movement, postural changes meant to compensate for the disturbance generated by the movement, precede the movement itself (3–7). These anticipatory postural adjustments, or APAs, represent the culmination of a predictive process that estimates the postural disturbance associated with an impending movement. In order to support effective movement APAs must be highly adaptable to enable the close correspondence required between the voluntary act and its associated stabilizing activity.

The generation of APA's, and movement, involve broad interconnected networks that span much of the central nervous system: from the lowest levels of the spinal cord to the brainstem, and ultimately the cerebral cortex. These expansive networks provide the computational power necessary to flexibly adapt APAs to complex and uncertain environments. The spinal circuitry, for example, can be set in advance to shape imminent APA's (see the next section) while further up the neural hierarchy, the brainstem contributes to the coordination and, perhaps, generation of APA's and subsequent movement. Recording electrodes within the pontomedullary reticular formation in the brainstem of cats reveal a population of neurons that operate as a coordinated unit to control one forelimb during a voluntary

reach while stabilizing posture with the other forelimb (8). This observation suggests a basic substrate for linking body segments to provide stability suited to movement demands. In addition, within this region there are also separate populations of neurons that encode the initiation of APAs, the initiation of volitional movement and the combination of the two (9). The divergence in the encoding of APA's and movement suggests at least some independence of the mechanisms underlying the two of them but regions that generate these predictions remain unclear. As we will see, independent encoding of the APA and movement is also prevalent further up the neural hierarchy.

Several higher-level neural networks including the basal ganglia, cerebellum and cerebral cortex—all with roles in learning and adaptation (10)—have also recently been associated with the generation and implementation of anticipatory postural behavior and therefore prediction (11–19). The basal ganglia, for example, is proposed to facilitate reinforcement learning (10) and coincidentally patients with Parkinson's disease, are less able to adapt their APAs to novel contexts (20), in addition to having smaller amplitude and even delayed responses in some instances (21–23). Similarly, the cerebellum is associated with error-based supervised learning, which contributes to the adaptability of APAs. This adaptability is impaired in patients with cerebellar degeneration (15) and such disorders can also lead to changes in the shape and/or timing of APAs (12), but this latter point remains a topic of debate as there are some reports that well-learned relationships remain largely intact following degeneration (24). Lastly, the integrative processing power of the cerebral cortex also provides the functionality to develop high-level associations between sensory stimuli and context specific responses. Recent evidence suggests that both the supplementary and primary motor cortices contribute to the generation of APAs. The supplementary motor area modulates the size of the APAs independently of the associated volitional movement, implying that the APA and movement are represented separately at this stage of processing (11). In addition, patients with lesions of the supplementary motor area have impairments in the shape and timing of their APAs (25) which can be loosely simulated in healthy adults by functional lesion of the supplementary motor area using repetitive transcranial magnetic stimulation (18). In contrast, the primary motor cortex maintains a shared representation of both APA and movement and is proposed to shape the amplitude and timing of APAs (13, 17, 25–28). In general, the cerebral cortex appears to play a key role in refining the mapping of postural adjustments to voluntary acts. As discussed next, cortical involvement in predictive postural control extends beyond the APAs that precede self-initiated movement. The observed increase in excitability of projections from the primary motor cortex to the spinal cord that occurs prior movement (14, 17) implies that the cerebral cortex contributes to setting the state of the spinal cord in anticipation of a postural disturbance so that the spinal circuitry behaves appropriately in the event of a disturbance.

Central Set

Explicit awareness of a forthcoming perturbation is perhaps the most obvious scenario where one can envision a prominent role for prediction in compensatory balance. Essentially many features of a response can be covertly prepared in advance by setting the state, or set, of the central nervous system via descending commands, thereby reducing delays associated with stabilizing an impending movement or generating an appropriate counter reaction. In a seminal exploration of central set, Horak et al. used a fixed-support, platform translation paradigm to investigate systematically the relative influence of central set vs. peripheral drive on generating automatic postural responses (29). Their study exposed participants to varying magnitudes of postural perturbation while researchers controlled the amount of information provided in advance about the size and speed of the impending perturbation. They found that participants scaled the amplitude of their early muscle responses to the expected amplitude of the perturbation, particularly after repeated exposure to a specific platform translation. This result demonstrated that the central nervous system shapes the amplitude of muscle responses based on a prediction, developed over time, of what is going to happen. Presumably, such advance preparation reduces or eliminates the delay with which the body can respond to a perturbation and helps shape the body's response to the perturbation (30–32).

Since the seminal findings of Horak et al. (29), researchers have used more direct measures of corticospinal excitability and spinal reflex modulation to reveal the preparatory activity that occurs in spinal and cortical networks in advance of a predictable perturbation (33). Several electroencephalography studies have shown that prior to a predictable postural disturbance, a slow wave potential builds under central scalp electrodes (34–36). This potential continues to build until the postural disturbance occurs, at which point a separate post-perturbation cortical potential known as the N1 response is observed (36). More recent studies have shown that this anticipatory cortical activity is similar regardless of whether the disturbance is self or externally induced (37) and it scales with the amplitude of the impending perturbation (32). Concurrent changes in the circuitry of the spinal cord accompany these anticipatory cortical potentials (33) implying that the purpose of this cortical activity may be to modify the "central set" or state of the nervous system (35), however, a causal relationship between the two remains to be defined.

Dynamic Prediction of Instability and Sway

Sensory signals indicating an impending loss of balance can stimulate preparatory changes throughout the nervous system to compensate for the future disturbance to equilibrium. Such advance signaling is important because without prediction, online estimates of body position rely on outdated information due to the lag in signal transmission. In many large postural disruptions, advance preparation is necessary to maintain postural equilibrium because there is insufficient time to respond to the disturbance. Thus, the central nervous system must consistently monitor sensory information for evidence of a threat to stability in order to recognize events in advance that might require postural compensation. In some instances, such as during standing balance, specific characteristics of the sway pattern can provide predictive cues as to whether intervention is necessary

to maintain postural equilibrium. Virtual time to contact (VTC) has been proposed as a low dimensional variable that the central nervous system could monitor in order to predict instability during standing balance (38). Specifically, VTC is defined as the time it would take for the body to reach the boundary of our stability if it were to continue on its current trajectory from its current state (position and velocity) with constant acceleration (39). When nearing a loss of balance, changes in the minimum value and variance of the VTC measure are correlated with changes in electroencephalographic power estimated at the anterior cingulate cortex, precuneus and the parietal and occipital lobes (40). The authors propose that since these concomitant changes in VTC and accompanying neural markers precede loss of balance, they provide a predictive cue to the future instability of our posture.

Certain populations may also be at increased risk of falling because they fail to use the most recently available data to predict a coming disturbance to balance. For example, when stepping is induced by an external perturbation, older adults (especially those with higher fall risk) step earlier than young adults once they detect a postural threat, even though the perturbation could have been managed by using a fixed-support reaction (41). This earlier step appears to be a default strategy, absent appropriate scaling to the disturbance, and one that is often insufficient to compensate for the disturbance, thus requiring multiple follow-up adjustments/steps. These findings underscore the value of accurately interpreting the evolving sensory state in the brief time prior to the fall to the generation of appropriate and appropriately scaled corrective actions.

Postural sway itself is also often thought to be, at least partially, the product of a predictive control mechanism. Fitzpatrick et al. (42) examined the gain of postural reflexes during human standing and found it insufficient to maintain postural equilibrium on its own (42). Because of this insufficiency, the authors concluded that the control of sway must involve a feed-forward control component. Moreover, a positive phase shift in lateral gastrocnemius muscle activity relative to ankle loading has also been observed during maintenance of postural equilibrium (43). If sway used only sensory feedback to control ankle muscle stiffness, the muscle's activation pattern should lag ankle loading. In reality however, muscle activation in the lateral gastrocnemius precedes ankle loading suggesting the timing of muscle activation likely involves an anticipatory process. Gatev et al. (43) also questioned whether the sway observed during postural equilibrium is secondary to the control process, i.e. random variance associated with maintaining postural equilibrium, or whether it is the intended consequence of an exploratory control process (43). Recently this hypothesis has been tested and has seen further support (44, 45). Under this control scheme, sway is potentially promoted to allow exploration of the base of support. If true, such exploration could involve the use of forward models (discussed in more depth below) to predict the sensory consequences of the exploration in order to isolate better deviations from expectation. Support for a predictive contribution to sway also arises from the unique control scheme required to control the lower limb during standing balance. Due to a poor match between the stiffness of the connective tissues and musculo-tendinous unit at the ankle, and the load-stiffness of the body (46, 47), the central nervous system is thought to activate the muscles of the lower limb in a predictive and intermittent manner (48–52). However, a recent modeling effort suggests that some of these behaviors could also emerge without a predictive control mechanism (53).

Predicting the Consequences of Ones Actions–Internal Models

One of many important functions of the central nervous system is to learn relationships. These relationships represent our understanding of how our body interacts with itself and the world. In motor control, one prominent encapsulation of these relationships is the abstract concept of an internal model. Internal models represent a learned relationship that can be used, among other things, to generate or simulate behavior, and conceptually it may provide a useful framework to understand how the brain might develop contextually appropriate compensatory behaviors. Neural networks that map a movement to its outcome are called forward models, and they can be used to simulate the sensory consequences of one's actions. Because of their ability to predict movement outcomes, forward models are believed to serve an important role in the supervised learning mechanisms associated with the cerebellum (54–56) by permitting comparison between what the body expects to sense as a consequence of movement, to what it actually senses. Differences between the expected and actual sensory feedback can represent a stimulus that requires compensation, or a prediction/movement error that requires adaptation. A forward model could also be useful to calculate the postural compensation necessary for anticipated disturbances to postural equilibrium. Such mechanisms are proposed to contribute to the control of precision grip because grip force leads changes in grip load. This anticipatory gripping behavior is thought to arise because the central nervous system maintains a model of limb and load dynamics that it uses to generate predictions of the load force acting on the hand, in order to preemptively compensate for anticipated changes in load (57, 58). The use of a forward model is also thought to contribute to stability during proactive stepping and obstacle clearance. Specifically, when taking a step, the body's weight is first shifted to one leg to maintain stability while the other leg is lifted. In order to transfer weight effectively the body may use an internal forward model to estimate whether the APA's have achieved a sufficient shift of the body's weight to maintain stability while the other leg is lifted (41). A similar mechanism aids stability during obstacle avoidance while stepping. In this context, the CNS is thought to predict the destabilizing effect of gravity acting on the body to allow the development of APA's appropriate for controlling body posture while in a single leg stance (59).

In each of the above examples, the forward model provides predictions that are used in the generation of contextually appropriate behavior. However, the behaviors generated from the forward model's predictions could also be formalized as a second type of internal model known as an inverse model. Inverse models receive sensory predictions and generate the motor commands necessary to create the sensory prediction.

When paired with a forward model the combined neural network constitutes a means to generate motor compensation for predicted states of the body. Such a network has been proposed as a model for general sensorimotor learning and control (60–62) and is equally applicable to the subfield of postural control. Indeed, paired forward-inverse models could perform the duties of predicting the postural disturbance as well as generate the appropriate compensatory response from the prediction. From a general perspective, the power of internal models has already been suggested to have evolved in order to contend with conduction velocity delays with a larger body size (63), and this seems particularly relevant in the time-pressured world of compensatory balance.

PATTERN RECOGNITION AND LEARNED ASSOCIATIONS GUIDE FUTURE ACTION

Some patterns occur with such frequency that behaviors are seemingly hard wired into the nervous system. For example, coupling of the motion between body segments occurs so frequently that the movement of one limb often modifies the behavior of another. Modulation in the excitability of motor neurons in the upper limbs often occurs during lower limb tasks, and it suggests an anticipated cooperative integration of the extremities. Normally this contextual modification of motor neuron excitability occurs covertly, but if the limb becomes engaged in a postural task, these changes in excitability can become overt, resembling anticipatory postural responses (64–66). The behavior that results from such anticipatory or linked activities depends on the mechanical or sensory context under which they arise. For example, Esposti and Baldissera (67) suggest that there is an arborized pattern of behaviors from which one, or a select group, could become released from inhibition to affect behavior depending on the context. Release of such behaviors could arise via anticipatory mechanisms or a change in the mechanical or sensory context, such as the innocuous expectancy of visual information (68). These types of behaviors likely also contribute to the higher-level associations that allow us to effectively navigate and interact with complex environments.

The surrounding environment in which we generate a compensatory response is often filled with obstacles and distractions competing for our attention. The increased attentional resources and behavioral flexibility required to navigate these environments presumably raises the risk of a fall [For a comprehensive account of typical causes for falls in an assisted living setting and their relative incidence, see (69)]. As the complexity of the environment increases, the ability to recognize environmental patterns that support successful goal-directed action (and cueing on the most relevant pieces of the scene) becomes more important. For example, during an athletic competition, preparing a menu of possible behaviors based on fragmented, preliminary data can increase efficiency when performing under the time pressure of sports (70). Furthermore, experts are better at identifying relevant information from the visual scene, and do it much quicker than novices, indicating such pattern recognition can be learned. While this example pertains to performance in sport, it is also relevant to postural stability. Specifically, predictive cueing offers a way that the brain can use environmental stimuli presented at a much earlier point in time to identify a potentially successful behavior in the event that it is needed in the future. Central to the concept of predictive cueing is the idea that successful interaction with a specific object is strongly associated with a particular action. For example, a mug with handle is associated with a grasp, whereas while walking, an uncluttered space on the ground in front of you is likely the best location for the next step. Learned associations between the object and our actions such as these are reliant on experience interacting with the world in a variety of contexts. Moreover, the development of these associations likely depends upon the learning and associative power of cortical, basal ganglia, and cerebellar networks as mentioned earlier (10).

Affordances for Action and the Relevance to Balance Recovery

Considerable evidence from animal (71–74) and human research (75–82) has shown that viewing objects strongly associated with particular actions can potentiate these actions, suggesting that we encode our surroundings in terms of the movements the surroundings afford (**Figure 2**). This concept, known as "affordances" (83), has been demonstrated in humans using various neuroimaging and stimulation techniques, including functional Magnetic Resonance Imaging (78, 79) and Transcranial Magnetic Stimulation (TMS) (75–77, 80, 84), as well as behavioral outcomes such as improved reaction time (81). The predictive nature of visual priming based on these affordances is especially relevant given the processing delays inherent to a large, complex nervous system. Such a predictive mechanism potentially holds great value for controlling postural equilibrium.

Although control of postural equilibrium was long thought to be mediated subcortically (85, 86), a large body of evidence now attests to the involvement of the cerebral cortex in the control of postural equilibrium, including compensatory reactions to unexpected postural challenge (32, 33, 87, 88). Perhaps most crucial are compensatory reactions that require the limbs to establish a new base of support and catch a falling center of mass (89–91). Notably, these change-of-support reactions are the only line of defense when a disturbance to posture exceeds a certain threshold. The fact that high-level neural networks can play a role in responding to unexpected external postural perturbations seems remarkable given how quickly these whole-body responses must take place to avoid a fall. However, if suitable responses could be established *prior* to a fall, this would offer a viable solution for producing fast, yet sophisticated "context-appropriate" reactions. Thus, motor affordances could potentially bias specific recovery actions suited to our surroundings, even before the need for such action.

Since Gibson first presented the concept of affordances many years ago (83) several lines of evidence support the basic idea of affordances including animal studies that have identified premotor neurons activated by the mere appearance of graspable objects known as *canonical* neurons (74). Furthermore, human studies have demonstrated a measurable link between simple

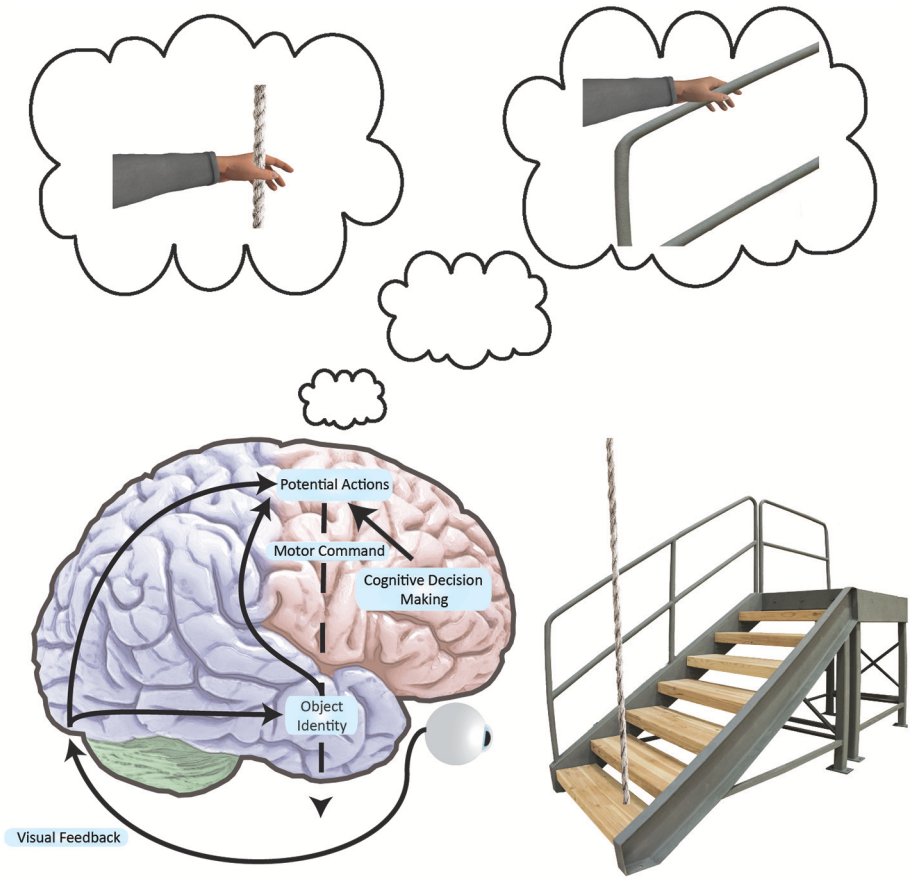


FIGURE 2 | Simplified neural networks underlying an affordance to grasp. Black arrows indicate how the brain converts visual information into movement plans for a variety of possible actions. As movements are encoded in frontal and parietal networks, action representations compete with one another. These actions are biased by the basal ganglia and prefrontal cortex at multiple locations in the brain as per the affordance competition model (103, 104)**.** We act when one of the possible actions wins the competition. In this example, we see that the stairs have a supporting railing. The railing affords a grasp and the rope affords a grasp, but since the railing is more stable, the railing grasp is primed. If the grasp is the most salient afforded action, we may execute it in the event of a stumble. Here, it is important to note that such directed arm action would conceivably be prompted by viewing a supportive handle—a handle associated with postural recovery from past experience. Furthermore, such action would only exist as an internal representation until called upon.

object observation and motor cortical activation even with no requirement to move (77). Remarkably, the rare clinical condition of alien hand syndrome (which sometimes results from a stroke in the frontal lobes) also offers support for this idea (92). These patients lack inhibitory oversight and instead are irresistibly compelled to interact with surrounding objects. These interactions are not random but give the appearance of goal-directed movement, despite a reported lack of intention to move.

While these concepts have not been considered in the domain of compensatory balance reactions, the potential applicability of setting contingent responses based upon the environment in advance is clear. Consider for example walking down a hallway with a handrail anchored along the wall. According to the notion of perceived affordances, arm movements may be prompted by simply viewing these handrails while any overt movement would remain dormant (or actively inhibited) until needed. In this instance, one can begin to see how such a mechanism holds great relevance for enlisting a rapid reach-to-handle reaction if a challenge to postural equilibrium occurs. Essentially, a contingent motor response may be automatically dictated by perception of the surrounding world and called into action (or released from inhibition) when circumstances warrant this action. Recently, the excitability of corticospinal projections to specific grasping muscles was shown to be modulated when participant's simply viewed a wall-mounted safety handle (93). This result provides some initial support for the idea that viewing an object associated with balance recovery can modify central nervous system activity.

Another important consideration when encoding the world in terms of afforded motor actions is that sometimes the environment will contain obstructions to potential actions. Understandably, the central nervous system should avoid priming actions that bring the body into an obstruction, requiring the inhibition of inappropriate actions. Inhibition is particularly important in situations when postural equilibrium is

disturbed and there is an obstacle preventing a recovery step. In such a case, equilibrium would normally be recovered by taking a forward step to prevent a forward fall, but doing so would accentuate the fall. This stepping response is salient given the highly automated nature of a recovery step used to recapture a falling center of mass (90, 91). Thus, an important aspect of pre-setting compensatory behavior prior to a fall would involve facilitation of appropriate action, as well as suppression of pre-potent but inappropriate action based on environmental context. The ability to override automatic, but unwanted actions and to filter out distracting information, ultimately relies upon oversight by the prefrontal cortex (94) suggesting it may play an important role in fall resistance.

NEURAL NETWORKS INVOLVED IN PLANNING FUTURE ACTIONS

At this point, we have reviewed various predictive mechanisms that could contribute to the control of postural equilibrium. Essential to all these mechanisms is the capacity to adapt or learn from experience to inform future action. Not surprisingly, a commonality among the various aspects of prediction is their association with cortical, basal ganglia and cerebellar networks. Each of these anatomical regions has been proposed to implement its own unique learning algorithm that could be used to develop and refine posture related predictions (10). Learning in the cerebral cortex is thought to occur through Hebbian plasticity, an "unsupervised" learning mechanism. Hebbian plasticity is based on the idea that temporally synchronous and causally related firing among networks of neurons results in a strengthening of the relationship between the two networks. This form of learning attempts to "map" associations in which a quantifiable error signal is absent and this 'mapping' may underlie the recognition and association of sensory cues deleterious to posture with their appropriate response. The basal ganglia, in contrast, is thought to shape our behavior through reinforcement learning. Reinforcement learning is a process where correct behaviors are rewarded to facilitate learning and this reward signal, and subsequent change in reward signal, is encoded by dopaminergic fibers from the substantia nigra within the basal ganglia (10). Behaviors, such as motor action, are selected in this learning paradigm by maximizing the predicted reward that each option could bring. Such a mechanism could be ideal for the selection and reinforcement of appropriate compensatory actions resulting from a loss of stability. Lastly, the cerebellum is proposed to implement an error based "supervised" learning mechanism whereby the consequences of our actions are predicted and compared to reality. The difference between the prediction and reality can be used to adjust our predictions, but also represents a disturbance to posture that must be reactively compensated for. Together, with the thalamus, these neural networks develop the associations between particular contexts, probable scenario's and appropriately matched compensatory behaviors that sub-serve predictive postural control as well as refine reactive postural mechanisms. As a final point, a characteristic of predictive control is the ability to regulate relative timing of events, such as the coupling of an APA prior to stepping. For example, a voluntary step would need to be actively delayed until sufficient weight transfer occurs through an APA (41). Such control over relative sequencing of events relies upon a time buffer or memory of sequence fragments (95), which suggests cerebellar involvement (96), as well as prefrontal cortex due to its important role in working memory (97, 98).

IMPROVING EXPERIMENTAL DESIGN TO EXPOSE AND EMPHASIZE PREDICTIVE ROLES

A big reason we fail to understand prediction's contribution to reactive balance may be due to the simplicity of research protocols that are frequently used. The status quo in postural equilibrium research is to provide relatively small perturbations in clutter-free environments, with an emphasis on fixed support (feet-in-place) reactions. However, when perturbations are large, change-of-support reactions are the only option to recovery stability (90, 91). Daily life often imposes obstacles, while also providing various movement options that can help us regain balance. In some cases, obstacles force a selection process requiring a limb to target a new support base if a loss of balance occurs. As the need for behavioral adaptation rises, so does the demand on higher brain resources (and foresight), particularly when we use the arms or legs to establish a new base of support amid complex surroundings. To truly emphasize the contribution of prediction to reactive balance, researchers may need to reintroduce the clutter and force a change-of-support strategy with the limbs.

Reliance on external measures such as muscle onsets, ground reaction forces, and video motion capture to infer neural processes may also limit our perspective on the control process involved in maintaining posture. Such external measures can miss what the central nervous system is doing to help us avoid a fall. In fact, this problem is compounded when you consider that much of what the brain may do to prevent a fall in complex environments may happen *before* the fall. This includes predicting future instability (40), building visuospatial maps as we move through our environment (99), and possibly forming contingencies based upon the environment even without foreknowledge of a fall (100). Without the use of direct neurophysiological probes, it is difficult to reveal such preparatory behavior.

Study designs that emphasize direct neural measures and change-of-support reactions within cluttered environments pose significant methodological challenges. However, these study designs also have great potential to reveal the predictive mechanisms underlying fall avoidance in the complex settings encountered in daily life. Thus, using direct neurophysiological stimuli or measures such as Transcranial Magnetic Stimulation (TMS), Electroencephalography, and/or functional Near-infrared Spectroscopy in the period *before* and after postural perturbation could provide important experimental advances. Furthermore, research designs where the limbs are required to establish a new base of support, all within cluttered and

choice-demanding environments, could expose higher brain processes where prediction is necessary to respond appropriately to a loss of stability. This combination of experimental features represents an important innovation in the field to expose how the brain contributes to fall resistance in complex, real-life settings.

CONCLUSIONS

Some of the ways in which prediction contributes to balance are now well understood, particularly in cases where self-initiated movement needs to be stabilized or when we need to counter a known perturbation originating from an external source. Both of these instances hinge on past-experience and learning to match postural adjustments with an internal representation of the forthcoming disruption to equilibrium. Perhaps less intuitive is how predictive mechanisms can operate behind the scenes to prepare contingent actions based on cues and contexts that have been implicitly acquired through interactive experience with the world. Such associative learning has been studied in fields outside the domain of postural control, but may hold great significance for regulating postural equilibrium in an unstable and choice-demanding world. Prediction, in theory, offers an important way that higher neural networks contribute to speeded recovery actions. Indeed, the need to forecast future instability and plan appropriate countermeasures may explain (at least partly) the correlation between cognitive decline and falls (101, 102). Determining how predictive mechanisms impact balance recovery will require some revision to traditional research paradigms that "start the clock" only after the perturbation has occurred. Furthermore, the use of simplistic lab settings may fail to sufficiently expose a need for predictive mechanisms and inadvertently bias our understanding of how balance is controlled to favor lower reflexes. Research designs frequently operate from a framework where postural reactions are purely reactive without the help of foresight. Therefore, broadening this perspective to consider the potential role for prediction in the field of balance control could begin to fill an important gap in understanding the mechanisms for how cognitive resources influence resistance to falls.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

REFERENCES

1. Horak FB. Postural orientation and equilibrium: what do we need to know about neural control of balance to prevent falls? *Age Ageing* (2006) 35 (Suppl. 2):7–11. doi: 10.1093/ageing/afl077
2. Ivanenko Y, Gurfinkel VS. Human postural control. *Front Neurosci.* (2018) 12:171. doi: 10.3389/fnins.2018.00171
3. Massion J. Movement, posture and equilibrium: interaction and coordination. *Prog Neurobiol.* (1992) 38:35–56. doi: 10.1016/0301-0082(92)90034-C
4. Belenkii VE, Gurfinkel VS, Paltsev EI. On the control elements of voluntary movements. *Biofizika* (1967) 12:135–41.
5. Bouisset S, Zattara M. A sequence of postural movements precedes voluntary movement. *Neurosci Lett.* (1981) 22:263–70. doi: 10.1016/0304-3940(81)90117-8
6. Cordo PJ, Nashner LM. Properties of postural adjustments associated with rapid arm movements. *J Neurophysiol.* (1982) 47:287–302. doi: 10.1152/jn.1982.47.2.287
7. Lee WA. Anticipatory control of postural and task muscles during rapid arm flexion. *J Mot Behav.* (1980) 12:185–96. doi: 10.1080/00222895.1980.10735219
8. Schepens B, Stapley P, Drew T. Neurons in the pontomedullary reticular formation signal posture and movement both as an integrated behavior and independently. *J Neurophysiol.* (2008) 100:2235–53. doi: 10.1152/jn.01381.2007
9. Schepens B, Drew T. Independent and convergent signals from the pontomedullary reticular formation contribute to the control of posture and movement during reaching in the cat. *J Neurophysiol.* (2004) 92:2217–38. doi: 10.1152/jn.01189.2003
10. Doya K. Complementary roles of basal ganglia and cerebellum in learning and motor control. *Curr Opin Neurobiol.* (2000) 10:732–9. doi: 10.1016/S0959-4388(00)00153-7
11. Bolzoni F, Bruttini C, Esposti R, Castellani C, Cavallari P. Transcranial direct current stimulation of SMA modulates anticipatory postural adjustments without affecting the primary movement. *Behav Brain Res.* (2015) 291:407–13. doi: 10.1016/j.bbr.2015.05.044
12. Bruttini C, Esposti R, Bolzoni F, Vanotti A, Mariotti C, Cavallari P. Temporal disruption of upper-limb anticipatory postural adjustments in cerebellar ataxic patients. *Exp Brain Res.* (2015) 233:197–203. doi: 10.1007/s00221-014-4103-x
13. Caronni A, Cavallari P. Supra-spinal circuits shape inhibitory postural adjustments anticipating voluntary index-finger flexion. *Exp Brain Res.* (2009) 198:19–28. doi: 10.1007/s00221-009-1931-1
14. Chiou S-Y, Hurry M, Reed T, Quek JX, Strutton PH. Cortical contributions to anticipatory postural adjustments in the trunk. *J Physiol.* (2018) 596:1295–306. doi: 10.1113/JP275312
15. Diedrichsen J, Verstynen T, Lehman SL, Ivry RB. Cerebellar Involvement in anticipating the consequences of self-produced actions during bimanual movements. *J Neurophysiol.* (2005) 93:801–12. doi: 10.1152/jn.00662.2004
16. Ng THB, Sowman PF, Brock J, Johnson BW. Neuromagnetic brain activity associated with anticipatory postural adjustments for bimanual load lifting. *NeuroImage* (2013) 66:343–52. doi: 10.1016/j.neuroimage.2012.10.042
17. Petersen TH, Rosenberg K, Petersen NC, Nielsen JB. Cortical involvement in anticipatory postural reactions in man. *Exp Brain Res.* (2009) 193:161. doi: 10.1007/s00221-008-1603-6
18. Richard A, Van Hamme A, Drevelle X, Golmard J-L, Meunier S, Welter M-L. Contribution of the supplementary motor area and the cerebellum to the anticipatory postural adjustments and execution phases of human gait initiation. *Neuroscience* (2017) 358:181–9. doi: 10.1016/j.neuroscience.2017.06.047
19. Varghese JP, Merino DM, Beyer KB, McIlroy WE. Cortical control of anticipatory postural adjustments prior to stepping. *Neuroscience* (2016) 313:99–109. doi: 10.1016/j.neuroscience.2015.11.032
20. Massion J, Ioffe M, Schmitz C, Viallet F, Gantcheva R. Acquisition of anticipatory postural adjustments in a bimanual load-lifting task: normal and pathological aspects. *Exp Brain Res.* (1999) 128:229–35. doi: 10.1007/s002210050842
21. Bleuse S, Cassim F, Blatt J-L, Labyt E, Bourriez J-L, Derambure P, et al. Anticipatory postural adjustments associated with arm movement in Parkinson's disease: a biomechanical analysis. *J Neurol Neurosurg Psychiatry* (2008) 79:881–7. doi: 10.1136/jnnp.2006.107318
22. Lee RG, Tonolli I, Viallet F, Aurenty R, Massion J. Preparatory postural adjustments in parkinsonian patients with postural instability. *Can J Neurol Sci.* (1995) 22:126–35. doi: 10.1017/S0317167100040208

23. Rocchi L, Chiari L, Mancini M, Carlson-Kuhta P, Gross A, Horak FB. Step initiation in Parkinson's disease: influence of initial stance conditions. *Neurosci Lett.* (2006) 406:128–32. doi: 10.1016/j.neulet.2006.07.027
24. Timmann D, Horak F. Perturbed step initiation in cerebellar subjects: 2. Modification of anticipatory postural adjustments. *Exp Brain Res.* (2001) 141:110–20. doi: 10.1007/s002210100858
25. Viallet F, Massion J, Massarino R, Khalil R. Coordination between posture and movement in a bimanual load lifting task: putative role of a medial frontal region including the supplementary motor area. *Exp Brain Res.* (1992) 88:674–84. doi: 10.1007/BF00228197
26. Bolzoni F, Bruttini C, Esposti R, Cavallari P. Hand immobilization affects arm and shoulder postural control. *Exp Brain Res.* (2012) 220:63–70. doi: 10.1007/s00221-012-3115-7
27. Bruttini C, Esposti R, Bolzoni F, Cavallari P. Ischemic block of the forearm abolishes finger movements but not their associated anticipatory postural adjustments. *Exp Brain Res.* (2014) 232:1739–50. doi: 10.1007/s00221-014-3866-4
28. Yakovenko S, Drew T. A motor cortical contribution to the anticipatory postural adjustments that precede reaching in the cat. *J Neurophysiol.* (2009) 102:853–74. doi: 10.1152/jn.00042.2009
29. Horak FB, Diener HC, Nashner LM. Influence of central set on human postural responses. *J Neurophysiol.* (1989) 62:841–53.
30. Coelho DB, Teixeira LA. Cognition and balance control: does processing of explicit contextual cues of impending perturbations modulate automatic postural responses? *Exp Brain Res.* (2017) 235:2375–90. doi: 10.1007/s00221-017-4980-x
31. Hammond PH. The influence of prior instruction to the subject on an apparently involuntary neuro-muscular response. *J Physiol.* (1956) 132:17–8.
32. Mochizuki G, Boe S, Marlin A, McIlRoy WE. Perturbation-evoked cortical activity reflects both the context and consequence of postural instability. *Neuroscience* (2010) 170:599–609. doi: 10.1016/j.neuroscience.2010.07.008
33. Wälchli M, Tokuno CD, Ruffieux J, Keller M, Taube W. Preparatory cortical and spinal settings to counteract anticipated and non-anticipated perturbations. *Neuroscience* (2017) 365:12–22. doi: 10.1016/j.neuroscience.2017.09.032
34. Adkin AL, Campbell AD, Chua R, Carpenter MG. The influence of postural threat on the cortical response to unpredictable and predictable postural perturbations. *Neurosci Lett.* (2008) 435:120–5. doi: 10.1016/j.neulet.2008.02.018
35. Jacobs JV, Fujiwara K, Tomita H, Furune N, Kunita K, Horak FB. Changes in the activity of the cerebral cortex relate to postural response modification when warned of a perturbation. *Clin Neurophysiol.* (2008) 119:1431–42. doi: 10.1016/j.clinph.2008.02.015
36. Mochizuki G, Sibley KM, Esposito JG, Camilleri JM, McIlroy WE. Cortical responses associated with the preparation and reaction to full-body perturbations to upright stability. *Clin Neurophysiol Int Fed Clin Neurophysiol.* (2008) 119:1626–37. doi: 10.1016/j.clinph.2008.03.020
37. Mochizuki G, Sibley KM, Cheung HJ, Camilleri JM, McIlroy WE. Generalizability of perturbation-evoked cortical potentials: independence from sensory, motor and overall postural state. *Neurosci Lett.* (2009) 451:40–4. doi: 10.1016/j.neulet.2008.12.020
38. Slobounov SM, Slobounova ES, Newell KM. Virtual time-to-collision and human postural control. *J Mot Behav.* (1997) 29:263–81. doi: 10.1080/00222899709600841
39. Haibach PS, Slobounov SM, Slobounova ES, Newell KM. Virtual time-to-contact of postural stability boundaries as a function of support surface compliance. *Exp Brain Res.* (2007) 177:471–82. doi: 10.1007/s00221-006-0703-4
40. Slobounov S, Cao C, Jaiswal N, Newell KM. Neural basis of postural instability identified by VTC and EEG. *Exp Brain Res.* (2009) 199:1–16. doi: 10.1007/s00221-009-1956-5
41. Rogers MW, Mille M-L. Timing paradox of stepping and falls in ageing: not so quick and quick(er) on the trigger. *J Physiol.* 594:4537–47. doi: 10.1113/JP271167
42. Fitzpatrick R, Burke D, Gandevia SC. Loop gain of reflexes controlling human standing measured with the use of postural and vestibular disturbances. *J Neurophysiol.* (1996) 76:3994–4008. doi: 10.1152/jn.1996.76.6.3994
43. Gatev P, Thomas S, Kepple T, Hallett M. Feedforward ankle strategy of balance during quiet stance in adults. *J Physiol.* (1999) 514:915–928. doi: 10.1111/j.1469-7793.1999.915ad.x
44. Carpenter MG, Murnaghan CD, Inglis JT. Shifting the balance: evidence of an exploratory role for postural sway. *Neuroscience* (2010) 171:196–204. doi: 10.1016/j.neuroscience.2010.08.030
45. Murnaghan CD, Carpenter MG, Chua R, Inglis JT. Keeping still doesn't "make sense": examining a role for movement variability by stabilizing the arm during a postural control task. *J Neurophysiol.* (2016) 117:846–52. doi: 10.1152/jn.01150.2015
46. Fitzpatrick RC, Taylor JL, McCloskey DI. Ankle stiffness of standing humans in response to imperceptible perturbation: reflex and task-dependent components. *J Physiol.* (1992) 454:533–547. doi: 10.1113/jphysiol.1992.sp019278
47. Loram ID, Lakie M. Direct measurement of human ankle stiffness during quiet standing: the intrinsic mechanical stiffness is insufficient for stability. *J Physiol.* (2002) 545:1041–53. doi: 10.1113/jphysiol.2002.025049
48. Finley JM, Dhaher YY, Perreault EJ. Contributions of feed-forward and feedback strategies at the human ankle during control of unstable loads. *Exp Brain Res.* (2012) 217:53–66. doi: 10.1007/s00221-011-2972-9
49. Gawthrop P, Loram I, Gollee H, Lakie M. Intermittent control models of human standing: similarities and differences. *Biol Cybern.* (2014) 108:159–68. doi: 10.1007/s00422-014-0587-5
50. Gawthrop P, Loram I, Lakie M, Gollee H. Intermittent control: a computational theory of human control. *Biol Cybern.* (2011) 104:31–51. doi: 10.1007/s00422-010-0416-4
51. Gawthrop P, Loram I, Lakie M. Predictive feedback in human simulated pendulum balancing. *Biol Cybern.* (2009) 101:131–46. doi: 10.1007/s00422-009-0325-6
52. Loram ID, Lakie M. Human balancing of an inverted pendulum: position control by small, ballistic-like, throw and catch movements. *J Physiol.* (2002) 540:1111–24. doi: 10.1113/jphysiol.2001.013077
53. Elias LA, Watanabe RN, Kohn AF. Spinal mechanisms may provide a combination of intermittent and continuous control of human posture: predictions from a biologically based neuromusculoskeletal model. *PLoS Comput Biol.* (2014) 10:e1003944. doi: 10.1371/journal.pcbi.1003944
54. Brooks JX, Carriot J, Cullen KE. Learning to expect the unexpected: rapid updating in primate cerebellum during voluntary self-motion. *Nat Neurosci.* (2015) 18:1310–7. doi: 10.1038/nn.4077
55. Pasalar S, Roitman AV, Durfee WK, Ebner TJ. Force field effects on cerebellar Purkinje cell discharge with implications for internal models. *Nat Neurosci.* (2006) 9:1404–11. doi: 10.1038/nn1783
56. Popa LS, Hewitt AL, Ebner TJ. Predictive and feedback performance errors are signaled in the simple spike discharge of individual Purkinje cells. *J Neurosci.* (2012) 32:15345–58. doi: 10.1523/JNEUROSCI.2151-12.2012
57. Flanagan JR, Wing AM. The role of internal models in motion planning and control: evidence from grip force adjustments during movements of hand-held loads. *J Neurosci.* (1997) 17:1519–28. doi: 10.1523/JNEUROSCI.17-04-01519.1997
58. Wing AM, Flanagan JR, Richardson J. Anticipatory postural adjustments in stance and grip. *Exp Brain Res.* (1997) 116:122–30. doi: 10.1007/PL00005732
59. Yiou E, Artico R, Teyssedre CA, Labaune O, Fourcade P. Anticipatory postural control of stability during gait Initiation over obstacles of different height and distance made under reaction-time and self-Initiated instructions. *Front Hum Neurosci.* (2016) 10:449. doi: 10.3389/fnhum.2016.00449
60. Haruno M, Wolpert DM, Kawato M. MOSAIC Model for sensorimotor learning and control. *Neural Comput.* (2001) 13:2201–20. doi: 10.1162/089976601750541778
61. Haruno M, Wolpert DM, Kawato M. Hierarchical MOSAIC for movement generation. *Int Congr Ser.* (2003) 1250:575–90. doi: 10.1016/S0531-5131(03)00190-0
62. Wolpert DM, Kawato M. Multiple paired forward and inverse models for motor control. *Neural Netw.* (1998) 11:1317–29. doi: 10.1016/S0893-6080(98)00066-5
63. More HL, Hutchinson JR, Collins DF, Weber DJ, Aung SK, Donelan JM. Scaling of sensorimotor control in terrestrial mammals. *Proc Biol Sci R Soc.* (2010) 277:3563–8. doi: 10.1098/rspb.2010.0898

64. Cerri G, Borroni P, Baldissera F. Cyclic H-reflex modulation in resting forearm related to contractions of foot movers, not to foot movement. *J Neurophysiol.* (2003) 90:81–8. doi: 10.1152/jn.00030.2003
65. Borroni P, Cerri G, Baldissera F. Excitability changes in resting forearm muscles during voluntary foot movements depend on hand position: a neural substrate for hand–foot isodirectional coupling. *Brain Res.* (2004) 1022:117–25. doi: 10.1016/j.brainres.2004.07.003
66. Baldissera F, Esposti R. Postural constraints to coupling of ipsilateral hand–foot movements. *NeuroReport* (2005) 16:1615. doi: 10.1097/01.wnr.0000181586.49130.48
67. Esposti R, Baldissera FG. Combined recruitment of two fixation chains during cyclic movements of one arm. *Hum Mov Sci.* (2011) 30:213–26. doi: 10.1016/j.humov.2010.02.005
68. Esposti R, Bruttini C, Bolzoni F, Cavallari P. Anticipatory postural adjustments associated with reaching movements are programmed according to the availability of visual information. *Exp Brain Res.* (2017) 235:1349–60. doi: 10.1007/s00221-017-4898-3
69. Robinovitch SN, Feldman F, Yang Y, Schonnop R, Leung PM, Sarraf T, et al. Video capture of the circumstances of falls in elderly people residing in long-term care: an observational study. *Lancet* (2013) 381:47–54. doi: 10.1016/S0140-6736(12)61263-X
70. Yarrow K, Brown P, Krakauer JW. Inside the brain of an elite athlete: the neural processes that support high achievement in sports. *Nat Rev Neurosci.* (2009) 10:585–96. doi: 10.1038/nrn2672
71. Cisek P, Kalaska JF. Neural correlates of reaching decisions in dorsal premotor cortex: specification of multiple direction choices and final selection of action. *Neuron* (2005) 45:801–14. doi: 10.1016/j.neuron.2005.01.027
72. Murata A, Fadiga L, Fogassi L, Gallese V, Raos V, Rizzolatti G. Object representation in the ventral premotor cortex (Area F5) of the Monkey. *J Neurophysiol.* (1997) 78:2226–30.
73. Rizzolatti G, Camarda R, Fogassi L, Gentilucci M, Luppino G, Matelli M. Functional organization of inferior area 6 in the macaque monkey. *Exp Brain Res.* (1988) 71:491–507. doi: 10.1007/BF00248742
74. Rizzolatti G, Fadiga L. Grasping objects and grasping action meanings: the dual role of monkey rostroventral premotor cortex (area F5). *Novartis Found Symp.* (1998) 218:81–95; discussion 95–103.
75. Buccino G, Sato M, Cattaneo L, Rodà F, Riggio L. Broken affordances, broken objects: a TMS study. *Neuropsychologia* (2009) 47:3074–8. doi: 10.1016/j.neuropsychologia.2009.07.003
76. Cardellicchio P, Sinigaglia C, Costantini M. The space of affordances: a TMS study. *Neuropsychologia* (2011) 49:1369–72. doi: 10.1016/j.neuropsychologia.2011.01.021
77. Franca M, Turella L, Canto R, Brunelli N, Allione L, Andreasi NG, et al. Corticospinal facilitation during observation of graspable objects: a transcranial magnetic stimulation study. *PLoS ONE* (2012) 7:e49025. doi: 10.1371/journal.pone.0049025
78. Grafton ST, Fadiga L, Arbib MA, Rizzolatti G. Premotor cortex activation during observation and naming of familiar tools. *NeuroImage* (1997) 6:231–6. doi: 10.1006/nimg.1997.0293
79. Grèzes J, Tucker M, Armony J, Ellis R, Passingham RE. Objects automatically potentiate action: an fMRI study of implicit processing. *Eur J Neurosci.* (2003) 17:2735–40. doi: 10.1046/j.1460-9568.2003.02695.x
80. Makris S, Hadar AA, Yarrow K. Viewing objects and planning actions: on the potentiation of grasping behaviours by visual objects. *Brain Cogn.* (2011) 77:257–64. doi: 10.1016/j.bandc.2011.08.002
81. Tucker M, Ellis R. On the relation between seen objects and components of potential actions. *J Exp Psychol Hum Percept Perform.* (1998) 24:830–46. doi: 10.1037/0096-1523.24.3.830
82. Tucker M, Ellis R. Action priming by briefly presented objects. *Acta Psychol.* (2004) 116:185–203. doi: 10.1016/j.actpsy.2004.01.004
83. Gibson JJ. *The Ecological Approach to Visual Perception*. Boston, MA: Houghton Mifflin (1979).
84. Makris S, Hadar AA, Yarrow K. Are object affordances fully automatic? A case of covert attention. *Behav Neurosci.* (2013) 127:797–802. doi: 10.1037/a0033946
85. Magnus R. Cameron prize lectures on some results of studies in the physiology of posture. *Lancet* (1926) 208:583–632.
86. Sherrington CS. Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing. *J Physiol.* (1910) 40:28–121.
87. Bolton DA, Patel R, Staines WR, McIlroy WE. Transient inhibition of primary motor cortex suppresses hand muscle responses during a reactive reach to grasp. *Neurosci Lett.* (2011) 504:83–7. doi: 10.1016/j.neulet.2011.09.001
88. Bolton DA, Williams L, Staines WR, McIlroy WE. Contribution of primary motor cortex to compensatory balance reactions. *BMC Neurosci.* (2012) 13:102. doi: 10.1186/1471-2202-13-102
89. Maki BE, Cheng KC, Mansfield A, Scovil CY, Perry SD, Peters AL, et al. Preventing falls in older adults: new interventions to promote more effective change-in-support balance reactions. *J Electromyogr Kinesiol.* (2008) 18:243–54. doi: 10.1016/j.jelekin.2007.06.005
90. Maki BE, McIlroy WE, Fernie GR. Change-in-support reactions for balance recovery. *IEEE Eng Med Biol Mag.* (2003) 22:20–26. doi: 10.1109/memb.2003.1195691
91. Maki BE, McIlroy WE. The role of limb movements in maintaining upright stance: the "change-in-support" strategy. *Phys Ther.* (1997) 77:488–507.
92. Prochazka A, Clarac F, Loeb GE, Rothwell JC, Wolpaw JR. What do reflex and voluntary mean? Modern views on an ancient debate. *Exp Brain Res.* (2000) 130:417–32. doi: 10.1007/s002219900250
93. McDannald DW, Mansour M, Rydalch G, Bolton DAE. Motor affordance for grasping a safety handle. *Neurosci Lett.* (2018) 683:131–37. doi: 10.1016/j.neulet.2018.05.040
94. Fuster JM. *The Prefrontal Cortex*. San Diego, CA: Academic Press (2008).
95. Morasso PG, Baratto L, Capra R, Spada G. Internal models in the control of posture. *Neural Netw.* (1999) 12:1173–80. doi: 10.1016/S0893-6080(99)00058-1
96. Braitenberg V, Heck D, Sultan F. The detection and generation of sequences as a key to cerebellar function: experiments and theory. *Behav Brain Sci.* (1997) 20:229–45.
97. Müller NG, Knight RT. The functional neuroanatomy of working memory: contributions of human brain lesion studies. *Neuroscience* (2006) 139:51–8. doi: 10.1016/j.neuroscience.2005.09.018
98. D'Esposito M, Detre JA, Alsop DC, Shin RK, Atlas S, Grossman M. The neural basis of the central executive system of working memory. *Nature* (1995) 378:279–81. doi: 10.1038/378279a0
99. Maki BE, McIlroy WE. Cognitive demands and cortical control of human balance-recovery reactions. *J Neural Transm.* (2007) 114:1279–96. doi: 10.1007/s00702-007-0764-y
100. Bolton DA. The role of the cerebral cortex in postural responses to externally induced perturbations. *Neurosci Biobehav Rev.* (2015) 57:142–55. doi: 10.1016/j.neubiorev.2015.08.014
101. Herman T, Mirelman A, Giladi N, Schweiger A, Hausdorff JM. Executive control deficits as a prodrome to falls in healthy older adults: a prospective study linking thinking, walking, and falling. *J Gerontol Biol Sci Med Sci.* (2010) 65:1086–92. doi: 10.1093/gerona/glq077
102. Mirelman A, Herman T, Brozgol M, Dorfman M, Sprecher E, Schweiger A, et al. Executive function and falls in older adults: new findings from a five-year prospective study link fall risk to cognition. *PLoS ONE* (2012) 7:e40297. doi: 10.1371/journal.pone.0040297
103. Cisek P. Cortical mechanisms of action selection: the affordance competition hypothesis. *Philos Trans R Soc LondonSeries B Biol Sci.* (2007) 362:1585–99. doi: 10.1098/rstb.2007.2054
104. Cisek P, Kalaska JF. Neural mechanisms for interacting with a world full of action choices. *Annu Rev Neurosci.* (2010) 33:269–98. doi: 10.1146/annurev.neuro.051508.135409

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

REVIEW
published: 12 November 2018
doi: 10.3389/fneur.2018.00944

Potential Mechanisms of Sensory Augmentation Systems on Human Balance Control

Kathleen H. Sienko[1], Rachael D. Seidler[2], Wendy J. Carender[3], Adam D. Goodworth[4], Susan L. Whitney[5] and Robert J. Peterka[6]*

[1] Department of Mechanical Engineering, University of Michigan, Ann Arbor, MI, United States, [2] Department of Applied Physiology and Kinesiology, University of Florida, Gainesville, FL, United States, [3] Michigan Balance Vestibular Testing and Rehabilitation, Department of Otolaryngology, Michigan Medicine, Ann Arbor, MI, United States, [4] Department of Rehabilitation Sciences, University of Hartford, Hartford, CT, United States, [5] Departments of Physical Therapy and Otolaryngology, University of Pittsburgh, Pittsburgh, PA, United States, [6] Department of Neurology, Oregon Health & Science University and National Center for Rehabilitative Auditory Research, VA Portland Health Care System, Portland, OR, United States

Numerous studies have demonstrated the real-time use of visual, vibrotactile, auditory, and multimodal sensory augmentation technologies for reducing postural sway during static tasks and improving balance during dynamic tasks. The mechanism by which sensory augmentation information is processed and used by the CNS is not well understood. The dominant hypothesis, which has not been supported by rigorous experimental evidence, posits that observed reductions in postural sway are due to sensory reweighting: feedback of body motion provides the CNS with a correlate to the inputs from its intact sensory channels (e.g., vision, proprioception), so individuals receiving sensory augmentation learn to increasingly depend on these intact systems. Other possible mechanisms for observed postural sway reductions include: cognition (processing of sensory augmentation information is solely cognitive with no selective adjustment of sensory weights by the CNS), "sixth" sense (CNS interprets sensory augmentation information as a new and distinct sensory channel), context-specific adaptation (new sensorimotor program is developed through repeated interaction with the device and accessible only when the device is used), and combined volitional and non-volitional responses. This critical review summarizes the reported sensory augmentation findings spanning postural control models, clinical rehabilitation, laboratory-based real-time usage, and neuroimaging to critically evaluate each of the aforementioned mechanistic theories. Cognition and sensory re-weighting are identified as two mechanisms supported by the existing literature.

Keywords: biofeedback, sensory substitution, sensory augmentation, balance, sensory reweighting, balance prosthesis

OPEN ACCESS

Edited by:
Emily Keshner,
Temple University, United States

Reviewed by:
Robert Francis Burkard,
University at Buffalo, United States
L. Eduardo Cofré Lizama,
The University of Melbourne, Australia

****Correspondence:***
Kathleen H. Sienko
sienko@umich.edu

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *01 August 2018*
Accepted: *22 October 2018*
Published: *12 November 2018*

Citation:
Sienko KH, Seidler RD, Carender WJ, Goodworth AD, Whitney SL and Peterka RJ (2018) Potential Mechanisms of Sensory Augmentation Systems on Human Balance Control. Front. Neurol. 9:944. doi: 10.3389/fneur.2018.00944

INTRODUCTION

Active sensory augmentation (SA) for balance control is the focus of this critical review (1). We particularly highlight vibrotactile feedback but include other modalities of SA as well. We define SA as the delivery of additional sensory cues (e.g., via auditory, tactile, or visual modalities) that convey pertinent information about body orientation for balance. Passive forms of SA, such as mirrors,

have been used during stroke rehabilitation (2, 3) and for treating phantom pain in amputees (4) since the 1990s. The first active form of SA was developed in the 1960s by Bach-y-Rita to provide vibrotactile cues to inform people with visual impairments about the location of an object (5). Shortly thereafter, the Naval Aerospace Medical Research Laboratory developed and piloted the Tactile Situation Awareness System (TSAS), an array of vibrotactile actuators worn on the torso, to augment a pilot's situational awareness and provide information about orientation and targeting (6). In the 1990's Wall adapted the TSAS concept for people with vestibular deficits (7) and Allum developed a multimodal feedback display for people with balance impairments (8).

SA for balance has been a focus of much research since the 2000's, likely influenced by increased availability of wearable technologies, especially compact, wireless, and accurate inertial measurement units. Various patient populations with primarily sensory-driven balance deficits have been included in research: people with vestibular loss, peripheral neuropathy, mild traumatic brain injury, and older adults, as well as people with stroke, Parkinson's disease, and ataxia.

Despite the recent interest in SA technologies, limited studies have investigated the underlying mechanisms of their effectiveness. However, several hypotheses are conceivable and a few have been historically proposed. These hypotheses can be conceptualized by considering how they influence various aspects of balance as represented by a simple model of balance control (**Figure 1**). We note that more than one mechanism could occur simultaneously.

"Sensory Restoration" refers to a device that fully restores missing sensory information. In this case, various methods for measuring balance function would show balance control behavior identical to that measured in subjects with normal sensory function. More likely the sensory restoration would be partial or limited. For example, for the foreseeable future a vestibular implant device at best will restore semicircular canal information, but not information from otolith organs (9). Examples of sensory restoration include retinal implants (10), cochlear implants (11), and vestibular implants (12).

"Sensory Substitution" refers to a device that acts through an alternative sensory modality (e.g., encoded using patterns of skin vibration) to convey the motion information that is related to that of a damaged sensory source. Ideally, this substituted information could be combined with other naturally available information and recognized by the brain as being equivalent to the damaged sensory source. If the information from the alternative sensory modality differs substantially from the damaged sensory information for which it is meant to substitute, the nervous system may not be able to combine it with other sensory sources in a natural way. In this case, it may be more appropriate to consider that the device is providing "Sensory Addition" (13, 14). Both sensory substitution and addition mechanisms can be thought of as augmenting balance control by making a "sixth sense" contribution to available sensory cues. Historically, sensory substitution and addition have been proposed as mechanisms when vibrotactile (15), auditory (16), or tactile (17) cues have been used to enhance visual inputs.

"Sensory Integration" refers to a mechanism that combines orientation information (often represented as a weighted combination) from various sources to serve as a basis for generating corrective actions that facilitate balance stabilization. Sensory restoration, substitution, and addition alter the available sensory information and are likely to have an impact on sensory integration via sensory reweighting. It has been posited that

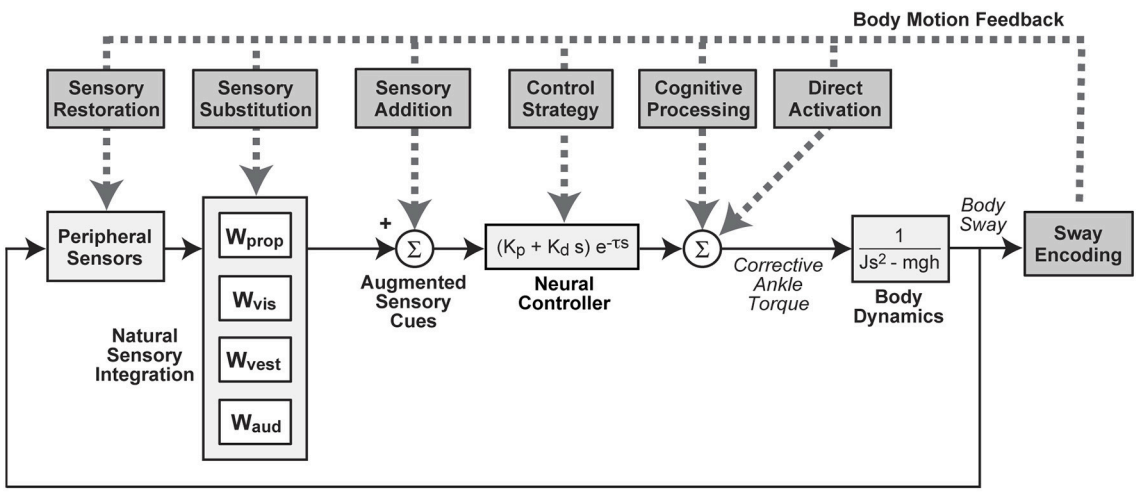


FIGURE 1 | Block diagram representation of a simple feedback control model of balance showing potential modes of action by which measures of body sway could be used to improve balance control via sensory augmentation effects on different subsystems or by direct activation (e.g., functional electrical stimulation). Natural sensory integration is represented by a weighted combination of proprioceptive (W_{prop}), visual (W_{vis}), vestibular (W_{vest}), and auditory (W_{aud}) orientation information. Corrective torque generation is represented by a "neural controller" with stiffness (K_p), damping (K_d), and time delay (τ) parameters. Corrective torque is applied at ankle joint level to an inverted pendulum representation of the body with moment of inertia (J), mass (m), center of mass height (h). "s" is the Laplace variable and "g" is acceleration due to gravity.

repeated exposure to an additional "channel" of body motion information provides the CNS with a correlate to the inputs from its intact sensory channels, promoting increased weighting of these intact channels and thereby promoting retentive (i.e., balance improvements are observed for the activities that were practiced/included in the training regime) and/or carryover (i.e., balance improvements are observed for activities that were not practiced/included in the training regime) effects once the additional channel of information is removed (18). Longer-term training with SA devices may affect sensory integration and context-specific adaptation by allowing time for the nervous system to develop optimal combinations/weights of sensory cues. Therefore, SA used during balance rehabilitation may lead to beneficial changes in sensory integration that are maintained even without the continued use of an SA device. Other SA benefits might arise from their influence on motor mechanisms. One could imagine that a device might motivate a change in "Control Strategy" that causes an individual to generate more or less corrective torque as a function of available sensory information. This could be represented by modification of neural control parameters where, for example, an increase in corrective torque generated per unit of body sway would cause a reduction in sway evoked by external disturbances even though sensory integration mechanisms remained unchanged. Temporary use of SA during balance rehabilitation may promote long-term changes in control strategy. Control strategy changes have been seen in subjects with Parkinson's Disease when receiving sensory cueing (19) and are likely influenced by individual motivation as well (20).

"Cognitive Processes" could have a role in explaining effects to the extent that subjects use conscious processing to generate voluntary actions to control balance. The TSAS for pilot situational awareness likely mediates cognitive processes and sensory addition (6). Finally, a device using functional electrical stimulation provides "Direct Activation" of muscles, thereby bypassing or partially bypassing natural sensory integration and muscle activation processes when they are not available or damaged (e.g., due to spinal cord injury) (21, 22). The aim of this critical review is to interpret aggregate findings in SA through the lens of several hypothesized mechanisms by first providing a brief overview of SA technologies for balance, then summarizing general outcomes for real-time use, balance rehabilitation, feedback modeling, and neuroimaging.

SENSORY AUGMENTATION TECHNOLOGIES

Visual (e.g., mirrors) and haptic feedback provided through touch (e.g., walking aids such as canes, and real-time extrinsic feedback provided by a treating physical therapist via tactile cues and/or manual assistance to enhance movement, balance, and motor re-learning) are two of the most common forms of passive SA for balance applications. Modern technology-driven active SA devices typically couple inertial measurement units to estimate body kinematics and/or force plates or pressure-sensitive surfaces to estimate body kinetics with a wearable or off-body processor and a display (**Figure 2**). A variety of displays have been developed and reported in the literature to explore standing and gait-based feedback applications including arrays of vibrating actuators (7, 24), electrotactile arrays (15), televisions, or other various types of screens, headphones, or speakers (8, 25, 26), and combinations of multiple feedback modalities (27). Processors have included wearable computers, laptops or desktops, gaming systems (e.g., Nintendo Wii, Kinect), and smartphones (28). Specific feedback modalities may be preferential for certain patient populations based on compatibility with intact sensory systems (e.g., non-auditory information transfer for people with hearing loss). Likewise, for prolonged use, certain display modalities may pose challenges during activities of daily living. Presently, several devices (e.g., BalanceFreedom™ and SwayStar International™, and Vertiguard™) have been approved for use in Europe and South America. To date, a limited number of active SA devices have been approved by the FDA for use within the U.S. as a real-time balance or rehabilitation tool (e.g., Biodex Vibrotactile™ System). For the purposes of this critical review, we will explore potential general mechanisms of use as opposed to focusing on mechanisms associated with specific feedback modalities.

REAL-TIME USE FINDINGS

Based on the published studies to date, the most likely dominant mechanism underlying balance benefits with real-time use of SA involves cognition; specifically, real-time SA cues are perceived, cognitively processed, and acted on based on the behavioral instructions assigned to the cues. The cognition hypothesis is supported by data that demonstrates that people's balance improves during the real-time use of SA cues compared to when no cues are provided, people's balance worsens when inaccurate cues are provided, people's balance is further improved when more information about body motion is provided, and people's temporal responses to the cues are on the order of several hundred milliseconds, which is consistent with response times associated with perceiving, processing, and responding to the cue.

To the extent that the effectiveness of an SA device depends on cognitive processing, sensory systems that naturally have good conscious representations, such as the auditory system, may be a better choice for delivering SA cues than sensory systems with poorer conscious representations. However, there is a tradeoff to be considered since the SA cues may interfere with the natural contribution to balance control provided by the sensory system used for SA. The auditory system is a good example since SA based on auditory feedback is commonly employed (8, 25–27, 29). Multiple studies have reported associations between hearing loss and increased fall risk in older adults (30, 31). The natural auditory contribution to spatial awareness likely involves unconcious processing of sound field cues that would likely be degraded by sound-based SA feedback.

The prominent literature base that supports this interpretation is a collection of numerous studies that have shown that people with vestibular deficits (28, 32) as well as older adults can use real-time SA cues to reduce sway when the

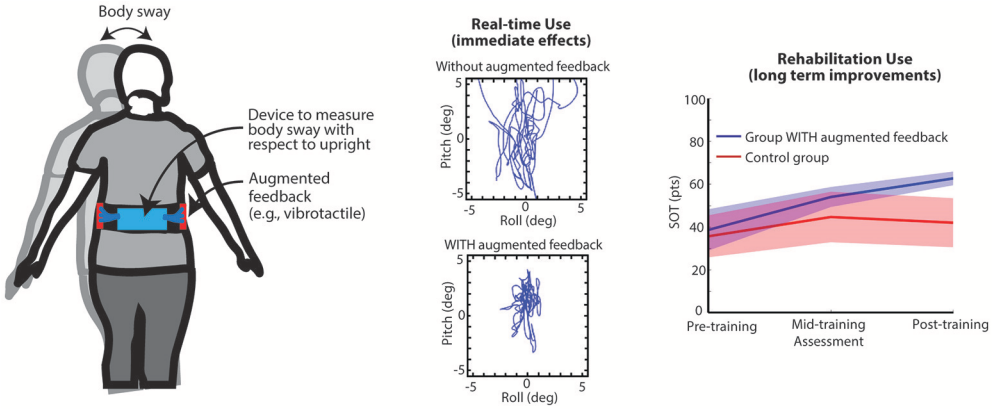


FIGURE 2 | Left: Illustration of trunk-based IMU and vibrating actuators. **Center**: Bird's eye view of illustrative trunk sway data from a subject with cerebellar ataxia; top panel—real-time use without cues, bottom—real-time use with cues. **Right**: Pre-/per-/post-training computerized Dynamic Posturography SOT scores for two groups of older adults that performed balance training exercises 3x/week for 8 weeks in their homes either with or without (Control group) vibrotactile sensory augmentation (23).

stance position, support surface, or visual inputs are modified during standing balance tasks compared to conditions when cues regarding their body motion are not provided (27) (**Figure 2**). Young healthy adults (33), people with peripheral neuropathies (34), people with mild cognitive impairments (35), and stroke (36) have likewise shown reductions in postural sway related metrics compared with baseline. Real-time cues to inform modifications to gait have been shown to reduce M/L trunk tilt during paced heel-to-toe walking (37) and during narrow stance walking (38) in people with vestibular deficits. Young adults have also been shown to reduce their trunk sway and sway velocity when feedback was provided in the A/P or M/L directions during a variety of gait tasks (e.g., normal and tandem walking, climbing up and down stairs, walking over barriers), and gait velocity significantly increased when cues were provided (39). Older adults have been shown to increase their Dynamic Gait Index scores while using feedback (40). Young and older adults had reduced A/P and M/L tilt and A/P tilt velocity during normal walking (41). Cues have also been used to reduce knee adduction moments in people with knee osteoarthritis (42), alter plantar foot loading in people with stroke (43), and reduce gait asymmetry in people with cerebral palsy (44). When provided with combined auditory and vibrotactile SA, people with bilateral vestibular loss demonstrated decreased EMG amplitudes and less EMG background activity when standing on a compliant surface with their eyes closed (29).

When provided with erroneous cues, people with vestibular deficits initially demonstrate increased postural sway (24). However, it is believed that participants quickly ascertain that the erroneous cues conflict with other intact sensory inputs and participants ignore the inputs. This finding demonstrates that the cues are not simply serving as an alerting mechanism to prompt people to attend to their balance. However, it is possible that an alerting mechanism contributes to the observed improved postural control outcomes in the various real-time studies performed to date.

Continuous visual feedback has been shown to result in better performance than discrete visual or vibrotactile feedback, but some subjects reported dizziness when using continuous visual feedback (32). The improved results with the use of continuous feedback further support the cognitive hypothesis since people are provided with more complete information about their body motion and therefore are more likely to make more frequent and specific body corrections compared with discrete (less frequent, less information content) feedback.

Several studies have explored the effects of balance and gait parameters while simultaneously using an SA device and performing a secondary task; the findings partially support the cognition hypothesis because performance on the primary task generally declines when the secondary task is performed. Young subjects were able to use multimodal SA to reduce their trunk sway while walking and simultaneously counting backwards or carrying a tray of water (41). Older adults, however, were less responsive to the SA and subsequently less successful at reducing their trunk sway while concurrently performing a cognitive or motor task, potentially due to a lower residual processing capacity.

Interestingly, Lin et al. demonstrated that both younger and older adults had slower reaction times when performing an auditory reaction time test while using vibrotactile SA (45); however the older adults slowed disproportionally more on the reaction time task compared to the younger adults. There may have been more cognitive resources required to maintain balance with the dual task demands in the older subjects. However, balance differences based on kinetic measurements were not observed between persons with unilateral vestibular disorders and age-matched controls when tasked with using vibrotactile SA while simultaneously performing an auditory reaction time task on a computerized dynamic posturography platform (46). Both groups had slower reaction times when vibrotactile SA was provided, but the persons with vestibular loss were affected more profoundly.

Mechanical perturbations of the support surface have been employed to study how balance is affected by the use of vibrotactile SA feedback on the trunk. Significant reductions in falls during computerized dynamic posturography sensory organization test (SOT) conditions 5 and 6, which require more reliance on vestibular inputs, have been observed in people with severe vestibular deficits (47, 48). However, subjects with mild to moderate vestibular deficits did not fall as frequently as the severe group, and the number of their falls did not change significantly when they used feedback (47). Feedback may also promote faster recovery from discrete surface perturbations; specifically, peak tilt and the time to recover are decreased (47) (49). In a similar study examining the effects of vibrotactile feedback on the stepping responses of people with Parkinson's disease (PD) and age-matched controls, feedback cues did not affect the timing or the length of the steps, but it reduced trunk displacements prior to step initiation (50). Among young adults, older adults, people with bilateral vestibular deficits, and people with peripheral neuropathies, only older adults who exhibited slower stepping times during baseline trials showed significantly shorter stepping reaction times with versus without the feedback cue (51). These collective findings suggest that feedback is effective in reducing sway during normal stance and during recovery from perturbations, but not during the ballistic phase of a perturbation.

It should be noted that multiple studies have shown no reductions in sway during various gait tasks (8) and during non-challenging gait tasks (38) when vibrotactile SA feedback was provided on the trunk. Non-intended changes in gait patterns have also been observed, e.g., less natural gait patterns and altered segmental control strategies, although these changes may be due to inadequate training periods with the SA device. Multimodal SA may be more effective for improving gait performance compared to single sensory feedback in healthy older adults (26, 40, 52) and individuals post stroke (53–55).

Another potential mechanism that may contribute in a limited manner is the non-volitional response that has been observed when participants were presented with vibrotactile stimuli over the internal oblique and erector spinae locations; in addition to the small magnitude, the timing of the responses are likely too slow to have a significant impact on the initiation of postural corrections. Small, non-volitional sway responses to torso-based vibrotactile stimulation have been demonstrated when vibrations were applied over the internal oblique and erector spinae muscles. In these studies, participants were instructed to maintain an upright posture while standing with their arms at their sides. Movements on the order of approximately one degree were observed in the direction of the applied vibration (i.e., stimulation over the internal right oblique area resulted in a forward right movement), however, no motion was observed when stimuli were applied to the external oblique areas (56–60).

Vibration has also been used to improve signal detection in individual sensory channels. This particular use of vibration does not directly fit with our definition of SA because the vibration does not directly "convey pertinent information about body orientation for balance" but rather indirectly provides pertinent information by aiming to improve the detection of information obtained from existing peripheral receptors. This method of vibration has been termed stochastic resonance and relies on the theory that noise can improve the transmission and detection of information in some non-linear systems (61). Stochastic resonance applied as vibration to the bottom of the feet has been shown to reduce posture sway in quiet stance (61), one marker of improved feedback control. Others have applied the concept of stochastic resonance to activate the vestibular system via sub-threshold galvanic vestibular stimulation and also showed improvements in posture sway (62); these researchers also noted that a high noise level actually creates a distortion in vestibular feedback, increasing posture sway. Stochastic resonance could influence multiple mechanisms in the posture system. Clearly, the first mechanism is partial sensory restoration because the goal of stimulation is to improve the transmission of information from the peripheral sensors. With the improved transmission within one sensor, it is likely that sensory reweighting would take place because sensory reweighting is influenced by the accuracy and magnitude of peripheral feedback (63–65). The extent to which stochastic resonance impacts cognitive processes that contribute to balance is not well known.

REHABILITATION USING AUGMENTED SENSORY FEEDBACK

As a rehabilitation tool, SA can enrich and mimic the tactile and verbal cues provided by a physical therapist, thereby facilitating retraining of postural control for different patient populations, especially those with chronic imbalance (18). For SA to be an effective training tool, balance improvements achieved during the intervention should be retained after the feedback is removed and ideally carried over to other activities of daily living. The addition of SA to clinical and home exercise programs has the potential to provide the user with knowledge of results and maximize the participant's motivation and engagement (20).

Preliminary, small-scale studies showing balance improvements following training with SA versus. training alone suggest that augmentation facilitated training improves the utilization of available sensory cues via a sensory reweighting process. Sensory organization is an adaptive CNS regulated process, which enables a person to utilize the available, useful and accurate inputs to maintain balance in changing conditions or environments (66). Persons with compromised sensory systems (visual, vestibular, proprioceptive) may be able to use SA via a rehabilitation device to "upweight" (67) the available accurate information from the non-compromised system(s), or possibly enhance the "weakened signal" resulting in improved postural control. It appears that longer duration training with SA has better potential to enhance sensory reweighting (44). Persons with more severe sensory impairment have been found to benefit more from SA compared to those with moderate deficits, thus supporting the use of SA in acute stages of rehabilitation (47).

Several studies have demonstrated short-term retentive effects (24, 68–70) following short-term training with SA. However, many of the studies performed to date have been uncontrolled and therefore context-specific adaptation and/or habituation

cannot be ruled out as a potential mechanism to explain the findings. In an uncontrolled study with Parkinson's population using Vertiguard, improvements in SOT scores were retained at three months post training and falls were reduced (71) following 10 training sessions within a two-week period. A limited number of controlled studies have examined retention and carryover effects following training with SA. In a randomized long-term home-based study in healthy older adults, participants trained for eight weeks using a smart phone balance trainer (28). The vibrotactile feedback group had greater improvements in SOT composite scores, which were maintained at six months, and both groups demonstrated improved vestibular reliance (23). In a recent clinical-based randomized preliminary study, a 6-week (18 sessions) vestibular rehabilitation program augmented with vibrotactile feedback was found to be beneficial for persons with unilateral vestibular disorders (72). The most significant finding was improved postural stability during balance exercises with head movements suggesting improved reliance on the available, but compromised, vestibular inputs. In a randomized control study, people with Parkinson's disease participated in 12 sessions of clinical balance training to compare the effects of virtual reality (VR) augmented balance training using a dynamic balance board (VR group) to conventional balance training (73). The VR group improved significantly on SOT condition 6 (unreliable vision and somatosensory inputs) immediately after training, however this finding was not significant at the four week follow-up suggesting limited retention effects.

Several studies have examined the incorporation of the Wii Fit balance board, which provides center of pressure (COP) information to the user, for balance training (74–82). Studies comparing the effectiveness of conventional physical therapy to Wii Fit balance training in older adults and persons with unilateral peripheral vestibular hypofunction found that balance training with virtual reality alone was not superior to traditional balance therapy (83, 84). Based on a recent systematic review, there is moderate evidence that visual feedback is beneficial in older adults with balance impairment (85). One study showed no overall benefit of balance training in healthy older adults when training was performed both with and without multimodal (vibrotactile, auditory, and visual) SA (86). Conversely, in a systematic review of frail older adults, both visual and auditory SA were noted to decrease sway although no large-scale randomized control trials were among the studies included (87).

Overall, there is moderate evidence to support the use of SA to improve postural control and gait during rehabilitation. In these balance-training scenarios, the real-time use of SA most likely involves cognition as described in the real-time use findings section above. Additionally, vibrotactile, visual, and/or auditory cues may simply alert users to momentarily attend to the balance or gait task at hand. There is limited evidence thus far for retention and/or carryover effects when the stimulus is removed following multiple training sessions. Longer use of SA has the potential to promote sensory reweighting and central compensation necessary to translate into longer-term retention and/or carryover, however, observed improvements in both control and intervention groups suggest that context-specific adaptation and/or habituation are also occurring.

SENSORY AUGMENTATION ASSESSMENT USING BALANCE MODELS

It can be difficult to ascertain causal relationships in standing balance because of complex time-delayed feedback interactions. To help interpret complex balance behavior, feedback models of posture control have been used for nearly two decades. To a remarkable extent, a relatively simple mathematical model of balance control, related to the model shown in **Figure 1**, has been shown to account very well for the dynamic characteristics of body sway evoked by continuously applied rotations of the stance surface or visual scene (88, 89). In the model, the body is represented by a single-segment inverted pendulum. Sensory integration is represented by a weighted summation of body orientation information derived from sensory cues; proprioception (signaling body sway relative to the surface), vision (signaling body sway relative to the visual scene), and vestibular (signaling body motion in space). Spatial cues derived from auditory information may also contribute to body orientation estimates used for balance control. Sensory-to-motor transformation is represented by a "neural controller" that generates time-delayed corrective ankle torque as a function of the integrated sensory information. The parameters of this model (mainly sensory weights, neural controller parameters, and time delay) can be estimated by optimally accounting for the experimentally observed relationship between a perturbing stimulus and the evoked sway response.

This simple model can serve as a reference for considering how SA devices affect different balance mechanisms. Although feedback modeling of SA for balance has not been widely used, three examples are presented below that provide insight into the mechanisms subjects use.

In one set of studies, vibrotactile feedback was provided to the torso of standing participants with vibration encoding a combination of body sway angle and sway velocity (13, 14). Body sway in healthy subjects was evoked in the sagittal plane with continuous pseudorandom surface tilts in eyes closed conditions, requiring participants to use both vestibular and proprioceptive feedback for balance. Experimental results were used to calculate frequency response functions that characterized the sensitivity and timing of sway responses across a wide range of frequencies (0.017–2.2 Hz). At low frequencies, vibrotactile feedback caused a reduction in sensitivity to the perturbing stimulus meaning that the subjects were better able to compensate for the perturbing influence of the stimulus and maintain a more vertical body orientation. But surprisingly, sensitivity to the stimulus slightly increased across higher frequencies. Additionally, vibrotactile feedback caused systematic changes in the timing of sway responses relative to the stimulus. To understand these results, the simple **Figure 1** model was altered to investigate potential mechanisms of prosthesis action that could explain the experimental data. The investigators concluded that a "Sensory Addition" mechanism was best able to account for the results. Specifically, vibrotactile feedback provided a new sensory cue that summed with natural sensory cues, and did so without changing other characteristics of the balance control system. Additionally, the modeling results showed that the vibrotactile feedback was

heavily low-pass filtered and time delayed (representing filtering of signal transduction across skin and/or CNS processing). Moreover, the model indicated that reliance on the vibrotactile feedback was highly dependent on the type of information encoded: participants relied upon the vibrotactile feedback more when it encoded body sway angle compared to sway velocity. A related study was able to predict how reliance changed with different combinations of angular position and velocity feedback by assuming participants optimally used augmented feedback to minimize a linear combination of sway angular position and jerk (the third derivative of displacement) (90).

A second set of studies demonstrated how the modeling results described above contributed to understanding the limited benefits obtained when the vibrotactile feedback was tested in subjects with bilaterally absent vestibular function (14, 91). Only limited improvements in balance were demonstrated and vestibular loss subjects were not able to maintain balance with eyes closed when the stance surface was sway-referenced (a condition that requires vestibular information). These experimental results rule out a "Sensory Substitution" mechanism, and are also consistent with the predictions of the "Sensory Addition" model developed from results in subjects with normal sensory function. Specifically, the model predicts unstable stance control if the only available cues about body sway in space are heavily filtered and time delayed.

A third study investigated "Sensory Restoration" provided via galvanic vestibular stimulation (GVS) in a subject with bilaterally absent vestibular function (92). The GVS delivered a current across electrodes applied to the mastoid processes behind the ears. In subjects with normal vestibular function GVS evokes sway in the frontal plane. If a vestibular loss subject retains sensitivity to GVS, the possibility exists that GVS feedback could partially restore a vestibular signal that encodes frontal plane body sway. When GVS was applied as a real-time function of frontal plane sway angle and sway velocity, application of system identification methods demonstrated that GVS feedback caused a reduction in sensitivity to a surface-tilt perturbation performed with eyes closed, consistent with a partial restoration of vestibular information for balance control. Since GVS is considered to have its primary net influence on head velocity information encoded by the semicircular canals, experiments using GVS feedback may be directly relevant to predicting changes in balance control afforded by future vestibular prostheses that target electrical activation of the canals.

It is important to note that the studies described above examined only short-term applications of SA devices. It is entirely possible that sensorimotor learning mechanisms could improve effectiveness over time.

NEUROIMAGING OF SENSORY AUGMENTATION

Functional neuroimaging has provided insight into the neural control of movement in human subjects, and how control networks change in response to a variety of interventions and rehabilitation training programs. Not as much progress has been made in understanding the functional brain networks which contribute to static and dynamic balance, however, because most neuroimaging technologies require subjects to lay supine during brain scanning. Moreover, head movements can result in motion artifacts for neuroimaging data. Therefore, most neuroimaging studies of vestibular function have been conducted while participants passively receive vestibular stimulation laying supine and still.

Given the challenges of using neuroimaging tools to study balance control, it is perhaps not surprising that only a few studies have investigated the neural correlates of SA-induced improvements in balance. One exception is a line of work from Wildenberg et al. (93–95), which extends work by Bach-y-Rita using electrotactile tongue stimulation to convey relative head position information [cf. (96)]. This work provides some insight into the underlying mechanisms of at least one form of SA. Initial studies with this device were focused on real-time benefits; it should be noted, however, that the neuroimaging work has all been conducted using a rehabilitation approach. That is, functional neuroimaging was conducted before and after multiple sessions of SA, and, because participants were supine and still during the imaging, the SA system was not used in the scanner.

BRAIN CHANGES ASSOCIATED WITH REHABILITATION-BASED SENSORY AUGMENTATION

Wildenberg and colleagues conducted neuroimaging before and after several sessions in which participants wore an accelerometer on the head and had real-time head position information conveyed to them via electrotactile tongue stimulation. This technique has been shown to improve both objective and subjective measures of gait and balance both during real-time use and also extending beyond the stimulation sessions, in both healthy individuals and those with vestibular or visual deficits (97–101). The initial hypothesis was that this particular form of SA was effective due to "spillover" of neural activity from the tongue afferent pathway to the vestibular nuclei, adjacently located in the brainstem (102). To evaluate this hypothesis, Wildenberg et al. (94, 102) acquired functional MRI while balance impaired subjects passively viewed either static or expanding and retracting visual flow both before and after nine sessions of quiet stance coupled with tongue electrotactile SA. The subjects showed greater activity in response to visual flow patterns in brain regions that process visual motion including in the occipital lobe and cerebellar vermis. Interestingly, after training with this SA, postural sway was less susceptible to disturbance when subjects viewed optic flow stimuli, and the over-activation of visual motion processing regions was reduced. These findings support the notion that balance training coupled with SA acted via a sensory reweighting mechanism to reduce reliance on visual cues in balance impaired subjects who were initially overly reliant on visual inputs. There was also increased activity post training in the brainstem, supporting the possibility that activity in the tongue afferent pathway may have spread to vestibular brainstem regions as well.

These authors have also shown that tongue electrotactile stimulation aids balance even when the stimulation carries no information about body position. That is, the pattern of stimulation does not have to be coupled with head motion in order to result in decreased postural sway (93, 102). Stimulation that is not coupled to body position does not meet our definition of SA; we present the findings here however because the studies are direct follow ups to those described in the preceding paragraph. To more precisely investigate the brainstem changes occurring with stimulation, Wildenberg et al. (93) conducted a high resolution MRI study of changes in brainstem activity from 19 sessions of tongue electrotactile stimulation. Prior to the intervention, optic flow stimuli produced activation in several brainstem regions including the trigeminal and vestibular nuclei as well as the superior colliculus. After the stimulation sessions, there was increased activation in the pons. The authors suggested that this increased activity in the pons was in the trigeminal nucleus, part of the tongue afferent pathway. They further hypothesized that spread of excitation from this region to the vestibular nucleus resulted in enhanced balance.

A recent study that evaluated vibrotactile feedback delivered to the torso as a rehabilitation balance aid, coupled with in-home balance training, found evidence that this form of SA also affected sensory reweighting. The group of healthy older adults that trained with SA showed a greater increase in reliance on vestibular inputs from pre to post training than the group that performed balance exercises alone (23). A subset of the subjects underwent fMRI scans pre and post training while receiving vestibular stimulation with a pneumatically powered tapper device that elicited ocular vestibular evoked myogenic potentials (oVEMPs) and activation in vestibular cortex (103). The fMRI results showed increased activity in brain regions which process somatosensory, visual, and vestibular inputs following training suggesting that SA with balance training alters sensory processing and integration. Further research with additional subjects is required to determine whether and how these brain changes relate to functional balance improvements, how long the brain changes are retained, and whether they differ between participants that receive balance training alone and those that receive training plus SA. It is interesting that both the brain and behavioral changes suggest shifts in sensory reliance and integration with training; participants increased their reliance upon vestibular inputs for balance following training with vibrotactile SA. The work discussed in this section on rehabilitation-based SA supports sensory reweighting as an underlying proposed mechanism. The activation "spillover" described above could play a role in this reweighting, or the brain may instead rely upon this as a "sixth sense" type of proposed mechanism. Regardless, it appears that real-time SA may be effective by eliciting new cognitive strategies, whereas rehabilitation-based SA appears to result in sensory reweighting.

SUMMARY

Current SA applications impact balance control through a variety of mechanisms. Because each mechanism has its own characteristic features, it is worth considering which mechanism applies to a given application in order to anticipate its limitations and potential benefits. Real-time feedback via a sensory restoration mechanism likely has the greatest potential for restoring normal balance function since the sensory information flows through neural channels specifically involved in natural balance control. SA using future vestibular implants, galvanic vestibular stimulation, and foot vibrations to enhance proprioception are sensory restoration applications. For real-time use of SA, results favor a cognitive or sensory addition mechanism, but not a sensory substitution mechanism since substitution implies an equivalency between information provided by the SA and natural sensory systems. A cognitive feedback loop that relies on voluntary commands to control balance could have similar functional characteristics to a sensory addition mechanism (e.g., both having long time delays), but reliance on cognitive control would be inferior to sensory addition as a balance aid due to a need for constant attentiveness. Studies that apply long-term SA are needed to see if a balance aid with features of a sensory addition mechanism can evolve through motor learning to behave as a sensory substitution mechanism where the augmented sensory information is used in a manner that is essentially indistinguishable from natural sensory feedback. Prolonged balance training with SA would ideally improve balance after the augmentation is removed. However, there are mixed results supporting this positive retention and carryover. When retention and carryover are found, evidence supports the notion that SA altered sensory integration via a sensory reweighting mechanism. Finally, application of system identification methods employing model-based interpretation of experimental results can provide detailed quantitative measures of the balance control system to assess the effectiveness of SA technologies and rehabilitation strategies.

AUTHOR CONTRIBUTIONS

KS, RS, WC, AG, SW, and RP wrote the manuscript. AG and RP created the figures.

ACKNOWLEDGMENTS

We thank Catherine Kinnaird and Tian Bao for their assistance with creating a figure.

REFERENCES

1. Grant MJ, Booth A. A typology of reviews: an analysis of 14 review types and associated methodologies. *Health Info Libr J.* (2009) 26:91–108. doi: 10.1111/j.1471-1842.2009.00848.x
2. Altschuler EL, Wisdom SB, Stone L, Foster C, Galasko D, Llewellyn DM, et al. Rehabilitation of hemiparesis after stroke with a mirror. *Lancet* (1999) 353:2035–6. doi: 10.1016/S0140-6736(99)00920-4
3. Sathian K, Greenspan AI, Wolf SL. Doing it with mirrors: a case study of a novel approach to neurorehabilitation. *Neurorehabil*

Neural Repair (2000) 14:73–6. doi: 10.1177/154596830001400109
4. Ramachandran VS, Rogers-Ramachandran D, Cobb S. Touching the phantom limb. *Nature* (1995) 377:489–90. doi: 10.1038/377489a0
5. Bach-Y-Rita P, Collins CC, Saunders FA, White B, Scadden L. Vision substitution by tactile image projection. *Nature* (1969) 221:963–4. doi: 10.1038/221963a0
6. Rupert AH. Tactile situation awareness system: proprioceptive prostheses for sensory deficiencies. *Aviat Space Environ Med.* (2000) A92–9.
7. Wall C III, Weinberg MS, Schmidt PB, Krebs DE. Balance prosthesis based on micromechanical sensors using vibrotactile feedback of tilt. *IEEE Trans Biomed Eng*. (2001) 48:1153–61. doi: 10.1109/10.951518
8. Hegeman J, Honegger F, Kupper M, Allum JH. The balance control of bilateral peripheral vestibular loss subjects and its improvement with auditory prosthetic feedback. *J Vestib Res*. (2005) 15:109–17.
9. Lewis RF. Vestibular implants studied in animal models: clinical and scientific implications. *J Neurophysiol*. (2016) 116:2777–88. doi: 10.1152/jn.00601.2016
10. Zrenner E. Will retinal implants restore vision? *Science* (2002) 295:1022–5. doi: 10.1126/science.1067996
11. Rubinstein JT. How cochlear implants encode speech. *Curr Opin Otolaryngol Head Neck Surg*. (2004) 12:444–8. doi: 10.1097/01.moo.0000134452.24819.c0
12. Golub JS, Ling L, Nie K, Nowack A, Shepherd SJ, Bierer SM, et al. Prosthetic implantation of the human vestibular system. *Otol Neurotol*. (2014) 35:136–47. doi: 10.1097/MAO.0000000000000003
13. Goodworth AD, Wall C III, Peterka RJ. Influence of feedback parameters on performance of a vibrotactile balance prosthesis. *IEEE Trans Neural Syst Rehabil Eng*. (2009) 17:397–408. doi: 10.1109/TNSRE.2009.2023309
14. Goodworth AD, Wall C III, Peterka RJ. A balance control model predicts how vestibular loss subjects benefit from a vibrotactile balance prosthesis. *Conf Proc IEEE Eng Med Biol Soc*. (2011) 2011:1306–9. doi: 10.1109/IEMBS.2011.6090307
15. Bach-Y-Rita P. Tactile sensory substitution studies. *Ann NY Acad Sci*. (2004) 1013:83–91. doi: 10.1196/annals.1305.006
16. De Volder AG, Toyama H, Kimura Y, Kiyosawa M, Nakano H, Vanlierde A, et al. Auditory triggered mental imagery of shape involves visual association areas in early blind humans. *Neuroimage* (2001) 14:129–39. doi: 10.1006/nimg.2001.0782
17. Collins CC, Bach-Y-Rita P. Transmission of pictorial information through the skin. *Adv Biol Med Phys*. (1973) 14:285–315. doi: 10.1016/B978-0-12-005214-1.50010-8
18. Sienko KH, Whitney SL, Carender WJ, Wall C III. The role of sensory augmentation for people with vestibular deficits: Real-time balance aid and/or rehabilitation device? *J Vestib Res*. (2017) 27:63–76. doi: 10.3233/VES-170606
19. Dibble LE, Nicholson DE, Shultz B, Macwilliams BA, Marcus RL, Moncur C. Sensory cueing effects on maximal speed gait initiation in persons with Parkinson's disease and healthy elders. *Gait Posture*. (2004) 19:215–25. doi: 10.1016/S0966-6362(03)00065-1
20. Wulf G, Lewthwaite R. Optimizing performance through intrinsic motivation and attention for learning: the OPTIMAL theory of motor learning. *Psychon Bull Rev*. (2016) 23:1382–414. doi: 10.3758/s13423-015-0999-9
21. Ho CH, Triolo RJ, Elias AL, Kigore KL, Dimarco AF, Bogie K, et al. Functional electrical stimulation and spinal cord injury. *Phys Med Rehabil Clin N Am*. (2014) 25:631–54. doi: 10.1016/j.pmr.2014.05.001
22. Audu ML, Lombardo LM, Schnellenberger JR, Foglyano KM, Miller ME, Triolo RJ. A neuroprosthesis for control of seated balance after spinal cord injury. *J Neuroeng Rehabil*. (2015) 12:8. doi: 10.1186/1743-0003-12-8
23. Bao T, Carender WJ, Kinnaird C, Barone VJ, Peethambaran G, Whitney SL, et al. Effects of long-term balance training with vibrotactile sensory augmentation among community-dwelling healthy older adults: a randomized preliminary study. *J Neuroeng Rehabil*. (2018) 15:5. doi: 10.1186/s12984-017-0339-6
24. Sienko KH, Balkwill MD, Oddsson LI, Wall C III. Effects of multi-directional vibrotactile feedback on vestibular-deficient postural performance during continuous multi-directional support surface perturbations. *J Vestib Res*. (2008) 18:273–85.
25. Dozza M, Chiari L, Horak FB. Audio-biofeedback improves balance in patients with bilateral vestibular loss. *Arch Phys Med Rehabil*. (2005) 86:1401–3. doi: 10.1016/j.apmr.2004.12.036
26. Dozza M, Horak FB, Chiari L. Auditory biofeedback substitutes for loss of sensory information in maintaining stance. *Exp Brain Res*. (2007) 178:37–48. doi: 10.1007/s00221-006-0709-y
27. Davis JR, Carpenter MG, Tschanz R, Meyes S, Debrunner D, Burger J, et al. Trunk sway reductions in young and older adults using multi-modal biofeedback. *Gait Posture*. (2010) 31:465–72. doi: 10.1016/j.gaitpost.2010.02.002
28. Lee BC, Kim J, Chen S, Sienko KH. Cell phone based balance trainer. *J Neuroeng Rehabil*. (2012) 9:10. doi: 10.1186/1743-0003-9-10
29. Allum JH, Honegger F. Vibro-tactile and auditory balance biofeedback changes muscle activity patterns: Possible implications for vestibular implants. *J Vestib Res*. (2017) 27:77–87. doi: 10.3233/VES-170601
30. Lin FR, Ferrucci L. Hearing loss and falls among older adults in the United States. *Arch Intern Med*. (2012) 172:369–71. doi: 10.1001/archinternmed.2011.728
31. Campos J, Ramkhalawansingh R, Pichora-Fuller MK. Hearing, self-motion perception, mobility, and aging. *Hear Res*. (2018) 369:42–55. doi: 10.1016/j.heares.2018.03.025
32. Bechly KE, Carender WJ, Myles JD, Sienko KH. Determining the preferred modality for real-time biofeedback during balance training. *Gait Posture*. (2013) 37:391–6. doi: 10.1016/j.gaitpost.2012.08.007
33. Ma CZ, Lee WC. A wearable vibrotactile biofeedback system improves balance control of healthy young adults following perturbations from quiet stance. *Hum Mov Sci*. (2017) 55:54–60. doi: 10.1016/j.humov.2017.07.006
34. Grewal GS, Schwenk M, Lee-Eng J, Parvaneh S, Bharara M, Menzies RA, et al. Sensor-based interactive balance training with visual joint movement feedback for improving postural stability in diabetics with peripheral neuropathy: a randomized controlled trial. *Gerontology* (2015) 61:567–74. doi: 10.1159/000371846
35. Schwenk M, Sabbagh M, Lin I, Morgan P, Grewal GS, Mohler J, et al. Sensor-based balance training with motion feedback in people with mild cognitive impairment. *J Rehabil Res Dev*. (2016) 53:945–58. doi: 10.1682/JRRD.2015.05.0089
36. Jung S, Lee K, Kim M, Song C. Audiovisual biofeedback-based trunk stabilization training using a pressure biofeedback system in stroke patients: a randomized, single-blinded study. *Stroke Res Treat* (2017) 2017:6190593. doi: 10.1155/2017/6190593
37. Dozza M, Wall C III, Peterka RJ, Chiari L, Horak FB. Effects of practicing tandem gait with and without vibrotactile biofeedback in subjects with unilateral vestibular loss. *J Vestib Res*. (2007) 17:195–204.
38. Sienko KH, Balkwill MD, Oddsson LI, Wall C III. The effect of vibrotactile feedback on postural sway during locomotor activities. *J Neuroeng Rehabil*. (2013) 10:93. doi: 10.1186/1743-0003-10-93
39. Janssen LJ, Verhoeff LL, Horlings CG, Allum JH. Directional effects of biofeedback on trunk sway during gait tasks in healthy young subjects. *Gait Posture* (2009) 29:575–81. doi: 10.1016/j.gaitpost.2008.12.009
40. Wall C III, Wrisley DM, Statler KD. Vibrotactile tilt feedback improves dynamic gait index: a fall risk indicator in older adults. *Gait Posture* (2009) 30:16–21. doi: 10.1016/j.gaitpost.2009.02.019
41. Verhoeff LL, Horlings CG, Janssen LJ, Bridenbaugh SA, Allum JH. Effects of biofeedback on trunk sway during dual tasking in the healthy young and elderly. *Gait Posture* (2009) 30:76–81. doi: 10.1016/j.gaitpost.2009.03.002
42. Shull PB, Lurie KL, Cutkosky MR, Besier TF. Training multi-parameter gaits to reduce the knee adduction moment with data-driven models and haptic feedback. *J Biomech*. (2011) 44:1605–9. doi: 10.1016/j.jbiomech.2011.03.016
43. Ma CZ, Zheng YP, Lee WC. Changes in gait and plantar foot loading upon using vibrotactile wearable biofeedback system in patients with stroke. *Top Stroke Rehabil*. (2018) 25:20–7. doi: 10.1080/10749357.2017.1380339
44. Levin I, Lewek MD, Feasel J, Thorpe DE. Gait training with visual feedback and proprioceptive input to reduce gait asymmetry in adults with cerebral palsy: a case series. *Pediatr Phys Ther*. (2017) 29:138–45. doi: 10.1097/PEP.0000000000000362
45. Lin CC, Whitney SL, Loughlin PJ, Furman JM, Redfern MS, Sienko KH, et al. The effect of age on postural and cognitive task performance

while using vibrotactile feedback. *J Neurophysiol*. (2015) 113:2127–36. doi: 10.1152/jn.00083.2014
46. Lin CC, Whitney SL, Loughlin PJ, Furman JM, Redfern MS, Sienko KH, et al. The use of vibrotactile feedback during dual-task standing balance conditions in people with unilateral vestibular hypofunction. *Otol Neurotol*. (2018) 39:e349–56. doi: 10.1097/MAO.0000000000001764
47. Wall C III, Kentala E. Control of sway using vibrotactile feedback of body tilt in patients with moderate and severe postural control deficits. *J Vestib Res*. (2005) 15:313–25.
48. Goebel JA, Sinks BC, Parker BEJr, Richardson NT, Olowin AB, Cholewiak RW. Effectiveness of head-mounted vibrotactile stimulation in subjects with bilateral vestibular loss: a phase 1 clinical trial. *Otol Neurotol*. (2009) 30:210–6. doi: 10.1097/MAO.0b013e318194f84d
49. Sienko KH, Balkwill MD, Wall C III. Biofeedback improves postural control recovery from multi-axis discrete perturbations. *J Neuroeng Rehabil*. (2012) 9:53. doi: 10.1186/1743-0003-9-53
50. Lee PY, Gadareh K, Naushahi MJ, Gresty M, Bronstein AM. Protective stepping response in Parkinsonian patients and the effect of vibrotactile feedback. *Mov Disord*. (2013) 28:482–9. doi: 10.1002/mds.25227
51. Asseman F, Bronstein AM, Gresty MA. Using vibrotactile feedback of instability to trigger a forward compensatory stepping response. *J Neurol*. (2007) 254:1555–61. doi: 10.1007/s00415-007-0587-7
52. Wall C III, Wrisley D, Oddsson L. Vibrotactile feedback of mediolateral trunk tilt or foot pressure increases locomotor performance in healthy older adults–a pilot study. *Conf Proc IEEE Eng Med Biol Soc*. (2012) 2012:6145–8. doi: 10.1109/EMBC.2012.6347396
53. Deutsch JE, Merians AS, Adamovich S, Poizner H, Burdea GC. Development and application of virtual reality technology to improve hand use and gait of individuals post-stroke. *Restor Neurol Neurosci*. (2004) 22:371–86.
54. Fung J, Richards CL, Malouin F, Mcfadyen BJ, Lamontagne A. A treadmill and motion coupled virtual reality system for gait training post-stroke. *Cyberpsychol Behav*. (2006) 9:157–62. doi: 10.1089/cpb.2006.9.157
55. Genthe K, Schenck C, Eicholtz S, Zajac-Cox L, Wolf S, Kesar TM. Effects of real-time gait biofeedback on paretic propulsion and gait biomechanics in individuals post-stroke. *Top Stroke Rehabil*. (2018) 25:186–93. doi: 10.1080/10749357.2018.1436384
56. Lee BC, Ho A, Martin BJ, Sienko KH. Effects of co-vibrotactile stimulations around the torso on non-volitional postural responses. *Conf Proc IEEE Eng Med Biol Soc*. (2012) 2012:6149–52. doi: 10.1109/EMBC.2012.6347397
57. Lee BC, Martin BJ, Sienko KH. Directional postural responses induced by vibrotactile stimulations applied to the torso. *Exp Brain Res*. (2012) 222:471–82. doi: 10.1007/s00221-012-3233-2
58. Lee BC, Martin BJ, Ho A, Sienko KH. Postural reorganization induced by torso cutaneous covibration. *J Neurosci*. (2013) 33:7870–6. doi: 10.1523/JNEUROSCI.4715-12.2013
59. Lee BC, Martin BJ, Sienko KH. The effects of actuator selection on non-volitional postural responses to torso-based vibrotactile stimulation. *J Neuroeng Rehabil*. (2013) 10:21. doi: 10.1186/1743-0003-10-21
60. Martin BJ, Lee BC, Sienko KH. A cutaneous positioning system. *Exp Brain Res*. (2015) 233:1237–45. doi: 10.1007/s00221-014-4194-4
61. Collins JJ, Priplata AA, Gravelle DC, Niemi J, Harry J, Lipsitz LA. Noise-enhanced human sensorimotor function. *IEEE Eng Med Biol Mag*. (2003) 22:76–83. doi: 10.1109/MEMB.2003.1195700
62. Goel R, Kofman I, Jeevarajan J, De Dios Y, Cohen HS, Bloomberg JJ, et al. Using low levels of stochastic vestibular stimulation to improve balance function. *PLoS ONE* (2015) 10:e0136335. doi: 10.1371/journal.pone.0136335
63. Ernst MO, Banks MS. Humans integrate visual and haptic information in a statistically optimal fashion. *Nature* (2002) 415:429–33. doi: 10.1038/415429a
64. Mergner T, Schweigart G, Maurer C, Blumle A. Human postural responses to motion of real and virtual visual environments under different support base conditions. *Exp Brain Res*. (2005) 167:535–56. doi: 10.1007/s00221-005-0065-3
65. van der Kooij H, Peterka RJ. Non-linear stimulus-response behavior of the human stance control system is predicted by optimization of a system with sensory and motor noise. *J Comput Neurosci*. (2011) 30:759–78. doi: 10.1007/s10827-010-0291-y
66. Oie KS, Kiemel T, Jeka JJ. Multisensory fusion: simultaneous re-weighting of vision and touch for the control of human posture. *Brain Res Cogn Brain Res*. (2002) 14:164–76. doi: 10.1016/S0926-6410(02)00071-X
67. Umphred D, Lazaro R. Chapter 23: Balance and vestibular disorders. In: Umphred DA, editor. *Neurological Rehabilitation*. 5th ed. Maryland Heights, MI: Mosby (2006), p. 732–74.
68. Wall C III, Kentala, E. Effect of displacement, velocity, and combined vibrotactile tilt feedback on postural control of vestibulopathic subjects. *J Vestib Res*. (2010) 20:61–9. doi: 10.3233/VES-2010-0369
69. Basta D, Rossi-Izquierdo M, Soto-Varela A, Greters ME, Bittar RS, Steinhagen-Thiessen E, et al. Efficacy of a vibrotactile neurofeedback training in stance and gait conditions for the treatment of balance deficits: a double-blind, placebo-controlled multicenter study. *Otol Neurotol*. (2011) 32:1492–9. doi: 10.1097/MAO.0b013e31823827ec
70. Brugnera C, Bittar R, Greters M, Basta D. Effects of vibrotactile vestibular substitution on vestibular rehabilitation — preliminary study. *Braz J Otorhinolaryngol*. (2015) 81:616–21. doi: 10.1016/j.bjorl.2015.08.013
71. Rossi-Izquierdo M, Ernst A, Soto-Varela A, Santos-Perez S, Faraldo-Garcia A, Sesar-Ignacio A, et al. Vibrotactile neurofeedback balance training in patients with Parkinson's disease: reducing the number of falls. *Gait Posture*. (2013) 37:195–200. doi: 10.1016/j.gaitpost.2012.07.002
72. Bao T. *Vibrotactile Sensory Augmentation and Machine Learning Based Approaches for Balance Rehabilitation*. Ph.D, University of Michigan (2018).
73. Yen CY, Lin KH, Hu MH, Wu RM, Lu TW, Lin CH. Effects of virtual reality-augmented balance training on sensory organization and attentional demand for postural control in people with Parkinson disease: a randomized controlled trial. *Phys Ther*. (2011) 91:862–74. doi: 10.2522/ptj.20100050
74. Clark RA, Bryant AL, Pua Y, Mccrory P, Bennell K, Hunt M. Validity and reliability of the Nintendo Wii Balance Board for assessment of standing balance. *Gait Posture*. (2010) 31:307–10. doi: 10.1016/j.gaitpost.2009.11.012
75. Meldrum D, Herdman S, Moloney R, Murray D, Duffy D, Malone K, et al. Effectiveness of conventional versus virtual reality based vestibular rehabilitation in the treatment of dizziness, gait and balance impairment in adults with unilateral peripheral vestibular loss: a randomised controlled trial. *BMC Ear Nose Throat Disord*. (2012) 12:3. doi: 10.1186/1472-6815-12-3
76. Fu AS, Gao KL, Tung AK, Tsang WW, Kwan MM. Effectiveness of exergaming training in reducing risk and incidence of falls in frail older adults with a history of falls. *Arch Phys Med Rehabil*. (2015) 96:2096–102. doi: 10.1016/j.apmr.2015.08.427
77. Bonnechere B, Jansen B, Omelina L, Van Sint Jan S. The use of commercial video games in rehabilitation: a systematic review. *Int J Rehabil Res*. (2016) 39:277–90. doi: 10.1097/MRR.0000000000000190
78. Gandolfi M, Geroin C, Dimitrova E, Boldrini P, Waldner A, Bonadiman S, et al. Virtual reality telerehabilitation for postural instability in parkinson's disease: a multicenter, single-blind, randomized, controlled trial. *Biomed Res Int*. (2017) 2017:7962826. doi: 10.1155/2017/7962826
79. Iruthayarajah J, Mcintyre A, Cotoi A, Macaluso S, Teasell R. The use of virtual reality for balance among individuals with chronic stroke: a systematic review and meta-analysis. *Top Stroke Rehabil*. (2017) 24:68–79. doi: 10.1080/10749357.2016.1192361
80. Tripette J, Murakami H, Ryan KR, Ohta Y, Miyachi M. The contribution of Nintendo Wii Fit series in the field of health: a systematic review and meta-analysis. *PeerJ*. (2017) 5:e3600. doi: 10.7717/peerj.3600
81. Morrison S, Simmons R, Colberg SR, Parson HK, Vinik AI. Supervised balance training and wii fit-based exercises lower falls risk in older adults with type 2 diabetes. *J Am Med Dir Assoc. (2018) 19:185.e187–5.e113*. doi: 10.1016/j.jamda.2017.11.004
82. Phillips JS, Fitzgerald J, Phillis D, Underwood A, Nunney I, Bath A. Vestibular rehabilitation using video gaming in adults with dizziness: a pilot study. *J Laryngol Otol*. (2018) 132:202–6. doi: 10.1017/S0022215118000075
83. Alahmari KA, Sparto PJ, Marchetti GF, Redfern MS, Furman JM, Whitney SL. Comparison of virtual reality based therapy with customized vestibular physical therapy for the treatment of vestibular disorders. *IEEE Trans Neural Syst Rehabil Eng*. (2014) 22:389–99. doi: 10.1109/TNSRE.2013.2294904

84. Meldrum D, Herdman S, Vance R, Murray D, Malone K, Duffy D, et al. Effectiveness of conventional versus virtual reality-based balance exercises in vestibular rehabilitation for unilateral peripheral vestibular loss: results of a randomized controlled trial. *Arch Phys Med Rehabil*. (2015) 96:1319–28.e1311. doi: 10.1016/j.apmr.2015.02.032
85. Alhasan H, Hood V, Mainwaring F. The effect of visual biofeedback on balance in elderly population: a systematic review. *Clin Interv Aging* (2017) 12:487–97. doi: 10.2147/CIA.S127023
86. Lim SB, Horslen BC, Davis JR, Allum JH, Carpenter MG. Benefits of multi-session balance and gait training with multi-modal biofeedback in healthy older adults. *Gait Posture*. (2016) 47:10–7. doi: 10.1016/j.gaitpost.2016.03.017
87. Zijlstra A, Mancini M, Chiari L, Zijlstra W. Biofeedback for training balance and mobility tasks in older populations: a systematic review. *J Neuroeng Rehabil*. (2010) 7:58. doi: 10.1186/1743-0003-7-58
88. Peterka RJ. Sensorimotor integration in human postural control. *J Neurophysiol*. (2002) 88:1097–118. doi: 10.1152/jn.2002.88.3.1097
89. Peterka RJ. Simplifying the complexities of maintaining balance. *IEEE Eng Med Biol Mag*. (2003) 22:63–8.
90. Goodworth AD, Wall C III, Peterka RJ. Application of optimization methods to predict performance of a vibrotactile balance prosthesis. In: *Proceedings of 3rd International IEEE EMBS Conference on Neural Engineering Kohala Coast*. (2007). p. 510–3.
91. Peterka RJ, Wall C III, Kentala E. Determining the effectiveness of a vibrotactile balance prosthesis *J Vestib Res*. (2006) 16:45–56.
92. Peterka RJ. Use of galvanic vestibular feedback for a balance prosthesis. Conf Proc IEEE Eng Med Biol Soc. (2012) 2012:6137–40. doi: 10.1109/EMBC.2012.6347394
93. Wildenberg J, Tyler ME, Danilov YP, Kaczmarek KA, Meyerand ME. High-resolution fMRI detects neuromodulation of individual brainstem nuclei by electrical tongue stimulation in balance-impaired individuals. *Neuroimage* (2011) 56:2129–37. doi: 10.1016/j.neuroimage.2011.03.074
94. Wildenberg J, Tyler ME, Danilov YP, Kaczmarek, KA, Meyerand ME. Electrical tongue stimulation normalizes activity within the motion-sensitive brain network in balance impaired subjects as revealed by group independent component analysis. *Brain Connect* (2011) 1:255–65. doi: 10.1089/brain.2011.0029
95. Wildenberg J, Tyler ME, Danilov YP, Kaczmarek KA, Meyerand ME. Altered connectivity of the balance processing network after tongue stimulation in balance-impaired individuals. *Brain Connect* (2013) 3:87–97. doi: 10.1089/brain.2012.0123
96. Tyler M, Danilov YP, Bach-Y-Rita P. Closing an open-loop control system: vestibular substitution through the tongue. *J Integr Neurosci*. (2003) 2:159–66. doi: 10.1142/S0219635203000263
97. Danilov Y, Tyler ME, Skinner Kl, Bach-Y-Rita P. Efficacy of electrotactile vestibular substitution in patients with bilateral vestibular and central balance loss. In: *Conference Proceedings– IEEE Engineering in Medicine and Biology Society* New York, NY. (2006). p. 6605–9.
98. Danilov Y, Tyler M , Skinner K, Hogle R, Bach-Y-Rita P. Efficacy of electrotactile vestibular substitution in patients with peripheral and central vestibular loss. *J Vesti Res*. (2007) 17:119–30.
99. Vuillerme N, Pinsault N, Fleury A, Chenu O, Demongeot J, Payan Y. Effectiveness of an electro-tactile vestibular substitution system in improving upright postural control in unilateral vestibular-defective patients. *Gait Posture*. (2008) 28:711–15. doi: 10.1016/j.gaitpost.2008.05.017
100. Robinson B, Cook JL, Richburg CMC, Price SE. Use of an electrotactile vestibular substitution system to facilitate balance and gait of an individual with gentamicin-induced bilateral vestibular hypofunction and bilateral transtibial amputation. *J Neurol Phys Ther*. (2009) 33:150–9. doi: 10.1097/NPT.0b013e3181a79373
101. Vuillerme N, Cuisinier R. Sensory supplementation through tongue electrotactile stimulation to preserve head stabilitation in space in the absence of vision. *Invest Ophthalmol Vis Sci*. (2009) 50:476–81. doi: 10.1167/iovs.07-1595
102. Wildenberg J, Tyler ME, Danilov YP, Kaczmarek KA, Meyerand ME. Sustained cortical and subcortical neuromodulation induced by electrical tongue stimulation. *Brain Imag Behav*. (2010) 4:199–211. doi: 10.1007/s11682-010-9099-7
103. Noohi FKC, Dedios Y, Kofman IS, Wood S, Bloomberg J, Mulavara A, Seidler R. Functional brain activation in response to a clinical vestibular test correlates with balance. *Front Syst Neurosci*. (2017) 11:11. doi: 10.3389/fnsys.2017.00011

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 22 November 2018
doi: 10.3389/fneur.2018.00986

An Initial Passive Phase That Limits the Time to Recover and Emphasizes the Role of Proprioceptive Information

Maeva Le Goic [1], Danping Wang [2,3], Catherine Vidal [1], Elodie Chiarovano [1], Jennyfer Lecompte [4], Sebastien Laporte [4], Jacques Duysens [5] and Pierre-Paul Vidal [2,1]*

[1] COGNAC-G (COGNition and ACtion Group), Université Paris Descartes–CNRS UMR-MD–SSA, Paris, France, [2] Institute of Information and Control, Hangzhou Dianzi University, Hangzhou, China, [3] Plateforme d'Etude de la Sensorimotricité, Université Paris Descartes, Paris, France, [4] Arts et Metiers ParisTech, Institut de Biomecanique Humaine Georges Charpak, Paris, France, [5] Movement Control and Neuroplasticity Research Group, Department of Kinesiology, KU Leuven, Leuven, Belgium

In the present experiments, multiple balance perturbations were provided by unpredictable support-surface translations in various directions and velocities. The aim of this study was to distinguish the passive and the active phases during the pre-impact period of a fall. It was hypothesized that it should be feasible if one uses a specific quantitative kinematic analysis to evaluate the dispersion of the body segments trajectories across trials. Moreover, a multi-joint kinematical model was created for each subject, based on a new 3-D minimally invasive stereoradiographic X-ray images to assess subject-specific geometry and inertial parameters. The simulations allowed discriminating between the contributions of the passive (inertia-induced properties) and the active (neuromuscular response) components during falls. Our data show that there is limited time to adjust the way one fall from a standing position. We showed that the pre-impact period is truncated of 200 ms. During the initial part of a fall, the observed trajectory results from the interaction between the destabilizing external force and the body: inertial properties intrinsic to joints, ligaments and musculotendinous system have then a major contribution, as suggested for the regulation of static upright stance. This passive phase is later followed by an active phase, which consists of a corrective response to the postural perturbation. We believe that during a fall from standing height, it takes about 300 ms for postural responses to start correcting the body trajectory, while the impact is expected to occur around 700 ms. It has been argued that this time is sufficient to change the way one falls and that this makes it possible to apply safer ways of falling, for example by using martial arts fall techniques. Also, our results imply visual and vestibular information are not congruent with the beginning of the on-going fall. This consequence is to be noted as subjects prepare to the impact on the basis of sensory information, which would be uniquely mainly of proprioceptive origin at the fall onset. One limitation of the present analysis is that no EMG was included so far but these data are the subject of a future study.

Keywords: accidental fall, disequilibrium, stability, postural control, perturbation, sensory information, biomechanics, multi-joint kinematical model

OPEN ACCESS

Edited by:
Emily Keshner,
Temple University, United States

Reviewed by:
Laurence Mouchnino,
Aix-Marseille Université, France
Thurmon E. Lockhart,
Arizona State University, United States

****Correspondence:***
Danping Wang
danping.wang@parisdescartes.fr

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *31 May 2018*
Accepted: *01 November 2018*
Published: *22 November 2018*

Citation:
Le Goic M, Wang D, Vidal C, Chiarovano E, Lecompte J, Laporte S, Duysens J and Vidal P-P (2018) An Initial Passive Phase That Limits the Time to Recover and Emphasizes the Role of Proprioceptive Information. Front. Neurol. 9:986. doi: 10.3389/fneur.2018.00986

INTRODUCTION

Falls are a threat to the health and independence of the older part of the population. In this context, it is crucial to know how far it is possible to adjust the way a person falls, in order to prevent damage, or in the best case, in order to guarantee recovery. This is even more so in patients. For instance, the reduced ability to accurately adjust foot placement during walking in individuals with focal cerebellar lesions appears to be a movement control deficit, which could contribute to increased fall risk (1).

Upright human stance is considered as an unstable multi-articulated system which has to face a constant but disturbing force acting on the body: gravity. In the absence of stabilizing torques controlled by the postural system involving both active and passive mechanisms to maintain upright body stance, a fall would occur (2, 3). The phase of the fall preceding the ground impact is crucial for preparation of landing, but it lasts no more than 750 ms in a standing subject (4, 5).

It is argued here that it is possible to subdivide this period into two phases, depending on the absence or presence of body corrective movements. In the first period, the movements of the various body parts are very stereotyped and mostly explained by inertia. This part is termed therefore "passive," defined as devoid of evidence of active involvement of corrective movements. It is hypothesized that during this part, there is very little dispersion of displacements of the head when individual reactions to the same perturbation are compared. This inertial phase may ultimately determine the ability to trigger efficient muscle activities as it potentially leaves a short time-window available to actively compensate a loss of balance. However, the mechanical behavior of the body in reaction to an external destabilization has not generated much interest even though it may be important for the availability and redundancy of the sensory information upon which the subjects prepare to the impact (6). In contrast, in the second part of the fall, the displacements are expected to show large variability as corrective motor strategies are displayed. This part will be termed "active." This subdivision is valid as long as the reactions are mostly due to feedback. This requires a protocol in which randomization of conditions prevent feedforward mechanisms, as is the case in ecological conditions when perturbations are unexpected. The value of this approach is that one can obtain insight in the time scale required for appropriate corrective movements (7).

Some authors claimed that the passive mechanisms arising from biomechanical properties of the musculo-articular system (muscle tissues, aponeurosis, synovial fluid, ligaments, articular capsule, joint friction, skin) or the muscle-tendon unit (visco-elasticity, damping, stiffness) help to counter gravity forces and maintain balance (8) without necessarily a continuous muscle activity (9) in the same way a spring resists when displaced from its resting equilibrium (10). This mechanical view of postural regulation was opposed to a neurological model (2, 11) which favors a postural regulation via an internal model based of sensory inputs that detect CoP movements and result in the control of CoM displacement. The question whether both contributions of passive properties and active control mechanisms to maintain upright stance while a perturbation occurs (floor tilts, moving scenes, or galvanic stimulation) are independent from each other remains uncertain (12). Some studies also suggest the existence of an $\ll$ effective time delay $\gg$ based on an independent channel model that may even not be linked to delays in neural processing, transmission of information nor muscle activation time (11)

To explore these issues, one needs experiments that include high-threatening perturbations i.e., challenging enough to induce real and non-recoverable falls. Such experiments can be performed by suddenly shifting a platform that is sufficiently wide to allow falls or corrective responses. In a ground-breaking study, Hsiao and Robinovitch (4) disturbed the balance of young adults standing on large mattresses that were translated quickly. They found that it takes approximately 700 ms before touchdown. Review of their stick-figure animations revealed that active movements appeared to start some 300 ms after fall onset but this aspect was not studied in detail. Similarly, except for hip and wrist, the body segment movements were only documented with stick diagrams without detailed analysis. The diagrams in this article seemed to suggest that the head did not move in the first 150 ms of the fall but more specific information was not available.

Such information on head motion is important if one wants to judge the contribution of vestibular reflexes in balance corrective responses. The role of the vestibulo-spinal reflex is relatively clear in responses to free fall (13), but it remains largely unknown for surface-translation type studies. In forward falls after tether release the head starts to move within 10–20 ms, hence one could expect a contribution of the vestibular system to balance-correcting responses in lower leg muscles, occurring as early as 60 ms after the stimulus (14). Yet the onset of the responses was identical in patients with vestibular loss. Similarly for experiments with a moving support surface, Allum and Honegger (15) showed that vestibular loss caused no change in the amplitude of balance-correcting responses. These and similar data (16), question the role of vestibular inputs in fall-recovery but the definite proof requires a detailed examination of the head movement during platform translations. Another reason to study head motion in experiments with a moving platform is that it allows to judge the functional contribution of early muscle activations, provided by stretch reflexes, automatic postural responses, and startle. If these responses influence the fall behavior in providing stiffness and generate an appropriate torque at ankle joint, then it is also important to see from what point in time it affects the head trajectory.

During a fast support translation triggering a potential fall, it is proposed that these responses have little effect in the "passive" phase. Rather it is probably the delayed component (long latency responses) of muscle activations occurring in the "active" phase which help to compensate substantial balance disturbances and determine the outcome of the fall or recovery (17). This is

Abbreviations: ANOVA, analysis of variance; BoS, base of support; BMI, body mass index; CoM, center of mass; CoP, center of pressure; EMG, electromyography; DLT, direct linear transform; FS, fall score; F, fall; NF, recovery; PO, perturbation onset; SAS, statistical analysis software; SD, standard deviations; TTC, time to contact.

reminiscent of the responses to tripping where it was found that early EMG activations (up to 100 ms) did not correlate with the behavioral response [elevating or lowering strategy, (18)].

In the present experiments on a large sample of subjects, multiple balance perturbations were provided by unpredictable support-surface translations in various directions and velocities. The aim of this study was to distinguish the passive and the active phases during the pre-impact period of a fall. It was hypothesized that it should be feasible to evaluate the dispersion of the body segments trajectories across trials. Moreover, a multi-joint kinematical model was created for each subject, based on a new 3-D minimally invasive stereoradiographic X-ray image. The latter were used to assess subject-specific geometry and inertial parameters. The simulations allowed disentangling the contributions of the passive and the active components during falls. Finally, the present study is relevant in the context of perturbation training. It was proposed that such training could be valuable to facilitate generalization of effective responses to various perturbations (19). If so, the relevant question arises as to what number of repetitions of multidirectional perturbations is needed to obtain such beneficial generalization.

A follow-up study (unpublished data) focus on which strategies are used to successfully avoid falling.

MATERIALS AND METHODS

Participants

The ability to react to sudden perturbation was investigated in 23 healthy, young and physically active volunteers (9 women and 14 men, 28.6 ± 8.2 years). All participants were free of any diagnosed diseases that may have affected their control of balance or limb movement. Subjects were normal bodied (172.3 ± 8.2 cm and 66.1 ± 8.8 kg) and selected in order to cover a representative range of anthropometric properties. All but two were right-side dominant. Their body mass index (22.3 ± 2 kg/m^2) corresponded to a "normal" range "body mass index (BMI) classification" and "Global Database on Body Mass Index" (20). The participants' levels of physical activity was assessed by asking them whether they practiced more or <3 h of endurance exercise per week (21). All experiments were performed according to the Declaration of Helsinki, and the experimental procedures were approved by the Human Ethics Committee on Human Research of the University of Pierre-et Marie-Curie (CPP 06036). All the subjects provided written informed consent prior to their participation.

Apparatus and Procedure

While subjects were standing upright quietly in a standard position with their eyes open, balance was disturbed using a servomotor controlled movable platform driven by a pneumatic piston. The perturbation was provided by sudden multidirectional horizontal translation of the support surface in one block of 32 trials. The amplitude of displacement was 40 cm and the imposed waveform was a ramp. These translations were randomly presented either sideways (rightward, leftward) or in the anteroposterior (forward, backward) directions. Postural control was further challenged as two magnitudes of perturbation were randomly applied in combination with each direction: a low-threatening perturbation (mean velocity: 35 cm/s, peak acceleration value: 7.8 m/s^2) and a high-threatening perturbation (90 cm/s; 10.78 m/s^2). These two velocity ranges were selected on the basis of pilot trials to ensure successful recovery in about 80% of the time in "slow" trials whereas "fast" perturbations were sufficiently challenging to trigger non-recoverable falls. Some unpredictable aspects of a fall were a prerequisite to design our protocol, such that no training trials were given and the trials were randomized. The body movements were quantified from the first impulse, and the instant at which the perturbation was delivered as well as its velocity and direction were unknown to the subjects. No specific instructions were given with regard to the postural reaction. A standard initial position (12 cm spacing between heels, 10 deg angle between the medial margins) was used in all trials. At all times, participants were securely harnessed in order to abort a complete fall, without otherwise restricting movement in the first 500 ms. The inter-trial time interval was dictated by participant readiness and platform resetting time.

Data Collection

The onsets of platform translation as well as displacement of the body segments were calculated as the first inflection above 2 standard deviations (SD) from the baseline displacement for each individual trial. All timing measures were defined relative to this perturbation onset (PO).

Kinematics

Body kinematic data were collected at a sampling rate of 200 Hz using a three-dimensional motion-capture system (Codamotion-CX1 system, Charnwood Dynamics, and Leicestershire, UK) with a spatial resolution of 0.3 mm. Four Coda CX1 unities tracked the coordinates of 27 infrared active LED markers placed bilaterally on the anatomical landmarks: head of the fifth metatarsal ("toe"), head of the first metatarsal, lateral malleolus ("ankle"), external and lateral femoral condyles ("knee"), greater trochanter ("hip"), anterior superior iliac spine ("pelvis"), zyphoid process at the lower part of the sternum and L5/S1 joint ("thorax" and "trunk"), C4 and C7 spinous processes ("neck"), left and right tragus and nasion ("head"), acromion process ("shoulder"), olecranon ("elbow") and processus styloideus ("wrist"). One marker was placed on the platform and an accelerometer, sampling at 1,000 Hz, was fixed on the platform to calibrate the starting moment. The measured marker coordinates data, together with Dempster's anthropometric data (21) adapted by Winter (22), made it possible to determine the weighted summation of individual segments from which the trajectory of the whole Center of Mass (CoM) was derived. Marker displacement data were low-pass filtered at marker-specific optimal cut-off frequencies (range: 4.5–9 Hz) using a recursive second-order Butterworth Filter.

Determination of the Passive Phase of a Fall

To determine the duration of the passive phase, the onset of displacement of each body segment was first assessed. Then, for each subject and body segment, the four individual trials in a

given condition were superposed (see **Figure 1A**). The instant at which the trajectories were considered to vary from one trial to another was determined based on the inflection point, which was based on the instantaneous standard deviation curve (**Figure 1B**). This point (± 200 ms) was assessed using sliding least-squares lines originating from both sides of the inflection. The intersection point of these lines was associated to a minimal value, which corresponds to the inflection point (**Figure 1C**).

Stability Assessment

The positions of the markers on the toes, heels, and lateral malleolus were used to define the fore-aft and medial-lateral support boundaries. Additional length measurements were made to assess foot anthropometry, such as foot length, to evaluate the distance between the markers and the anteroposterior foot extremities (line joining the heels to the big toes). The motion state of the CoM (23, 24) in relation to the leading edge of the base of support (BoS; either the rear of the heel-for a forward translation-, the front or the lateral side) was calculated as the margin of stability, taking into account both the projected CoM position expressed relatively to the boundaries of the BoS and normalized to foot length, and the CoM velocity expressed relatively to BoS velocity. An instantaneous Time To Contact (TTC) value was calculated dividing the instantaneous distance of the CoM to the stability boundary toward which it was moving by its closing directional velocity, a first derivative of CoM positional data (25, 26). Furthermore, the trials in which the CoM motion state never reached the boundary, those in which it almost crossed it (approaching distance < 5 mm; TTClim) and finally those in which it exceeded the boundary had to be considered in order to determine quantitative measures of a person's stability. In the latter case, it characterized a backward, forward or lateral loss of balance (depending on the direction of the perturbation), with regards to the computed limits of stability (27–29). Of particular interest was the comparison between the instant at which a recovery step was initiated and this time-data point, henceforth referred to as the stability boundary.

Fall-Recovery Outcome

A putative fall was detected using three redundant criteria. Firstly, a "fall" was registered each time the subject ended in a seated position in the harness. Secondly, a fall occurred when the midpoint connecting the hip joint centers descended within 5% body height of its initial standing height (30); otherwise, the trial was classified as a recovery. Thirdly, the automated classification was checked using a video recording of the trial. The outcome of each trial was scored 0 for recovery or 1 for a fall; all trial scores were added up to calculate a subject's "Fall score."

Postural Strategies

Different strategies have been identified in the literature, among which we can mention the feet-in-place strategy, such as the hip and ankle strategies, and the change of support strategy such as stepping. As explained above, the trials were first distinguished as successful recovery or fall and further qualified by the strategy in use and its efficiency. The methodological approach is presented here although the active phase analysis is the topic of future study (unpublished data). Trials including at least one step were identified through different sources: the observation of the presence of steps during the experimentation supported by the control video, the movement of the feet detected by the motion capture analysis (both a toes and ankle marker displacement recorded along the vertical axis). Further analysis consisted in identifying a single vs. multiple steps strategy and the use of a so-called "cross over" vs. a "side step" (loaded or not) in mediolateral trials (31). Several parameters were then analyzed to better characterize the steps: the instant of step initiation or "foot off" (determined as the first sample after PO in which the ankle marker started moving in upward direction), the step duration and length (evaluated with the determination of the instant of touch down), the height of the step (maximum value reached on the z axis), the preferential limb used for the first step and the stability margin at step initiation and the number of steps. In addition, among other measures used to quantify modifications in the subject's response strategies to the perturbation, angular kinematics were calculated through onset times, peak amplitude and peak velocity of the following joint motions: ankle {flexion, extension, pro-supination}, knee {flexion, extension}, hip {flexion, extension, abduction}, trunk {forward and lateral flexion/extension}, shoulder abduction, elbow flexion, neck {forward and lateral flexion, rotation} and finally, the head linear and angular displacement in space. These angular displacements were evaluated according to the initial state calculated over the 2,000 ms preceding PO: a comfortable vertical upright position, arms at sides, with forearms naturally rotated in a relaxed posture {pronation}.

Fall Modeling

An accurate 3D personalized model of each subject was built from biplanar (anteroposterior-AP and lateral-LAT) stereoradiographic images of their whole body using the low dose technological X-ray system EOS® (Biospace Instrument, Paris, France). Specific 3D reconstruction methods—based first on an identification of specified 2D anatomical marks and contours digitized in both radiographs, then on a fast computation of a generic model followed by local deformations—made it possible to assess accurately subject-specific geometry and each body segment inertial parameters (32–34). The body shape reconstruction was divided into 11 segments: head, neck, thorax, abdomen, hip, thighs, legs, and feet. The segment boundaries were those described by Dumas (35), and by Sandoz (36) for the neck and the abdomen. For each body segment, the masses, 3D CoM location and inertial matrixes were calculated thanks to specific software developed using Matlab and densities as derived from the literature (21, 37). Because of inside air, lung density was defined in order to have a global density of the thorax (lungs and all the other organs) in accordance with the literature. As the 3D reconstruction was not yet completed for the upper limbs, they were represented by rigid bodies and reconstructed using DLT algorithms based on the digitization of anatomical landmarks such as acromion, olecranon, wrist joints, and fingertips. The masses and CoM location of the arm, forearm and hand were assessed according to the Dempster database. The total body mass was calculated by the addition of the masses of

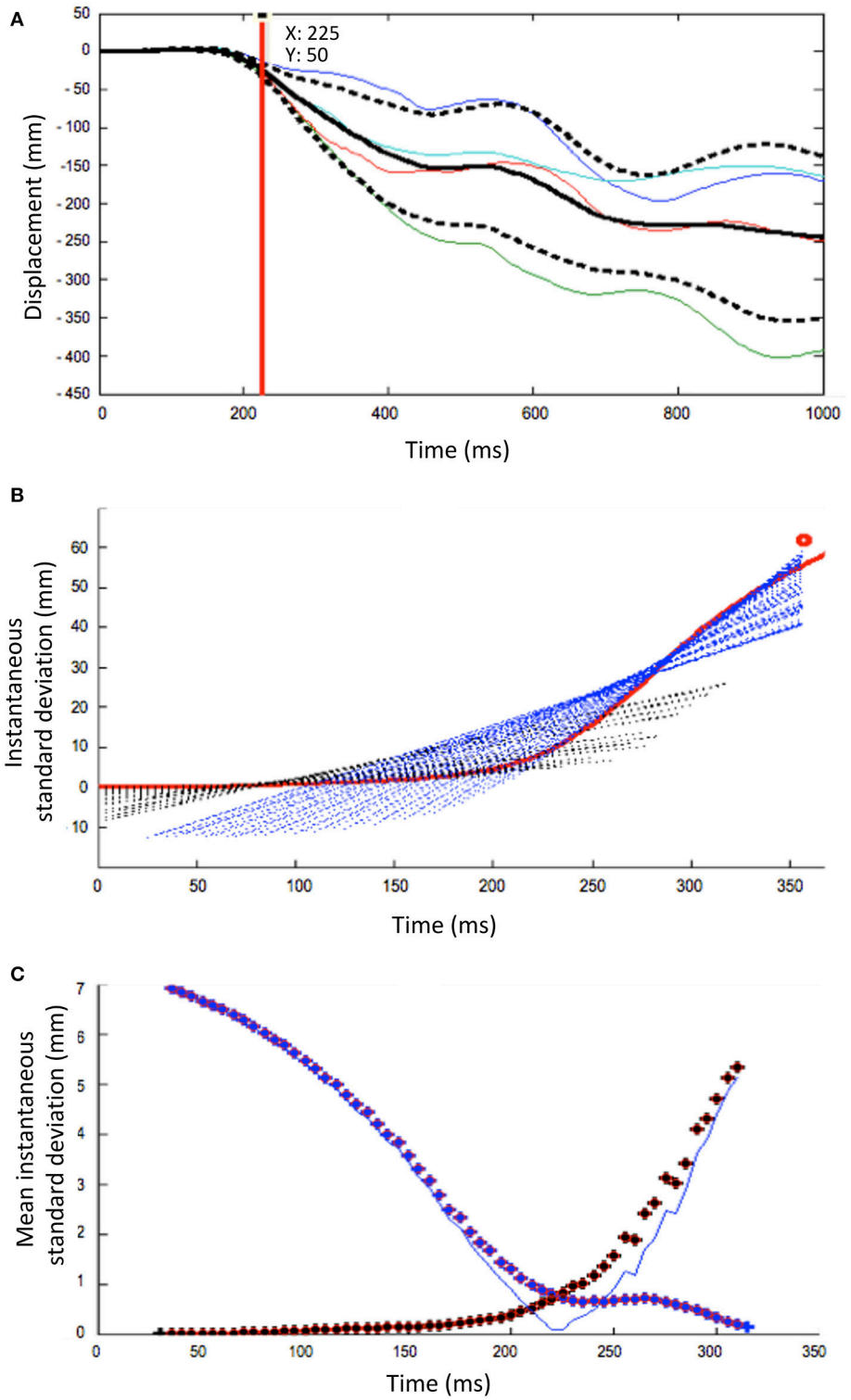


FIGURE 1 | Methodological process to determine the increase of the inter-trial variability at a given condition for a single subject. The illustration is here based on the head segment displacement after a forward fast platform translation. **(A)** The mean displacement (black solid line) ± 1 s.d. (black dotted lines) is calculated from the superposition of 4 trials (colored solid lines). **(B)** Instantaneous standard deviation curve against time (mean s.d), as used to determine inflection point (here at about 200 ms). Added are the sliding least-squares lines originating from both sides of the inflection. **(C)** Determination of the inflection point of the mean instantaneous standard deviation curve (blue squares), from which the inter-trial variability increases significantly (red squares). It corresponds to the intersection point of these lines, which is the minimal value (blue thin line).

each virtual body segment. The global body CoM was defined as the weighted barycenter of all segmental CoM. This whole-body reconstruction method was established for a standing subject (36).

In a second step, these parameters served as inputs for the following numerical and personalized model including 17 rigid segments (head, neck, thorax, abdomen, pelvis, arms, forearms, hands, thighs, legs, and feet) connected with 16 revolute or ball joints offering 92° of freedom. Its simulated movement after the same imposed destabilization as used in the experimental part (in terms of perturbation nature, direction, velocity, and acceleration) served as a database for a comparison with the kinematic behavioral data collected during the experiments on the movable platform. Outputs included the displacements of each segment's center of gravity (x, y, z components) in the global coordinate system, the translations and rotations of the head markers and local frame of reference and the angular displacements described earlier. **Figure 2** summarizes the whole procedure.

Statistical Analyses

Statistical analyses were performed using the Statistical Analysis Software (SAS) for Windows. All means throughout this paper are given with their associated standard deviation (mean ± SD). The groups were compared using the chi-squared or Fisher test for categorical data (age, weight, height, direction, velocity). A general linear model repeated-measures ANOVA with the Bonferroni correction for multiple comparisons was used to compare the differences between falls and recoveries for each recorded dependent variable (38).

The comparison of individual characteristics between the two groups (Fall vs. Recovery) was analyzed by a Wilcoxon Rank Scores test for continuous variable (age, weight, height, and BMI); and by a Fisher test for categorical variables (gender and fitness level). Then, in a base including all the tests combined, a Chi2 test (1 ddl law) was used to study the effect of direction and speed on fall occurrence. A general linear model with repeated measures (subjects) was used to compare calculated variables such as latency of movement, steps characteristics, spatiotemporal aspect of muscle activity. Indeed, a classical analysis was not possible in our main experimental study: the samples were not independent and did not contain an identical number of falls and recoveries by subject (paired study). Intra-individual and inter-individual variability were evaluated using a mixed model. Adjustments on the subject, the number of steps, and the experimental condition were made. We thus conducted an analysis in subgroups i.e., separate analyzes by direction and speed (experimental condition). Further planned contrasts isolated effects with the Bonferroni correction were then performed to compare two by two the differences between conditions.

For kinematic analyzes, we used a non-parametric paired-averaging test, the Wilcoxon test.

The level of statistical significance for all tests was $p < 0.05$.

RESULTS

From the 25 subjects, a total of 526 trials were investigated in detail and considered for the main analysis. These trials were unambiguously classified as a successful or a failed recovery (i.e., a fall). The other 210 trials were excluded from statistical analyses due to excessive movement occurring prior to the perturbation, missing marker data, harness rope-assisted behaviors or platform translation abnormalities.

Occurrence of Falls and Recoveries

As mentioned in the Materials and Methods section, a fall score was calculated for each subject separately in order to describe inter-individual variability in the trial's outcome (i.e., fall vs. recovery). A fall score (FS) of 1 indicated that the subject had fallen at every trial, whether it was a slow or a fast translation. On the other hand, a low FS was associated to few falls across all the subject's trials. **Figure 3A** illustrates the large between-subject variability as the subjects could arbitrary be divided in three groups: those who never or rarely fell (30.4% with a FS < 0.15), the ones who always or frequently fell (17.4% with a FS > 0.5), and the remaining majority of individuals (52.2%) who had variable FS as they either failed or successfully managed to

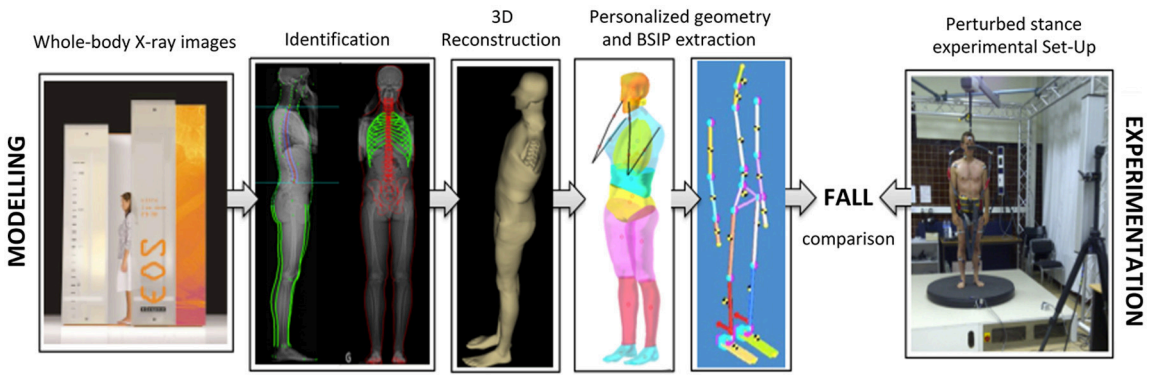


FIGURE 2 | Kinematic comparison of a real *vs.* a theoretical fall in human subjects (experimental data) and their personalized mechanical models (simulation data), respectively.

recover their balance. Within this group, the outcome variability (Fall (F) vs. Recovery (NF) amongst subjects was not related to age ($p = 0.85$, Wilcoxon test), gender ($p = 0.2$, Fisher test), height (F: 169.5 cm vs. NF: 173.2; $p = 0.23$, Wilcoxon test), weight (F: 63.6 kg vs. NF: 67.2; p = 0.85, Wilcoxon test), BMI (F: 22.05 vs. NF: 22.62; $p = 0.62$, Wilcoxon test), or fitness level ($p = 0.96$, Fisher test).

The occurrence of a fall varied according to the direction of platform movement ($p = 0.0003$, Chi2). As summarized in **Figure 3B**, forward trials (44% of falls) appeared to be significantly more challenging than backward (14%) and mediolateral trials (21%). As a rule, fast trials generated significantly more falls than slow translations ($p < 0.0001$, Chi2), with the exception of ipsilateral trials i.e., when the perturbation occurred toward the side of the dominant leg ($p = 0.06$, Chi2).

Hence, speed was clearly important. Out of 266 fast trials, 47% led to a fall with 31% occurring for the fast forward platform translation. The second most challenging condition was fast contralateral [i.e., when the perturbation occurred contralateral to the side of the dominant leg ($p = 0.06$)], leading to 16% of falls. The failed recoveries were episodic after a backward fast translation. In contrast, much less falls were induced by the slow platform movement. Out of 260 slow trials, 18% led to a fall. The backward falls (following a forward platform translation) remained the most frequent (13%) while the second most challenging condition was the contralateral translation, leading to 6% of falls. Slow backward trials only generated 3% of falls.

With respect to the question whether subjects are able to learn to recover balance, the data on the percentage of falls was plotted with respect to trial number. As shown in **Figure 4**, the occurrence of a fall did not depend on the rank of the trials during the first 25 trials. Later trials however, showed a decrease in fall rate, indicative that learning is possible but requires time and experience.

The relative absence of learning during the first 25 trials was probably related to the randomization and the unpredictability of the direction and/or speed of the upcoming disturbance. Nevertheless, the series always started with a "forward slow" trial (to limit startle reactions) and this significantly resulted in more falls than the rest of the tests in slow condition ("first trial effect"). The particular analysis of the first trial (for instance compared to a second absolute test or a second similar trial in speed and direction) for each individual constitutes an axis of improvement for future studies given its emphasis in the literature.

FIGURE 3 | (**A**, left): Variability of the subject (Si) performances. The individual Fall Scores are averaged for each subject and all experimental conditions (blue and pink colors: male and female, respectively). (**B**, right): Fall occurrence according to the perturbation direction and velocity. f, fast; s, slow, IPSILAT. and CONTRAL. refer to the mediolateral directions, relative to the dominant leg (hence ipsilateral refers to a platform translation toward the dominant leg).

The Three Phases of a Fall

As pointed out in the introduction, the pre-impact phase of a fall lasts no more than 750 ms in a standing subject, so it is important to identify the timing of active corrections to counteract a loss of balance. To evaluate this timing, we used a method based on the dispersion of the traces after perturbation onset. **Figure 5** illustrates this for the head segment.

Figure 5A shows that constant forward translations of the platform led to a series of head trajectories that started to diverge after some 300 ms. This divergence was further evaluated with an instantaneous dispersion curve as illustrated in **Figure 5B**. It shows the superposition of four trials after a forward fast

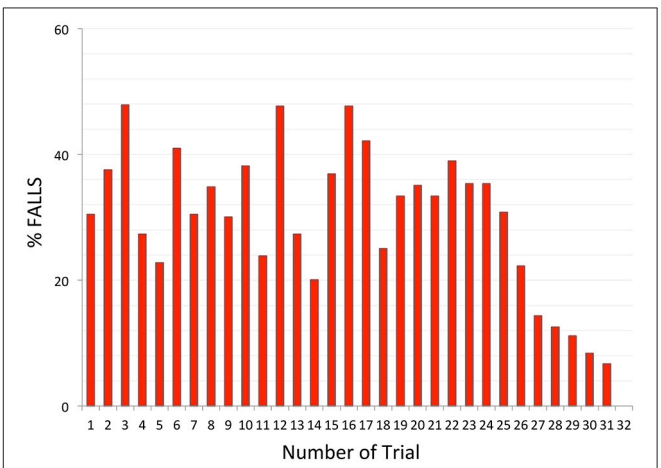


FIGURE 4 | Fall occurrence according to the number of trials.

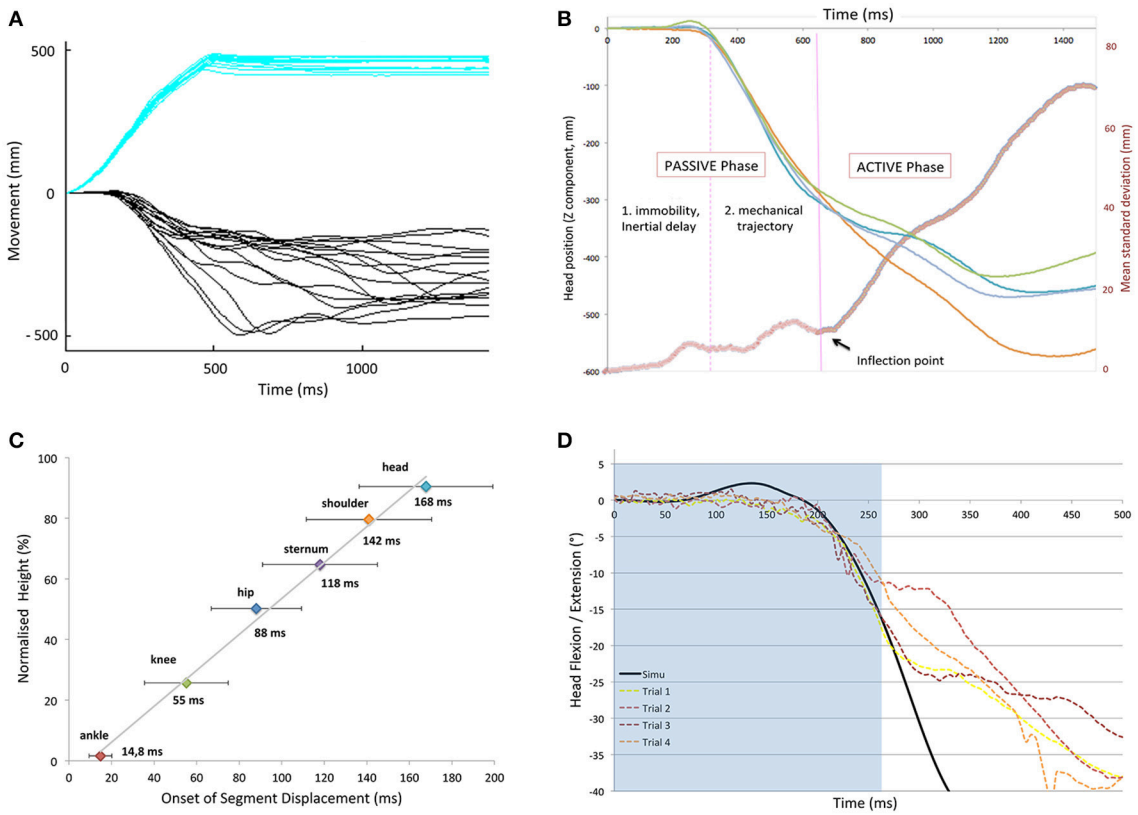


FIGURE 5 | (A) Platform (blue) and vertical head displacements (black) during the first second of a backward fall (forward translation) for several subjects. **(B)** Illustration of representative head kinematics: superposition of four trials after a forward fast translation of the support surface and instantaneous dispersion curve (red thick line). The "variability threshold" (separating passive and active phase), was determined using the inflection point on the curves separating the trajectories with low and high dispersion (purple line). **(C)** Onset of deviation of the various body parts with respect to height. Note that there is a linear relation between segment height and its inertial latency of displacement. **(D)** Simulated (black) vs. Experimental (colored dotted lines) data for the head displacement (z axis) of a subject after a forward fast translation. Note that both curves superimpose in the passive part (light blue background).

translation of the support surface applied to a subject. From such displacements, an inflection point was determined on the mean instantaneous standard deviation curve and referred to as a "variability threshold," separating the trajectories with low and high dispersion. The period after the inflection point was termed the "active phase" (T3) as it was assumed that the sudden increase in dispersion was due to subjects actively reacting to the perturbation with the whole body, including the head.

The period prior to the inflection point was termed the "passive phase" and could further be subdivided. Immediately after perturbation onset, a first phase of the fall was defined as the "immobility period" (T1) as there simply was an absence of movement, due to inertia. For the head, this immobility period could last until 200 ms, which is 1/3 of the available time to recover.

In the second phase of the fall, termed "free-fall period" (T2), the head did move but very consistently on a trial-to-trial basis, suggestive of passive motion. This reproducible low-variability was observed at all levels: once each segment started to move, they followed a similar trajectory on a trial-by-trial basis (reproducible low-variability). Each trial could be divided into these three phases, whether it ended in successful recovery or not.

Each body segment followed this chronological subdivision, but with different time-intervals. **Figure 5C** illustrates the onset of displacement of each body segment under study, in relation to its respective height, after a forward fast support surface translation. It shows the linear relation between the segment distance to the point of perturbation application. There was a clear toe-to-head progression despite an increasing variability according to height. This variability may be explained by the specific inertia of each body segment, as belonging to a group of heterogeneous solids. This linear relation was observed in each condition of perturbation (whatever the direction and velocity; $r = 0.95$, $SD = 0.027$).

The upper trunk and the head had the longest latencies. In particular, after a fast forward perturbation (backward fall), they remained motionless for T1 = 142 ms (SD 20) and 168 ms (SD 24), respectively. These T1 latencies were significantly longer than after a slow forward translation (T1 = 78 ms (SD 12) and 148 ms (SD 24), $p = 0.018$ respectively). Taken together over all velocities and directions, T1 lasted 106 (SD 22) and 142 ms

(SD 31) for the trunk and head, respectively. The duration of T2 was similar across all fast and slow trials whatever the direction and lasted 92 ms (SD 33) and 105 ms (SD 38), respectively for the trunk and the head, with the exception of mediolateral trials (trunk T2 phase shortened to 75 ms; SD 26). Conversely, the head was displaced earlier after a fast mediolateral translation ($p = 0.03$) compared to slow medial-lateral trials.

T3 duration was not calculated, as it was either truncated by landing in the harness (in falls), or characterized by a return to initial and stable position. No instructions were given to the subjects. However, a prevalent strategy was to respond to the imposed destabilization with a stepping reaction, occurring in 92% of the trials (unpublished study).

A global description of the body motion relied on the CoM movement analysis, in relation to the base of support displacement. The TTC (Time To Contact, see Methods) value is a calculated variable combining CoM projection and BoS positions and velocities (see Methods), which indicate the state of balance at each instant. In slow trials, the projection of the CoM stayed inside the base of support in 75% of the trials (90% in mediolateral trials). However, after fast perturbation onset, all subjects reached a state of disequilibrium around 218 ms (mean TTC, all directions taken together). The mean TTC values amounted, respectively to 235, 236, and 188 ms for forward, backward, and mediolateral fast perturbations, and were not significantly different between falls and recoveries.

Modeling the Head and Trunk Trajectories

As detailed in the Methods section, a 17-rigid-segment model (head, thorax, arms, forearms, hands, pelvis, thighs, legs, and feet) was personalized to fit each subject's characteristics using data recorded from a recent non-invasive tridimensional radiographic method. This model was used to simulate the postural response of the subjects following translational displacements of the basis of support identical to the experimental perturbations.

The trajectories of the head and the trunk of this purely passive model were compared to the experimental results in order to determine at what latencies these two sets of curve diverged.

The results of a representative subject are illustrated in **Figure 5D** for a fast forward translation. It shows that the head displacement matches the mechanical model during the first ∼250 ms. The head and trunk trajectories of the model fitted nicely until the end of the passive phase defined above (T1, T2), i.e., until these trajectories became extremely variable on a trial-to-trial basis, in particular in the forward and backward directions. The similarity between the model and the experimental kinematics was less pronounced in the mediolateral direction.

Analysis of the Active Phase: Angular Kinematics

Falls were most prominent for anteroposterior translations. After a fast-forward translation, the head, trunk and limbs first extended passively. Could there be a difference in this "passive phase" that is predictive of falls? To examine this question, we compared the body kinematics of the trials resulting in a fall with those resulting in a recovery.

The difference between passive and active phases is illustrated in **Figure 6** based on single trial responses to fast forward translations. It illustrates a typical successful trial (i.e., a recovery) compared to a fall after a fast-forward translation (backward fall). The first corrective step consisted of a passive extension followed by a fast flexion. Typically this flexion occurred faster in the trials with recovery, as compared to the fall trials. In contrast, note that the passive period (0–160 ms here) was similar for both types of trials. The limbs extend at the knee and ankle joint levels in both trials but more so and longer in falls. When all trials were considered, the ankle extended passively (plantar flexion) to a peak for 144 ms (SD 8 ms) in successful trials vs. 184 ms (SD 27ms) in fall trials. This difference was significant ($p = 0.002$) as was the difference in maximum added extension angle [4.5 (SD 1.3) and 8 (SD 1) degrees respectively; $p = 0.003$]. For the knee, a similar difference existed but it was not significant (peaks at 122 ms and 139 ms for recoveries and falls, respectively ($p = 0.1$), associated to peak extension magnitudes of 3 and 2° ($p = 0.06$). These data are indicative of different stiffness states at the onset of the perturbation (see Discussion).

A detailed analysis of the corrective responses and the discriminative variables between a fall and a recovery forms the subject of a subsequent paper but the data were in line with this typical result, shown here.

For forward fast trials, the head displacement was stabilized in space for a longer interval of time in recovery trials (298 ms, SD 20 ms) than in fall trials (205 ms, SD 14 ms).

Regarding the upper limbs, the data were very different than for the legs, as the expected passive part of their movement (pendulum-like) was barely visible to be analyzed. Overall, we observed early startle-like muscular activities, or functional movements (either flexion or abduction) for both outcomes (falls and recoveries).

During fast backward translations, only a few falls were observed (see earlier). The body swayed forward, leading to an

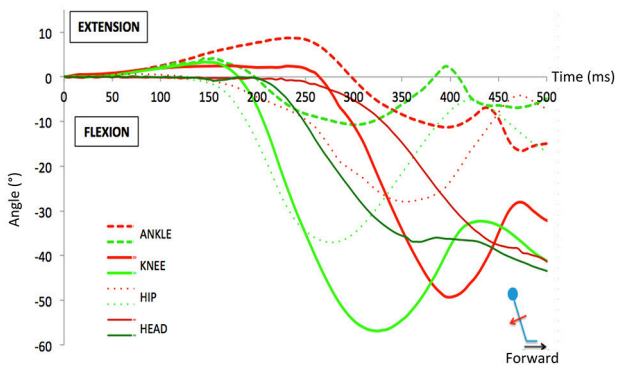


FIGURE 6 | Example of the angular variations during a typical successful trial (i.e., a recovery, in green) compared to a fall trial (in red) after a fast forward translation (backward fall). During the passive phase, one observes that the limbs extend at the knee and ankle joint levels similarly in both trials for the first 160 ms. However, the extension lasted longer in the fall trial because the active correction (flexion) occurred later than in the recovery trial.

anterior position of the CoM relatively to the base of support (BoS). A corrective step was then preferentially used to recover, and its absence was the signature of falls. Moreover, a startle-like arm movement was observed in fallers, with a significantly shorter latency of activation [F: 72 ms (SD 9) vs. Recovery (NC): 109 ms (SD 11), $p = 0.02$] but a smaller magnitude of activity (until 360 ms).

During slow anteroposterior translations (backward and forward trials), the CoM moved in phase with the platform and never crossed the BoS borders in recoveries. The head, trunk and limbs were kept aligned before a step occurred. Conversely, in falls, after slow translations, the body trajectory was en bloc and behaved as a non-controlled inverted pendulum.

DISCUSSION

The main findings of the present study were as follows. (1) By looking in detail to the movements of the body segments and their dispersion it appears that large corrective responses are observed only after 200 to 300 ms following the onset of perturbations, suggesting that inertia is the important element in this period (as confirmed with a 17-rigid-segment model) and that efforts aimed at recovery of falls should concentrate on the period 300–700 ms. (2) The head is the last segment to move thereby excluding an important role for vestibular and visual inputs for initiating the corrective responses. It leaves the proprioceptive sensors as sole source of information for 300 ms at the onset of unexpected fall. (3) Comparing the various directions of translations, the percentage falls for fast forward translations was highest [in line with (4)]. Better chances of recovery were seen when corrective steps were fast and infrequent. (4) With the randomization protocol used it took more than 20 trials to achieve a decrease in the rate of falls. These findings will be discussed in detail below.

Actively Preventing Damage During a Fall: A Short Time-Window Available

The pre-impact phase of a fall lasts some 700 ms in a standing subject (4). The present study shows that this period consists of a "passive phase" with an immobility period (T1) followed by a period of passive motion of the segments ("free fall") (T2). The term "passive" refers to the absence of large corrective responses involving changes in head position, which can apply to active or inactive muscles (4). The first period (T1) reflects an inertial delay as the onset of the detectable movement of each segment of the body was in linear relation to their respective height. Then, once it moved, the segments trajectory was similar from one trial to another (T2), until the variability started to increase, reflecting gain of control (T3).

The first two phases (T1 and T2) were considered to be mostly passive, dictated primarily by the inherent inertia and tone of a poly-articulated body translated at its basis, as strongly suggested by the simulated response of a mechanical model. Properties such as stiffness and damping intrinsic to the joints and muscles appeared to play a major role at the beginning of a fall, as previously suggested for the regulation of quiet upright stance (22, 25, 38–43). In contrast, it is suggested that the third phase (T3) is concomitant to the moment when active adjustments can be made, a point that is of major importance in the context of applying martial arts (or other) techniques for safe falling (see introduction). The present study identified the onset of this third phase by applying a quantitative measure of dispersion.

The passive phase is limited to approximately 200–300 ms (with a fall lasting typically about 700 ms). The "loss of balance point" was always reached in fast trials, supporting the hypothesis that there is an incompressible time lag, as the body behaves like a mechanical model composed of interconnected viscoelastic masses. Such a passive phase has been observed or described by others as well (27, 30). In their modeling study, Bortolami et al. (38) showed that a period of 125 ms after perturbation onset is needed before forces are generated for the CoP to go past the CoM, with the body performing a forward falling motion. Altogether then, it appears that one can start applying motor strategies aimed at preventing a fall at around 300 ms after the onset of perturbation (with a fall lasting typically about 700 ms). This result agrees with a modeling study showing that it should take about 300 ms delay before a reaction to a lateral fall can intervene to decrease hip impact (44). This pluriarticulated biomechanical behavior may generate compensatory feedback for additional stabilization that leads to a more effective control of the whole CoM even if adjustments in timing response are limited (45).

Conversely, muscle activities are recorded early (from 60 ms) but the analysis of the body trajectory suggests that they are initially insufficient to counteract the biomechanical forces resulting from the imposed external destabilization. In other words, the muscle activities at play in the initial phase of the fall influence the stiffness and damping of joints as well as the postural tone, but do not reflect yet a functional and active recovery strategy. We argue that this passive phase could be reduced according to the initial conditions of rigidity for instance. A remaining question is whether it is deleterious for the subject to shorten this "refractory period" driven by mechanical properties (lowest energy cost, mutimodality updated afferences, extra time).

What Patterns of Sensory Information Contribute to Postural Control During a Fall?

In addition, the present data throw light on the sensory source of the corrective responses. In fact, the deformation of the pluri-articulated body is specific to the type of perturbation (46). Here, a platform translation sends a "shock wave" through the body in a caudo-cranial ascendant progression. In accordance with this observation, we suspect that the sensory inputs follows such a temporal sequence. In fact, the head is the last segment to be impacted by the perturbation as it is the farthest from the point of external force application. It implies that visual and vestibular signals are the last to be involved in the on-going fall. This conclusion is specific for the perturbations as used here but it is important since it was occasionally speculated that vestibular inputs could play a role (47).

The present study shows that vestibular input is an unlikely source for reactions to translations since the head remains stationary during the first 200 ms of a fall. This is in line with several studies showing that postural reactions persist in the absence of a normal vestibular system (see introduction). It takes an additional 6 ms for vestibular information to reach several cortical areas (48) and from there, 41 ms to produce external force at the ankle. Altogether, a minimum latency of 247 ms would be required for vestibular information to contribute to the recorded dynamic responses.

In studies with a vertical drop, the situation is different since the head movement could directly trigger muscle synergies in about 60 ms in a pathway over the vestibular nuclei (49–51), leading to a vestibular contribution at about 270 ms. These long latencies explain why vestibulospinal responses would not be instrumental to control the CoM at the onset of a postural perturbation (52–54). However, they would be crucial for head–stabilizing reactions (55) and the processing of the postural vertical information needed to realign the body after recovery (56).

A retinal slip signaling the onset of a fall also requires a head movement. Furthermore, the pathway involved would be slow unless a subcortical pathway is involved (12). The fastest pathway to trigger a postural reaction would then relay through the vestibular nuclei in 28 ms (57). According to one source, after adding 60 ms for a descending volley and 11 ms for the electro-mechanical coupling, a minimum of 300 ms would be required for visual afferences to modulate the postural response, using the accessory optic system (58). Supporting the late contribution of visual inputs, Marigold et al. (59) showed that saccades to the ground were not initiated before 350 ms, after the appearance of an unexpected obstacle.

In contrast, input from the feet starts very early on in the presently described type of perturbations. In particular, the foot started to move 6 ms after the onset of the support-surface translation, generating shear forces after the acceleration of the support-surface upon which the subjects were standing. They conveyed early information about load variations (60). Later, the flow of proprioceptive inputs gradually involved more proximal segments (e.g., pelvis, lumbar column, neck). A delay of 40 ms was required for afferent signals to reach the cortex (61) and 30 more milliseconds were needed to trigger EMG activities in lower-leg muscles (62). Since there was an additional 11 ms for electro-mechanical coupling (63), it would take at least 87 ms to generate forces at the ankle joint, based on proprioceptive information, which is close to the 90 ms latency of the first muscle activities observed here and in previous studies on recoverable falls (64–67). Even if the automated postural responses are mediated by the brainstem, they still have latencies of this type. It is worthwhile noting that such responses do not contribute immediately to "dispersion" and to an increase in variability in head trajectory in the period of 90–150 ms. Possibly this has to do with the stereotyped nature of these responses. Weerdesteyn et al. (68) showed that these responses were basically similar in trials where subjects were instructed to fall and trials with recovery (except for a change in amplitude).

More generally the present data indicate that the earliest muscle activations have a relatively small impact on head and body motions in the first 200–300 ms. Hence it is proposed that interventions on recovery of falls concentrate on the period 300–700 ms, a period which is still long enough to allow the application of safe landing techniques, such as used in martial arts [see introduction (7, 20, 68–73)].

Ultimately, we think that the first synergies aimed at restoring balance are triggered by the most reliable sensors, which detect the onset of the postural disturbance at the earliest possible latency. Our results support that somatosensory receptors encoded the perturbation characteristics and triggered the initial corrective responses (67) in accordance with several studies on balance in older subjects with and without diabetic peripheral neuropathy (74–77).

Learning Not to Fall: The Added-Value of Feed-Forward Mechanisms to an Exclusive Feedback-Based Postural Control?

The purpose of the present work was to give a detailed picture at the stages before touchdown, to detect whether and when someone can intervene in changing the way he/she falls.

Two main postural mechanisms are used by the central nervous system (CNS) to maintain and restore balance during a perturbation: the anticipatory postural adjustments (APAs) and the compensatory postural adjustments (CPAs). Previously, it was assumed that small and/or predicted internal perturbations can be counteracted with a feed-forward control (APAs) whereas a feedback-based postural muscle activation (CPAs) is the main mechanism of balance restauration to cope with large and/or unexpected perturbations (78, 79). However, several studies reported an increase of efficiency in the reactive recovery response after unexpected perturbation training which challenged mechanisms for dynamic stability (70, 80).

As we were primarily interested in reactive behavior, care was taken to avoid feedforward mechanisms as much as possible using unpredictability and trials randomization to avoid anticipatory behavior. This was successful for the first twenty to twenty-five trials as there was no difference in the rate of falls, hence these trials will be discussed first. In these trials the recovery depended primarily on corrective responses and it is important to know how fast these reactions occur because one can hope to be able to change these reactions. In this sense, the present study is similar to the work by van Swigchem et al. (7), who showed that EMG amplitudes needed for a safe fall technique started as early as 180–190 ms after onset of the (sideways) fall. It was concluded that voluntary motor control is possible within the duration of a fall, even in inexperienced fallers. The present data (200 ms passive phase) are in line with this work and are of crucial significance for the debate whether humans can intervene in how they fall (Robinovitch, personal communication). It should be emphasized that the term "passive" is used here to indicate that there is no contribution of gross corrective responses. It does not exclude that there is a contribution of spinal stretch reflexes but these are limited to a contribution to local stiffness and have no effect on total body

behavior. Nichols and Houk (81) showed that the spinal stretch reflex is well-suited to provide muscle stiffness at a time when inherent muscle stiffness fails. This reflex is an active process but it is a local phenomenon and is considered here as part of the passive phase, when whole body responses are considered.

After the first twenty trials there was evidence for "learning" since there was a drop of % falls and a decrease in the rate of falls variability. In this case, one can assume that there is an ability to acquire "fall-resisting skills" during repeated exposure to slips, which would also be generalizable (27). This phenomenon called habituation (82) indicates that subjects are not naïve any more to the upcoming perturbations and the familiarization with the disturbance is accompanied by a greater number of catch-ups: compensatory strategies employed are more effective at recovery, even when the perturbations were presented in random order or onset.

Weerdesteyn et al. (83) also observed a success rate of 17% in the first trial vs. 92% in their last trial. This attempt to reproduce a postural response that increase the likelihood of successful recovery may be related to a shift from a sensory feedback-control-related reactive response based on error correction in the preceding trials to an adaptative feedforward CNS control in order to proactively improve stability (27). The observation that randomizations of postural perturbation does not completely eliminate improvement in corrective responses is in line with previous work (19, 84).

The strategies used to prevent falls were not studied in details here but in the literature several options were suggested. Among the emerging postural adjustments that were described elsewhere on re-exposure to external perturbations, we can mention a pluri-articulated response at hip and ankle levels (85), a better regulation of the CoM position relative to the BoS (27, 45) and a decrease of the amplitude of postural reactions (82, 86). Also, a more flexed knee joint allows the COM to be lower, thereby increasing stability (87, 88). Alternatively, a stiffness strategy can be implemented through muscle co-contraction (agonists/antagonists) as was observed in challenging postural threat conditions (78, 89, 90), pre-programmed reactions (83, 91) or startle reactions (47, 92, 93). In older subjects, co-contraction about the ankle is often seen during static balance challenges but it was shown that this is not necessarily a predictor of successful fall avoidance in this population (94).

Further studies should focus on assessing if predictive adjustments are being made (pre-perturbation behavior such as a squatting initial posture, center of pressure displacements,.) supporting the fact that learning not to fall rely on this interplay between reactive and predictive adaptations (hybrid control theory). In addition to these experimental observations, some laboratory-based measures of postural control (posturography) would be of great interest to reveal subtle deficits in the underlying control mechanisms (95) as it is aknowledged that the inability to produce APA is related to an increased likelihood of falls if older adults (96) or multiple sclerosis patients (97). Finally, a change in central set can also influence the postural response and the outcome (98).

Functional Implications

The present data show that there is limited time to adjust the way one falls from a standing position. We showed that the pre impact period is truncated of 200 ms or so. During the initial part of a fall, the observed trajectory results from the interaction between the destabilizing external force and the body: the inertial properties intrinsic to joints, ligaments and musculotendinous system have then a major contribution, as suggested for the regulation of static upright stance. This passive phase is later followed by an active phase, which consists of a corrective response to the postural perturbation. Thus, we believe that during a fall from standing height, it takes about 300 ms for postural responses to start correcting the body trajectory, while the impact is expected (to occur) around 700 ms. It has been argued that this time is sufficient to change the way one falls and that this makes it possible to apply safer ways of falling (7, 69, 70), for example by using martial arts fall techniques (68, 71–73). Despite these constraints, our study also supports the idea that learning is possible even though it may take a large number of trials.

Currently the training with balance perturbations is increasingly popular. One example is the work of Dijkstra et al. (84). It is of interest to note that this study failed to show generalization of improvements in stepping responses (anterior-posterior perturbation training did not generalize for lateral translations) and the authors suggested that multidirectional training possibly could facilitate generalization. This is exactly what the current paper showed, as indeed improvement occurred for all types of perturbations despite randomization. However, it did take more than 25 trials to obtain this result. This is of great importance as it can indeed encourage people in this field to invest in multidirectional training protocols, provided they are willing to use extended training periods.

ETHICS STATEMENT

Human Ethics Committee on Human Research of the University of Paris 6 (CPP 06036).

AUTHOR CONTRIBUTIONS

ML: principal work, redaction of the paper. DW: experiment, signal processing and helped with the redaction of the paper. EC: helped with signal processing of the EMG. JL: helped with EMG. SL: co-director of the PhD thesis for this work. JD: scientific expert, redaction of the paper. P-PV: director of this project, redaction of this paper. CV: help to do analysis of signal.

REFERENCES

1. Hoogkamer W, Potocanac Z, Van Calenbergh F, Duysens J. Quick foot placement adjustments during gait are less accurate in individuals with focal cerebellar lesions. *Gait Posture* (2017) 58:390–3. doi: 10.1016/j.gaitpost.2017.08.037
2. Loram ID, Lakie M. Direct measurement of human ankle stiffness during quiet standing: the intrinsic mechanical stiffness is insufficient

for stability. *J Physiol*. (2002) 545:1041–53. doi: 10.1113/jphysiol.2002.025049
3. Lakie M, Caplan N, Loram ID. Human balancing of an inverted pendulum with a compliant linkage: neural control by anticipatory intermittent bias. *J Physiol*. (2003) 551:357–70. doi: 10.1113/jphysiol.2002.036939
4. Hsiao ET, Robinovitch SN. Common protective movements govern unexpected falls from standing height. *J Biomech*. (1998) 31:1–9. doi: 10.1016/S0021-9290(97)00114-0
5. Liang D, Ivanov K, Li H, Ning Y, Zhang Q, Wang L. Exploration and comparison of the pre-impact lead time of active and passive falls based on inertial sensors. *Biomed Mater Eng*. (2014) 24:278–88. doi: 10.3233/BME-130809
6. Vibert N, MacDougall HG, de Waele C, Gilchrist DP, Burgess AM, Sidis A, et al. (2001). Variability in the control of head movements in seated humans: a link with whiplash injuries? *J Physiol*. 532:851–68. doi: 10.1111/j.1469-7793.2001.0851e.x
7. van Swigchem R, Groen BE, Weerdesteyn V, Duysens J. The effects of time pressure and experience on the performance of fall techniques during a fall. *J Electromyogr Kinesiol*. (2009) 19:521–31. doi: 10.1016/j.jelekin.2007.12.004
8. Winter DA, Patla AE, Prince F, Ishac M, Gielo-Perczak K. Stiffness control of balance in quiet standing. *J Neurophys*. (1998) 80:1211–21. doi: 10.1152/jn.1998.80.3.1211
9. Gatev P, Thomas S, Kepple T, Hallett M. Feedforward ankle strategy of balance during quiet stance in adults. *J Physiol*. (1999) 514:915–28. doi: 10.1111/j.1469-7793.1999.915ad.x
10. Cenciarini M, Loughlin PJ, Sparto PJ, Redfern MS. Stiffness and damping in postural control increase with age. *IEEE Trans Biomed Eng*. (2010) 57:267–75. doi: 10.1109/TBME.2009.2031874
11. Peterka RJ. Sensorimotor integration in human postural control. *J Neurophys*. (2002) 88:1097–8. doi: 10.1152/jn.2002.88.3.1097
12. Potocanac Z, Duysens J. Online adjustments of leg movements in healthy young and old. *Exp Brain Res*. (2017) 235:2329–48. doi: 10.1007/s00221-017-4967-7
13. Greenwood R, Hopkins, A Landing from an unexpected fall and a voluntary step. *Brain* (1976) 99:375:386.
14. Do MC, Breniere Y, Bouisset S. Compensatory reactions in forward fall: are they initiated by stretch receptors? *Electroencephalogr Clin Neurophysiol*. (1988) 69:448–52. doi: 10.1016/0013-4694(88)90067-3
15. Allum JH, Honegger F. Interactions between vestibular and proprioceptive inputs triggering and modulating human balance-correcting responses differ across muscles. *Exp Brain Res*. (1998) 121:478–94. doi: 10.1007/s002210050484
16. Keshner EA, Allum JH, Pfaltz CR. Postural coactivation and adaptation in the sway stabilizing responses of normal and patients with bilateral vestibular deficit. *Exp Brain Res*. (1987) 69:77–92.
17. Freyler K, Gollhofer A, Colin R, Brüderlin U, Ritzmann R. Reactive balance control in response to perturbation in unilateral stance: interaction effects of direction. displacement and velocity on compensatory neuromuscular and kinematic responses. *PLoS ONE* (2015) 10:e0144529. doi: 10.1371/journal.pone.0144529
18. Schillings AM, van Wezel BM, Mulder T, Duysens J. Muscular responses and movement strategies during stumbling over obstacles. *J Neurophys*. (2000) 83:2093–102 doi: 10.1152/jn.2000.83.4.2093
19. Krause A, Freyler K, Gollhofer A, Stocker T, Brüderlin U, Colin R, et al. Neuromuscular and kinematic adaptation in response to reactive balance training - a randomized controlled study regarding fall prevention. *Front Physiol*. (2018) 9:1075. doi: 10.3389/fphys.2018.01075
20. World Health Organization. *WHO Technical Report Series 894 Obesity: Preventing and Managing The Global Epidemic*. Geneva: World Health Organization (2000). Available online at: http://www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/
21. Bernstein MS, Morabia A, Sloutskis D. Definition and prevalence of sedentarism in an urban population. *Am J Public Health*. (1999) 89:862–7.
22. Winter DA. *Biomechanics and Motor Control of Human Movement*. Manchester, MI: John Wiley & Sons, Inc (1990).
23. Pai YC, Patton J. Center of mass velocity-position predictions for balance control. *J Biomech*. (1997) 30:347–54.
24. Yang F, Anderson FC, Pai YC. Predicted threshold against backward-balance loss following a slip in gait. *J Biomech*. (2008) 41:1823–31. doi: 10.1016/j.jbiomech.2008.04.005
25. Solomonow M, Zhou BH, Harris M, Lu Y, Baratta RV. The ligamento-muscular stabilizing system of the spine. *Spine* (1998) 23:2552–62. doi: 10.1097/00007632-199812010-00010
26. Hasson CJ, Van Emmerik RE, Caldwell GE. Predicting dynamic postural instability using center of mass Time-to-Contact information. *J Biomech*. (2009) 41:2121–9. doi: 10.1016/j.jbiomech.2008.04.031
27. Bhatt T, Pai YC. Generalization of gait adaptation for fall prevention: from moveable platform to slippery floor. *J Neurophys*. (2009) 101:948–57. doi: 10.1152/jn.91004.2008
28. Pai YC, Rogers MW, Patton J, Cain TD, Hanke TA. Static versus dynamic predictions of protective stepping following waist-pull perturbations in young and older adults. *J Biomech*. (1998) 31:1111–8. doi: 10.1016/S0021-9290(98)00124-9
29. Pai YC, Maki BE, Iqbal K, McIlroy WE, Perry SD. Thresholds for step initiation induced by support-surface translation: a dynamic center-of-mass model provides much better prediction than a static model. *J Biomech*. (2000) 33:387–92. doi: 10.1016/S0021-9290(99)00199-2
30. Pavol MJ, Pai YC. Feedforward adaptations are used to compensate for a potential loss of balance. *Exp Brain Res*. (2002) 145:528–38. doi: 10.1007/s00221-002-1143-4
31. Maki BE, Edmondstone MA, McIlroy WE, Age-related differences in laterally directed compensatory stepping behavior. *J Gerontol A Biol Sci Med Sci*. (2000) 55:M270–7. doi: 10.1093/gerona/55.5.M270
32. Laporte S, Skalli W, de Guise JA, Lavaste F, Mitton D. A biplanar reconstruction method based on 2D and 3D contours: application to the distal femur. *Comput Methods Biomech Biomed Engin* (2003) 6:1–6. doi: 10.1080/1025584031000065956
33. Pomero V, Mitton D, Laporte S, de Guise JA, Skalli W. Fast accurate stereoradiographic 3D-reconstruction of the spine using a combined geometric and statistic model. *Clin Biomech*. (2004) 19:240–7. doi: 10.1016/j.clinbiomech.2003.11.014
34. Jolivet E, Sandoz B, Laporte S, Mitton D, Skalli W. Fast 3D reconstruction of the rib cage from biplanar radiographs. *Med Biol Eng Comput*. (2010) 48:821–8. doi: 10.1007/s11517-010-0610-5
35. Dumas R, Chèze L, Verriest JP. Adjustments to body segment inertial parameters. *J Biomech*. (2007) 40:543–53. doi: 10.1016/j.jbiomech.2006.02.013
36. Sandoz B, Laporte S, Skalli W, Mitton D. Subject-specific body segment parameters'estimation using biplanar X-rays: a feaisibility study. *Comput Methods Biomech Biomed Engin* (2010) 13:649–54. doi: 10.1080/10255841003717608
37. White DR, Woodard HQ, Hammond SM. Average soft-tossue and bone models for use in radiation dosimetry. *Br J Radiol*. (1987) 60:907–13. doi: 10.1259/0007-1285-60-717-907
38. Bortolami SB, DiZio P, Rabin E, Lackner JR. Analysis of human postural responses to recoverable falls. *Exp Brain Res*. (2003) 151:387–404. doi: 10.1007/s00221-003-1481-x
39. Do MC, Breniere Y, Brenguier P. A biochemical study of balence recovery during the fall forward. *J Biomech*. (1982) 15:933–9. doi: 10.1016/0021-9290(82)90011-2
40. Cresswell AG, Oddsson L, Thorstensson A. The influence of sudden perturbations on trunk muscle activity and intra-abdominal pressure while standing. *Exp Brain Res*. (1994) 98:336–41. doi: 10.1007/BF00228421
41. Cholewicki J, Juluru K, McGill SM. Intra-abdominal pressure mechanism for stabilizing the lumbar spine. *J Biomech*. (1999) 32:13–7. doi: 10.1016/S0021-9290(98)00129-8
42. Moorhouse KM, Granata KP. Role of reflex dynamics in spinal stability: intrinsic muscle stiffness alone is insufficient for stability. *J Biomech*. (2007) 40:1058–65. doi: 10.1016/j.jbiomech.2006.04.018
43. Brown SH, McGill SM. The intrisic stiffness of the in vivo lumbar spine in response to quick releases. Implications for reflexive requirements. *J Electromyogr Kinesiol*. (2009) 19:727–36. doi: 10.1016/j.jelekin.2008.04.009
44. Lo J, Ashton-Miller JA. Effect of pre-impact movement strategies on the impact forces resulting from a lateral fall. *J Biomech*. (2008) 41:1969–77. doi: 10.1016/j.jbiomech.2008.03.022

45. Barrett RS, Cronin NJ, Lichtwark GA, Mills PM, Carty CP. Adaptive recovery responses to repeated forward loss of balance in older adults. *J Biomech*. (2012) 45:183–7. doi: 10.1016/j.jbiomech.2011.10.005
46. Ting LH, Macpherson JM. Ratio of shear to load ground-reaction force may underlie the directional tuning of the automatic postural response to rotation and translation. *J Neurophys*. (2004) 92:808–23. doi: 10.1152/jn.00773.2003
47. Oude Nijhuis LB, Allum JH, Borm GF, Honegger F, Overeem S, Bloem BR. Directional sensitivity of "first trial" reactions in human balance control. *J Neurophys*. (2009) 101:2802–14. doi: 10.1152/jn.90945.2008
48. de Waele C, Baudonnière PM, Lepecq JC, Tran Ba Huy P, Vidal PP. Vestibular projections in the human cortex. *Exp Brain Res*. (2001) 141:541–51. doi: 10.1007/s00221-001-0894-7
49. Greenwood R, Hopkins A. Muscle responses during sudden falls in man. *J Physiol*. (1976) 254:507–18.
50. Lacour M, Xerri C, Hugon M. Muscle responses and monosynaptic reflexes in falling monkey. Role of the vestibular system. *J Physiol*. (1978) 74:427–38.
51. Fitzpatrick R, Rogers DK, McCloskey DI. Stable human standing with lower-limb muscle afferents providing the only sensory input. *J Physiol* (1994) 480:395–403.
52. Dietz V, Horstmann G, Berger W. Involvement of different receptors in the regulation of human posture. *Neurosci Lett*. (1988) 94:82–7. doi: 10.1016/0304-3940(88)90274-1
53. Horak FB, Shupert CL, Dietz V, Horstmann G. Vestibular and somatosensory contributions to responses to head and body displacements in stance. *Exp Brain Res*. (1994) 100:93–106. doi: 10.1007/BF00227282
54. Goodworth AD, Peterka RJ. Contribution of sensorimotor integration to spinal stabilization in humans. *J Neurophys*. (2009) 102:496–512. doi: 10.1152/jn.00118.2009
55. Shupert CL, Horak FB. Effects of vestibular loss on head stabilization in response to head and body perturbations. *J Vestib Res*. (1996) 6:423–37. doi: 10.1016/S0957-4271(96)00096-1
56. Bortolami SB, Inglis JT, Castellani S, DiZio P, Lackner JR. Influence of galvanic vestibular stimulation on postural recovery during sudden falls. *Exp Brain Res*. (2010) 205:123–9. doi: 10.1007/s00221-010-2333-0
57. Azzena GB, Tolu E, Mameli O. Responses of vestibular units to visual input. *Arch Italienn Biol*. (1978) 116:120–9.
58. Precht W. Visual-vestibular interaction in vestibular neurons: functional pathway organization. *Ann NY Acad Sci*. (1981) 374:230–48.
59. Marigold DS, Weerdesteyn V, Patla AE, Duysens J. Keep looking ahead? Re-direction of visual fixation does not always occur during an unpredictable obstacle avoidance task. *Exp Brain Res*. (2007) 176:32–42. doi: 10.1007/s00221-006-0598-0
60. Schieppati M, Nardone A, Siliotto R, Grasso M,Schieppati M, et al. Early and late stretch responses of human foot muscles induced by perturbation of stance. *Exp Brain Res*. (1995) 105:411–22.
61. Wu XD, Zhu Y, Chen WJ, Jin X, Tsai N, Huang HY, et al. Somatosensory evoked potential from S1 nerve root stimulation. *Eur Spine J*. (2011) 20:1613–9. doi: 10.1007/s00586-011-1768-8
62. Bawa P, Chalmers GR, Stewart H, Eisen AA. Responses of ankle extensor and flexor motoneurons to transcranial magnetic stimulation. *J Neurophys*. (2002) 88:124–32. doi: 10.1152/jn.2002.88.1.124
63. Nordez A, Gallot T, Catheline S, Guével A, Cornu C, Hug F. Electromechanical delay revisited using very high-frame rate ultrasound. *J Appl Physiol*. (2009) 106:1970–5. doi: 10.1152/japplphysiol.00221.2009
64. Horak FB, Nashner LM. Central programming of postural movements. adaptation to altered support surface configurations . *J Neurophys*. (1986) 55:1369–81. doi: 10.1152/jn.1986.55.6.1369
65. Diener HC, Horak FB, Nashner LM. Influence of stimulus parameters on human postural responses. *J Neurophys*. (1988) 59:1888–905.
66. Henry SM, Fung J, Horak FB. EMG responses to maintain stance during multidirectional surface translations. *J Neurophys*. (1998) 80:1939–50. doi: 10.1152/jn.1998.80.4.1939
67. Horak FB, Hlavacka F. Vestibular stimulation affects medium latency postural muscle responses. *Exp Brain Res*. (2002) 144:95–102. doi: 10.1007/s00221-002-1041-9
68. Weerdesteyn V, Laing AC, Robinovitch SN. Automated postural responses are modified in a functional manner by instruction. *Exp Brain Res*. (2008) 186:571–80. doi: 10.1007/s00221-007-1260-1
69. Robinovitch SN, Brumer R, Maurer J. Effect of the "squat protective response" on impact velocity during backward falls. *J Biomech*. (2004) 37:1329–37. doi: 10.1016/j.jbiomech.2003.12.015
70. Kurz I, Gimmon Y, Shapiro A, Debi R, Snir Y, Melzer I. Unexpected perturbations training improves balance control and voluntary stepping times in older adults - a double blind randomized control trial. *BMC Geriatr*. (2016) 16:58. doi: 10.1186/s12877-016-0223-4
71. Sabick MB, Hay JG, Goel VK, Banks SA. Active responses decrease impact forces at the hip and shoulder in falls to the side. *J Biomech*. (1999) 32:993–8.
72. Groen BE, Weerdesteyn V, Duysens J. The relation between hip impact velocity and hip impact force differs between sideways fall techniques. *J Electromyogr Kinesiol*. (2008) 18:228–34. doi: 10.1016/j.jelekin.2007.06.002
73. Weerdesteyn V, Rijken H, Geurts AC, Smits-Engelsman BC, Mulder T, Duysens J. A five-week exercise program can reduce falls and improve obstacle avoidance in the elderly. *Gerontology* (2006) 52:131–41. doi: 10.1159/000091822
74. Rinalduzzi S, Serafini M, Capozza M, Accornero N, Missori P, Trompetto C. Stance postural strategies in patients with chronic inflammatory demyelinating polyradiculoneuropathy. *PLoS ONE* (2016) 11:e0151629. doi: 10.1371/journal.pone.0151629
75. Timar B, Timar R, Gai,?ă L, Oancea C, Levai C, Lungeanu D. The impact of diabetic neuropathy on balance and on the risk of falls in patients with type 2 diabetes mellitus: a cross-sectional study. *PLoS ONE* (2016) 11:e0154654. doi: 10.1371/journal.pone.0154654
76. Toosizadeh N, Mohler J, Armstrong DG, Talal TK, Najafi B. The influence of diabetic peripheral neuropathy on local postural muscle and central sensory feedback balance control. *PLoS ONE* (2015) 10:e0135255. doi: 10.1371/journal.pone.0135255
77. Richardson JK, Eckner JT, Allet L, Kim H, Ashton-Miller JA. Complex and simple clinical reaction times are associated with gait, balance. *and major fall injury in older subjects with diabetic peripheral neuropathy Am J Phys Med Rehabil*. (2017) 96:8–16. doi: 10.1097/PHM.0000000000000604
78. Mohapatra S, Kukkar KK, Aruin AS. Support surface related changes in feedforward and feedback control of standing posture. *J Electromyogr Kinesiol*. (2014) 24:144–52. doi: 10.1016/j.jelekin.2013.10.015
79. Santos MJ, Kanekar N, Aruin AS. The role of anticipatory postural adjustments in compensatory control of posture. *J Electromyogr Kinesiol*. (2010) 20:388–397. doi: 10.1016/j.jelekin.2010.01.002
80. McCrum C, Gerards MHG, Karamanidis K, Zijlstra W, Meijer K. A systematic review of gait perturbation paradigms for improving reactive stepping responses and falls risk among healthy older adults. *Eur Rev Aging Phys Act*. (2017) 14:3. doi: 10.1186/s11556-017-0173-7
81. Nichols TR, Houk JC. Improvement in linearity and regulation of stiffness that results from actions of stretch reflex. *J Neurophys*. (1976) 39:119–42. doi: 10.1152/jn.1976.39.1.119
82. Mierau A, Hülsdünker T, Strüder HK. Changes in cortical activity associated with adaptive behavior during repeated balance perturbation of unpredictable timing. *Front Behav Neurosci*. (2015) 9:272. doi: 10.3389/fnbeh.2015.00272
83. Weerdesteyn V, Laing AC, Robinovitch SN. The body configuration at step contact critically determines the successfulness of balance recovery in response to large backward perturbations. *Gait Post*. (2012) 35:462–6. doi: 10.1016/j.gaitpost.2011.11.008
84. Dijkstra BW, Horak FB, Kamsma YP, Peterson DS, Dijkstra BW, et al. Older adults can improve compensatory stepping with repeated postural perturbations. *Front Aging Neurosci*. (2015) 7:201. doi: 10.3389/fnagi.2015.00201
85. Marigold DS, Patla AE. Strategies for dynamic stability during locomotion on a slippery surface: effects of prior experience and knowledge. *J Neurophys*. (2002) 88:339–53. doi: 10.1152/jn.00691.2001
86. Van Ooteghem K, Frank JS, Horak FB. Practice-related improvements in posture control differ between young and older adults exposed to continuous. variable amplitude oscillations of the support surface. *Exp Brain Res*. (2009) 199:185–93. doi: 10.1007/s00221-009-1995-y
87. Pai YC, Bhatt T, Wang E, Espy D, Pavol MJ. Inoculation against falls: rapid adaptation by young and older adults to slips during daily activities. *Arch Phys Med Rehabil*. (2010) 91:452–9. doi: 10.1016/j.apmr.2009.10.032

88. Bhatt T, Yang F, Pai YC. Learning from falling: retention of fall resistin behavior derived from one episode of laboratory-induced slip training. *J Am Geriatr Soc*. (2011) 59:2392–3. doi: 10.1111/j.1532-5415.2011.03708.x
89. Carpenter MG, Frank JS, Silcher CP, Peysar GW. The influence of postural threat on the control of upright stance. *Exp Brain Res*. (2001) 138:210–8. doi: 10.1007/s002210100681
90. Krishnamoorthy V, Latash ML, Scholz JP, Zatsiorsky VM. Muscle modes during shifts of the center of pressure by standing persons: effect of instability and additional support. *Exp Brain Res* (2004) 157:18–31. doi: 10.1007/s00221-003-1812-y
91. Wolfson L, Whipple R, Derby C, Judge J, King M, Amerman P. Balance and strength training in older adults: intervention gains and Tai Chi maintenance. *J Am Geriat Soc*. (1996) 44:498–506. doi: 10.1111/j.1532-5415.1996.tb01433.x
92. Blouin JS, Inglis JT, Siegmund GP. Startle responses elicited by whiplash perturbations. *J Physiol*. (2006) 573:857–67. doi: 10.1113/jphysiol.2006.108274
93. Nieuwenhuijzen PH, Schillings AM, Van Galen GP, Duysens J. Modulation of the startle response during human gait. *J Neurophys*. (2000) 84:65–74. doi: 10.1152/jn.2000.84.1.65
94. Nelson-Wong E, Appell R, McKay M, Nawaz H, Roth J, Sigler R. Increased fall risk is associated with elevated co- contraction about the ankle during static balance challenges in older adults. *Eur J of Appl Physiol*. (2012) 112:1379–89. doi: 10.1007/s00421-011-2094-x
95. Findling O, Sellner J, Meier N, Allum JH, Vibert D, Lienert C Trunk sway in mildly disabled multiple sclerosis patients with and without balance impairment. *Exp Brain Res*. (2011) 213:363–70. doi: 10.1007/s00221-011-2795-8
96. Uemura K, Yamada M, Nagai K, Ichihashi N. Older adults at high risk of falling need more time for anticipatory postural adjustment in the precrossing phase of obstacle negotiation. *J Gerontol A Biol Sci Med Sci*. (2011) 66:904–9. doi: 10.1093/gerona/glr081
97. Tajali S, Rouhani M, Mehravar M, Negahban H, Sadati E, Oskouei AE. effects of external perturbations on anticipatory and compensatory postural adjustments in patients with multiple sclerosis and a fall history. *Int J MS Care* (2018) 20:164–72. doi: 10.7224/1537-2073.2016-098
98. Pater ML, Rosenblatt NJ, Grabiner MD. Expectation of an upcoming large postural perturbation influences the recovery stepping response and outcome. *Gait Posture*. (2015) 41:335–7. doi: 10.1016/j.gaitpost.2014.10.026

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

CORRECTION
published: 27 February 2019
doi: 10.3389/fneur.2019.00118

Corrigendum: An Initial Passive Phase That Limits the Time to Recover and Emphasizes the Role of Proprioceptive Information

Maeva Le Goic[1], *Danping Wang*[2,3]*, *Catherine Vidal*[1], *Elodie Chiarovano*[1], *Jennyfer Lecompte*[4], *Sebastien Laporte*[4], *Jacques Duysens*[5] and *Pierre-Paul Vidal*[2,1]

[1] COGNAC-G (COGNition and ACtion Group), Université Paris Descartes–CNRS UMR-MD–SSA, Paris, France, [2] Institute of Information and Control, Hangzhou Dianzi University, Hangzhou, China, [3] Plateforme d'Etude de la Sensorimotricité, Université Paris Descartes, Paris, France, [4] Arts et Metiers ParisTech, Institut de Biomecanique Humaine Georges Charpak, Paris, France, [5] Movement Control and Neuroplasticity Research Group, Department of Kinesiology, KU Leuven, Leuven, Belgium

Keywords: accidental fall, disequilibrium, stability, postural control, perturbation, sensory information, biomechanics, multi-joint kinematical model

OPEN ACCESS

Approved by:
Frontiers in Neurology Editorial Office, Frontiers Media SA, Switzerland

***Correspondence:**
Danping Wang
danping.wang@parisdescartes.fr

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *27 December 2018*
Accepted: *29 January 2019*
Published: *27 February 2019*

Citation:
Le Goic M, Wang D, Vidal C, Chiarovano E, Lecompte J, Laporte S, Duysens J and Vidal P-P (2019) Corrigendum: An Initial Passive Phase That Limits the Time to Recover and Emphasizes the Role of Proprioceptive Information. Front. Neurol. 10:118. doi: 10.3389/fneur.2019.00118

A Corrigendum on:

An Initial Passive Phase That Limits the Time to Recover and Emphasizes the Role of Proprioceptive Information

Le Goic, M., Wang, D., Vidal, C., Chiarovano, E., Lecompte, J., Laporte, S., et al. (2018). Front. Neurol. 9:986. doi: 10.3389/fneur.2018.00986

"Catherine Vidal" was not included as an author in the published article. The corrected **Author Contributions Statement** appears below.

ML: principal work, redaction of the paper. DW: experiment, signal processing and helped with the redaction of the paper. EC: helped with signal processing of the EMG. JL: helped with EMG. SL: co-director of the PhD thesis for this work. JD: scientific expert, redaction of the paper. P-PV: director of this project, redaction of this paper. CV: help to do analysis of signal.

Additionally, in the published article, there was an error regarding the affiliations for Pierre-Paul Vidal. Instead of affiliations "1 and 2" it should be affiliations "2 and 1".

The authors apologize for these errors and state that they do not change the scientific conclusions of the article in any way. The original article has been updated.

frontiers in Neurology

ORIGINAL RESEARCH
published: 05 December 2018
doi: 10.3389/fneur.2018.01044

Postural Dynamics Are Associated With Cognitive Decline in Parkinson's Disease

Annette Pantall[1], Piriya Suresparan[1†], Leanne Kapa[1], Rosie Morris[1,2], Alison Yarnall[3], Silvia Del Din[1] and Lynn Rochester[1,3]*

[1] Clinical Ageing Research Unit, Institute of Neuroscience, Newcastle University Institute of Ageing, Newcastle upon Tyne, United Kingdom, [2] Department of Neurology, Oregon Health and Science University, Portland, OR, United States, [3] The Newcastle upon Tyne NHS Foundation Trust, Newcastle upon Tyne, United Kingdom

OPEN ACCESS

Edited by:
Joyce Fung,
McGill University, Canada

Reviewed by:
Brett W. Fling,
Colorado State University, United States
Karen Zown-Hua Li,
Concordia University, Canada
Rachel Kizony,
University of Haifa, Israel

***Correspondence:**
Annette Pantall
annette.pantall@newcastle.ac.uk

†Present Address:
Piriya Suresparan,
Esteem Care Limited, Southall, United Kingdom

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: 30 June 2018
Accepted: 19 November 2018
Published: 05 December 2018

Citation:
Pantall A, Suresparan P, Kapa L, Morris R, Yarnall A, Del Din S and Rochester L (2018) Postural Dynamics Are Associated With Cognitive Decline in Parkinson's Disease. Front. Neurol. 9:1044. doi: 10.3389/fneur.2018.01044

Early features of Parkinson's disease (PD) include both motor and cognitive changes, suggesting shared common pathways. A common motor dysfunction is postural instability, a known predictor of falls, which have a major impact on quality of life. Understanding mechanisms of postural dynamics in PD and specifically how they relate to cognitive changes is essential for developing effective interventions. The aims of this study were to examine the changes that occur in postural metrics over time and explore the relationship between postural and cognitive dysfunction. The study group consisted of 35 people (66 ± 8years, 12 female, UPDRS III: 22.5 ± 9.6) diagnosed with PD who were recruited as part of the Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation—PD Gait (ICICLE-GAIT) study. Postural and cognitive assessments were performed at 18, 36, and 54 months after enrolment. Participants stood still for 120 s, eyes open and arms by their side. Postural dynamics were measured using metrics derived from a single tri-axial accelerometer (Axivity AX3, York, UK) on the lower back. Accelerometry metrics included jerk (derivative of acceleration), root mean square, frequency, and ellipsis (acceleration area). Cognition was evaluated by neuropsychological tests including the Montreal Cognitive Assessment (MoCA) and digit span. There was a significant decrease in accelerometry parameters, greater in the anteroposterior direction, and a decline in cognitive function over time. Accelerometry metrics were positively correlated with lower cognitive function and increased geriatric depression score and negatively associated with a qualitative measure of balance confidence. In conclusion, people with PD showed reduced postural dynamics that may represent a postural safety strategy. Associations with cognitive function and depression, both symptoms that may pre-empt motor symptoms, suggest shared neural pathways. Further studies, involving neuroimaging, may determine how these postural parameters relate to underlying neural and clinical correlates.

Keywords: posture, Parkinson's, cognition, balance, depression, longitudinal, accelerometer

INTRODUCTION

Parkinson's disease (PD) is a common progressive neurodegenerative disease with a UK incidence of 84 per 100,000 in adults over 50 years (1). Clinical characterizations include both motor and non-motor manifestations, indicative of a multisystem neurodegenerative disease (2). Common motor symptoms include resting tremor, bradykinesia, rigidity, and postural instability (3). Postural instability is clinically important as it is a predictor of falls, which impact on quality of life (4). Falls may result in injury, leading to possible loss of functional independence, institutionalization and a poor quality of life (5, 6). Previous studies indicate that 38–68% of people with PD are subject to falls, 25% of which have two or more falls every 6 months (7–10).

Postural instability is classically defined as the inability to maintain the center of mass within its base of support. Clinically, the retropulsion (pull) test is applied to assess postural instability (11). Postural sway is an indicator of postural instability and a measure of the sensorimotor control loop that regulates standing balance (12). Postural sway is greater in fallers than non-fallers, therefore is an important clinical marker (13). The traditional method of recording postural sway involves tracking the center of pressure using a force platform (14). More recently, body-worn sensors (e.g., accelerometers, gyroscopes, magnetometers, insole pressure sensors) have been developed which permit measurements to be made outside a laboratory setting (12). Strong correlations have been found between accelerometer parameters (postural dynamics) and force-platform derived center of pressure data, thereby validating the accelerometer as a method for assessing postural sway (15, 16). Accelerometry metrics during the first 30 s of standing have been reported to be discriminative of PD (17).

Mild cognitive impairment (MCI) is a non-motor feature present in over 20% of patients at initial diagnosis (18). Cognitive function deteriorates with disease progression, with a >2-fold increase in MCI reported over 3 years (19). Cognitive decline in PD is associated with dysfunction of both dopaminergic and cholinergic pathways as well as increased Lewy bodies and possible vascular pathology (20, 21). Performing a cognitive task while standing has been reported to increase postural parameters and by implication, postural instability in people with PD (22–24) compared to healthy older adults. This suggests a "posture second" prioritization, associated with decreased attentional resources available. With cognitive decline, one might anticipate increased postural instability and correlation between cognitive function and postural parameters. Studies have reported a relationship between cognitive changes and postural instability (25, 26) in addition to an association with fall risk (27, 28). This may reflect common shared pathways or adverse events affecting multiple networks. Another common non-motor symptom in PD is depression which has been observed in, on average, 40% of people with PD (29). In PD, Lewy bodies have been found in many subcortical nuclei including the locus coeruleus (30). The locus coeruleus is associated with arousal and also muscle tone critical for postural stability. Patients with depression have been reported to have greater changes in the locus coeruleus compared to non-depressed patients (31). Several studies have reported an association between depression and postural instability (32, 33). Changes in the locus coeruleus and noradrenergic system may partly account for the association between posture and depression. In PD, motor and non-motor features do not exist as separate entities, but rather display interactions, which warrant further investigation.

Information regarding the time-course of postural sway in people with PD is limited as few longitudinal postural studies have been undertaken. Understanding the progression of postural sway may improve our understanding of underlying mechanisms. Exploring the relationship between postural dynamics and cognitive function will inform us of the interaction between the motor and non-motor systems and the effect of diminishing attentional resources on postural stability. Examining the association between depression and postural instability may illuminate the effect of shared pathways on these motor and non-motor features. Clinically, understanding mechanisms underlying postural instability is important given the impact postural control has on falls, gait, and mobility. The main aim of this longitudinal study was to explore how postural dynamics change during quiet standing in people with PD over 36 months. Postural dynamics were determined from accelerometer recordings over the course of a 120 s standing balance test. The hypothesis was that measures of postural dynamics would increase over the 36 months period, indicating increased postural instability. A further hypothesis was that the greatest change in parameters would occur during the first 30 s of the postural task. The second aim was to investigate the relationship between postural instability and global cognition and depression. The hypothesis was that there would be a significant relationship between motor and non-motor features.

METHODS

Participants and Clinical Assessments

The study group consisted of 35 people recruited from the Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation—Parkinson's disease Gait study (ICICLE-PD GAIT) study (34). The participants underwent a baseline assessment, followed by cognitive and postural assessments at 18, 36, and 54 months. Not all participants underwent a baseline postural assessment; therefore, this study does not include baseline measurements. Participants were assessed at the Clinical Aging Research Unit, Newcastle University. The study was approved by the Newcastle and North Tyneside research ethics committee and conducted according to the declaration of Helsinki. All participants signed an informed consent form prior to testing.

The exclusion criteria included any neurological (other than PD), orthopedic or cardiothoracic condition that may adversely have affected the participant's gait or safety. Additional exclusion factors included cognitive impairment (Mini Mental State Exam (MMSE) ≤24) and difficulties comprehending English. Parkinson's disease was diagnosed according to the UK Parkinson's Brain Bank criteria (35).

At each assessment, demographic, clinical, and cognitive information were collected. The Hoehn and Yahr scale was used to measure the motor symptom severity in PD participants (36). The Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS—UPDRS) Part III (37) assessed motor function in PD (0-no motor symptoms, 132-severe motor symptoms). Balance confidence was assessed using the Activities Balance Self Confidence Scale (ABC), with a score of 0 indicating no confidence and a score of 100 indicating complete confidence in balance when performing various activities (38). Cognitive tests included the Montreal Cognitive Assessment (MoCA) (39) for global cognition (score range 0–30) with a score of 26–30 indicating normal cognitive function and <26 suggesting cognitive impairment. The Wechsler Forward Digit Span tested working memory (40), the average number of digits a healthy adult can recall being 7 ± 2 (41). The short Geriatric Depression Scale (GDS) (42) was used as a measure of depressive symptoms (score range 0–15). A score of 0–4 is considered normal, 5–8 indicates mild depression and a score of 12–15 indicates severe depression.

Standing Balance Test

The standing balance test was carried out an hour after medication intake. Participants stood in an upright position with their feet positioned within a predefined area (400 mm wide × 600 mm long), with their hands by their side (43) and looking straight ahead for 120 s. There were no foot placement restrictions and the participants wore their shoes during the test. The recording began 3 s after the participant had understood the instructions of the tests.

Equipment

A tri-axial accelerometer-based monitor (Axivity AX3, York, UK) on the lower back (L5) recorded acceleration at a sampling rate of 100 Hz (17). The accuracy of the accelerometer clock was ±20 parts per million, the resolution was 0.976 mg, the weight of the accelerometer was 9 g with dimensions of 6.0 × 21.5 × 31.5 mm. The Axivity AX3 accelerometer has been validated for recording high resolution movement (44). The accelerometer was attached to the skin with a hydrogel adhesive and Hypafix bandage.

Data Processing

The data processing and analysis have previously been described by Del Din et al. (17). In summary, the data were downloaded to a computer and analyzed by customized MATLAB (R2015a, Mathworks, Natick, MA, USA.) algorithms. Analyses included rotation of the data into anteroposterior (AP), mediolateral (ML), and vertical accelerations using the Moe-Nilssen transformation (45). The following features were then extracted:

a) Jerk ($m^2.s^{-5}$): the rate of change of acceleration (46).
   Jerk was calculated for AP and ML and combined axes.
b) Root mean square [RMS ($m.s^{-2}$)]: a measure of amplitude (46).
   RMS was calculated for AP and ML and combined axes.
c) Frequency (Hz): 95% of power of the acceleration power spectrum below frequency.
   Frequency was estimated for AP and ML axes (46).
d) Ellipsis ($m^2.s^{-4}$): the area comprising 95% of the AP and ML acceleration trajectories (14).

The four features were selected based on previous studies by Mancini et al. (16) who showed these to be sensitive to disease progression and disease discrimination. Additionally, these features can discriminate between different postural tasks in healthy older adults (47).

All accelerometer features were then determined for the following three phases of standing; the first 30 s, the first 60 s and the entire 120 s.

Statistical Analysis

The data were analyzed using SPSS software (v21; IBM, Chicago, IL, USA). Outliers >2 standard deviations from the mean were removed from the datasets. Linear mixed-effects models were applied to determine the main effects of time-points (18, 36, 54 months), axes (AP, ML, combined) and phase (30, 60, 120 s) and their interaction effects on accelerometry parameters ($p < 0.05$). The RANDOM subcommand was used to model the covariance between the three axes and between the three phases. Sidak corrections for multiple comparisons were applied. The Friedmann test was applied to non-parametric Levodopa equivalent daily dose (LEDD), Hoehn and Yahr, MDS-UPDRS III, ABC, MoCA, digit span and GDS scores. The Wilcoxon signed-rank test compared different time-points. Spearman's rank correlation was used to examine cross-sectional associations between postural parameters and the ABC, MoCA, and GDS scores. Pearson's product-moment correlation coefficient determined associations between changes in postural parameters and cognitive parameters between time-points. The magnitude of effect of the correlation coefficients was defined by the following: $r < 0.10$: negligible; $0.10 \leq r < 0.30$: weak; $0.30 \leq r < 0.50$: moderate; $r \geq 0.50$: strong (48).

RESULTS

Demographic and Clinical Data

Table 1 lists demographic and clinical information at baseline, 18, 36, and 54 months. There was a greater number of males in the cohort. Although, all participants satisfied the inclusion criterion of MMSE>24, the MoCA at Baseline ranged from 20 to 30 with 10 participants having MoCA scores ≤24. There was a significant effect of time for LEDD, Hoehn, and Yahr stage and MDS-UPDRS III [$X^2_{(3)} = 78.0$, $p < 0.001$; $X^2_{(3)} = 18.1$, $p < 0.001$; $X^2_{(3)} = 41.0$, $p < 0.001$, respectively]. H&Y was significantly greater at 18 months compared to baseline ($Z = -2.5$, $p = 0.012$). LEDD increased significantly between successive time-points (baseline to 18 months, $Z = -5.1$, $p < 0.001$; 18–36 months, $Z = -4.8$, $p < 0.001$; 36–54 months, $Z = -3.4$, $p = 0.001$). The MDS-UPDRS III score was significantly greater at baseline compared to 18 months ($Z = -4.7$, $p < 0.001$), 36 months compared to 18 months ($Z = -4.0$, $p < 0.001$) and 54 months compared to baseline ($Z = -4.8$, $p < 0.001$). There was

TABLE 1 | Demographic, cognitive, and clinical characteristics of participants at Baseline, 18, 36, and 54 months.

PARAMETER	Baseline	18 months	36 months	54 months
Age (years)*	65.86 ± 8.27	67.42 ± 8.15	68.86 ± 8.16	70.40 ± 8.18
Sex (Male, Female)	23, 12	23, 12	23, 12	23, 12
Body Mass Index (kgm^{-2})	27.20 ± 3.87	27.41 ± 4.29	27.35 ± 4.49	27.04 ± 4.90
PD duration (years)*	0.45 ± 0.33	2.01 ± 0.35	3.45 ± 0.40	4.99 ± 0.52
LEDD*	142.8 ± 113.1	337.6 ± 202.5	438.2 ± 227.0	631.5 ± 251.2
Hoehn and Yahr stage*	1.71 ± 0.52	2.00 ± 0.48	2.03 ± 0.17	2.14 ± 0.35
UPDRS III*	22.46 ± 9.61	28.80 ± 7.15	35.97 ± 10.12	37.11 ± 10.99
ABC	87.72 ± 13.72	85.35 ± 15.66	82.82 ± 19.87	80.87 ± 20.38
MoCA*	26.23 ± 2.65	26.89 ± 2.80	26.77 ± 3.25	25.54 ± 3.56
Digit span	6.09 ± 1.20	6.00 ± 1.19	6.17 ± 1.16	5.89 ± 0.95
GDS	2.71 ± 2.47	2.23 ± 2.70	2.63 ± 2.55	3.11 ± 2.25

PD, Parkinson's Disease; LEDD, Levodopa Equivalent Daily Dose; UPDRS III, Unified Parkinson's Disease Rating Scale Section III; MoCA, Montreal Cognitive Assessment; Digit, Wechsler Forward Digit Span; ABC, Activities Balance Self Confidence Scale; GDS, Geriatric Depression Scale.
**significant time effect ($p < 0.05$).*

a significant time effect for MoCA [$X^2_{(3)} = 9.9$; $p = 0.02$], with the score decreasing from 18 to 54 months ($Z = -2.5$, $p = 0.013$) and from 36 to 54 months ($Z = -2.9$, $p = 0.004$).

Accelerometer Metrics

Outliers

The metrics of Jerk, RMS, frequency, and ellipsis were analyzed for outliers using the threshold of two standard deviations above or below the mean. Data from these outliers were considered removed from further analysis. Jerk and frequency had the greatest number of outliers across axes, phases, and time-points (1.9%) compared to RMS (1.5%) and ellipsis (1.2%).

Postural Dynamics

a) Axis
   The axis had a significant effect on jerk, RMS and frequency (**Table 2**). Jerk and RMS were greater in the AP direction compared to the ML direction (jerk $p = 0.001$, effect size = 0.87, power = 65.9%; RMS $p < 0.001$, effect size = 2.58, power = 100%) (**Figure 1**). Frequency was however greater in the ML direction ($p < 0.001$, effect size = 2.60, power = 100%).
b) Time
   There was a significant effect of time for ellipsis, which decreased from 18 to 54 months ($p = 0.033$, effect size = 0.27, power = 45.3%) (**Table 2**) (**Figure 1**).

Interaction Effect of Phase and Time

The interaction effect of postural phase and time was significant for RMS and ellipsis (**Table 2**). Pairwise comparisons showed the RMS and ellipsis parameters for the initial 30 s to be significantly lower at 36 months (RMS $p = 0.005$, effect size = 0.52, power = 63.4%; ellipsis $p = 0.032$, effect size = 0.44, power = 47.7%) and 54 months (RMS $p = 0.001$,effect size = 0.52, power = 77.7%; ellipsis $p = 0.001$, effect size = 0.57, power = 75.6%) compared to 18 months. Additionally, for the initial 60 s there was a decrease from 18 to 54 months for ellipsis ($p = 0.023$, effect size = 0.41, power = 47.8%) (**Figure 1**).

TABLE 2 | Mixed linear model results for single and interaction effects of time (18, 36, and 54 months), axis (combined, mediolateral, anteroposterior) and phase (30, 60, 120 s) on gait accelerometry parameters.

	Jerk	RMS	Frequency	Ellipsis
Time	NS	NS	NS	$F_{(2, 35)} = 3.7$, $p = 0.034$
Axis	$F_{(2, 22)} = 107.3$, $p < 0.001$	$F_{(2, 57)} = 286.9$, $p < 0.001$	$F_{(1, 34)} = 223.8$, $p < 0.001$	NA
Phase	$F_{(2, 65)} = 133.9$, $p < 0.001$	NS	NS	NS
Axis×time	NS	$F_{(4, 591)} = 8.6$, $p < 0.001$	NS	NA
Phase×time	NS	$F_{(4, 590)} = 13.5$, $p < 0.001$	NS	$F_{(4, 141)} = 10.00$, $p < 0.001$
Axis×phase×time	$F_{(12, 588)} = 15.6$, $p < 0.001$	$F_{(12, 602)} = 2.1$, $p = 0.014$	NS	NA

Only findings with $p < 0.05$ are listed. RMS, Root Mean Square; NS, Not Significant; NA, Not Applicable.

Interaction Effect of Axis and Time

There was a significant interaction effect between axis and time for RMS (**Table 2**). Pairwise comparisons for the RMS parameter showed that, in the combined direction, 18 months was significantly >36 months ($p < 0.037$, effect size = 0.41, power = 44.1%) and 54 months ($p = 0.017$, effect size = 0.41, power = 49.4%). Along the AP axis, RMS was greater at 18 months compared to 36 months ($p = 0.022$, effect size = 0.43, power = 49.6%).

Interaction Effect of Axis, Phase, and Time

The interaction effect of axis, phase, and time was significant for jerk and RMS (**Table 2**). The 120 s combined jerk parameter was greater at 36 months compared to 18 months ($p = 0.036$ effect size = 0.24, power = 43.4%) and 36 months compared to 54 months ($p = 0.045$ effect size = 0.22, power = 41.1%)

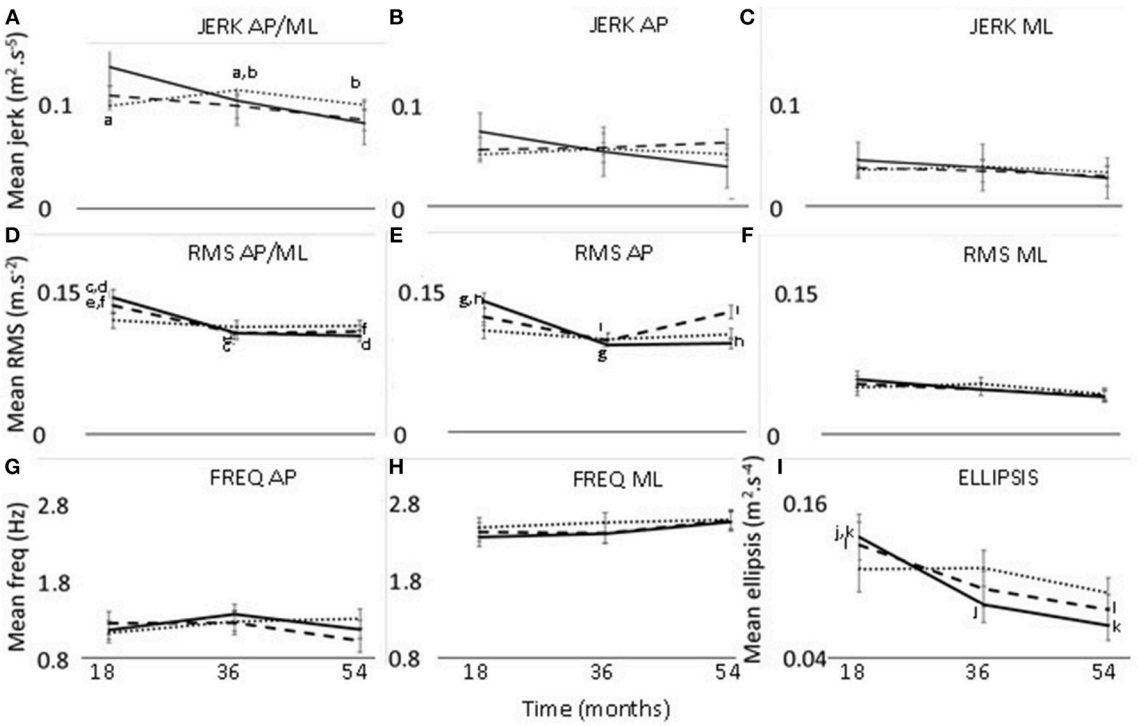


FIGURE 1 | Changes in jerk **(A–C)**, RMS **(D–F)**, frequency **(G,H),** and ellipsis **(I)** at 18, 36, and 54 months. Thirty seconds postural phase; 60 s postural phase; 120 s postural phase. AP, anteroposterior axis; ML, mediolateral axis; **a-l**—significant difference ($p < 0.05$) between two timepoints.

(**Figure 1A**). The RMS parameters along the combined axis decreased significantly from 18 to 36 months for 30 s ($p = 0.002$ effect size = 0.44, power = 70.2%) and 60 s ($p = 0.022$ effect size = 0.35, power = 48.0%) (**Figure 1D**). These RMS parameters also decreased from 18 to 54 months (30 s $p < 0.001$ effect size = 0.46, power = 83.9%, 60 s $p = 0.018$ effect size = 0.32, power = 50.0%). Additionally, along the AP axis, the 30 s RMS decreased from 18 to 36 months ($p < 0.001$ effect size = 0.56, power = 86.9%) and 54 months ($p < 0.001$ effect size = 0.53, power = 89.6%) (**Figure 1E**). However, for 60 s RMS increased from 36 to 54 months ($p = 0.011$ effect size = 0.19, power = 51.2%) (**Figure 1E**).

Association Between Postural Dynamics and Balance Confidence, Cognitive Function and Depression Measures

Table 3 lists cross-sectional correlations between postural measures of jerk, RMS, and ellipsis in the AP direction and ABC, MOCA, and GDS scores at 36 and 54 months. Few correlations were observed for frequency. No relationship was found at 18 months and only few associations for the first 30 and 60 s of standing. No correlations were present between postural measures and the digit span scores.

a) Jerk
   At 36 months, moderate negative correlations were found for jerk with ABC, MoCA, and a weak positive correlation with GDS. At 54 months, there was a moderate correlation between jerk and ABC and a weak negative correlation with MoCA.
b) RMS
   At 36 months, a moderate negative correlation was observed with ABC, a weak negative correlation between RMS and MoCA and moderate positive correlation with GDS. RMS was moderately negatively correlated with ABC at 54 months and weakly correlated with GDS.
c) Ellipsis
   Moderate negative correlations between ellipsis and ABC at 36 and 54 months were found. There was a positive correlation between ellipsis and GDS at 36 months.

Correlation Between Change in Postural Dynamics and Change in Balance Confidence, Cognitive Function, and Depression Measures

Correlations between changes in postural parameters for 120 s in the combined direction and ABC, MoCA, and GDS scores are presented in **Table 4** and **Figure 2**. There were no significant correlations from 18 to 36 months between postural parameters and the ABC, MoCA, and GDS scores. The decline in jerk from 36 to 54 months showed a moderate negative correlation with the change in MoCA (**Figure 3A**) and a moderate positive correlation with change in GDS scale (**Figure 3B**).

DISCUSSION

In this longitudinal study, we aimed to investigate how postural dynamics change during quiet standing in people with PD over 36 months. Additionally, we investigated the relationship between postural dynamics with balance confidence, global cognition and depression score. We hypothesized that postural dynamics of jerk, RMS, and ellipsis would increase, suggesting increased postural instability, with disease progression. However, our novel findings reported mainly a decline in jerk, RMS, and ellipsis with disease progression. Although most change over time for RMS, frequency and ellipsis was observed for the first 30 s of standing, we found that for jerk, significant changes were present only for the entire 120 s duration. We observed significant relationships between postural parameters with balance confidence, global cognition, and depression score suggesting shared neural pathways.

The decrease in RMS is in partial agreement with Mancini et al. (16). Although Mancini et al. (16) reported an increase over 6–9 months in postural parameters in five individuals not receiving dopaminergic medication, eight subjects on dopaminergic medication displayed trends toward decreased RMS (49). Another study, also reported decreased sway (measured with platform mounted potentiometer) in eight patients with moderate PD (Hoehn and Yahr III–IV) on dopaminergic medication, compared to healthy older adults (50). Interpretation of changes in postural dynamics in people with PD involves not only consideration of changes due to progression of pathology but also concomitant age-related neurodegenerative changes. Duarte and Sternad (51) reported older adults show reduced amplitude of postural sway during prolonged standing compared to younger adults (51). However, in a cross-sectional study, Park et al. (52) reported increased postural accelerometry parameters in older adults, apart from frequency and jerk in the ML direction, which decreased (52). It is unclear to what extent longitudinal changes in RMS in people with PD are the consequence of age-related changes rather than due to progression of PD.

The longitudinal decline in RMS and ellipsis from 18 to 54 months was most prominent for the first 30 s of standing. Del Din et al. (17) have reported that this period was most discriminative between people with PD and healthy older adults (17), suggesting that the initial period requires the greatest sensorimotor integration to achieve balance and is most impacted by PD. Theories to explain postural instability in PD include changes in intermittent and continuous control systems (53), impaired proprioception (54), and alteration in awareness of vertical body position relative to the global axes (55). The initial standing period may highlight more the intermittent and continuous control mechanisms needed to adjust the center of mass position to restore stability. Changes in the body position awareness may have a more prominent effect on postural dynamics with increasing standing duration. Dysfunction of sense of body positioning may result in a greater error in return of center of mass to the position optimal for equilibrium and necessitate faster adjustments (greater jerk) to achieve stability. The increase in jerk over 120 s from 18 to 36 months may be the result of faster corrections due to greater error in positioning of center of mass. The subsequent decrease in jerk over 120 s from to 54 months may reflect the complex interaction of disease progression and dopaminergic treatment on postural control mechanisms. There was approximately a 2-fold increase in LEDD from 36 to 54 months compared to 18 to 36 months, which could account for the decrease in 120 s jerk.

There was a significant effect of direction, with the AP direction showing greater change than ML, with a decrease in RMS value from 18 to 54 months. This finding is supported by a study that reported decreased AP sway during standing in people with PD compared to controls (50). A recent study analyzing postural data from a similar cohort of individuals with PD observed increased regularity of postural dynamics from 18 to 54 months along the AP axis suggesting possible modification of motor control along this axis (56). The reduction in AP postural dynamics may result from greater instability in the AP direction, associated with decreased knee flexion and greater difficulty initiating ankle dorsiflexion to maintain balance (57).

TABLE 3 | Spearman's correlation coefficient for mean postural parameters of jerk, RMS, and ellipsis in the AP direction across 120 s with clinical characteristics at 36 and 54 months.

	Jerk rho (p)	RMS rho (p)	Ellipsis rho (p)
36 MONTHS			
ABC	**−0.336 (0.024)**	**−0.462 (0.003)**	**−0.434(0.006)**
MoCA	**−0.392 (0.010)**	−0.291 (0.050)	−0.278 (0.058)
GDS	0.287 (0.047)	**0.380 (0.015)**	**0.433 (0.006)**
54 MONTHS			
ABC	**−0.441 (0.004)**	**−0.412 (0.009)**	**−0.455 (0.004)**
MoCA	–0.261(0.065)	–0.113 (0.266)	–0.197 (0.135)
GDS	0.129 (0.230)	0.233 (0.096)	0.215 (0.115)

ABC, Activities Balance Confidence Scale; MoCA, Montreal Cognitive Assessment; GDS, Geriatric Depression Scale. Moderate Correlations (0.5<rho>0.3) in bold.

TABLE 4 | Pearson's correlation coefficient for change in mean postural dynamic parameters of 120 s jerk, 30 s RMS, and 30 s ellipsis with change in clinical characteristics.

Time-points	Jerk r (p)	RMS r (p)	Ellipsis r (p)
18–36 MONTHS			
ABC	−0.043 (0.406)	0.145 (0.222)	0.092 (0.308)
MoCA	−0.152 (0.192)	−0.052 (0.390)	−0.018 (0.923)
GDS	0.092 (0.299)	−0.140 (0.227)	−0.250 (0.080)
36–54 MONTHS			
ABC	−0.204 (0.120)	0.088 (0.318)	−0.064 (0.361)
MoCA	**–0.422 (0.006)**	0.157 (0.200)	0.156 (0.193)
GDS	**0.484 (0.005)**	−0.246 (0.123)	−0.172 (0.201)

ABC, Activities Balance confidence Scale; MoCA, Montreal Cognitive Assessment; GDS, Geriatric Depression Scale. Moderate Correlations (0.5<rho>0.3) in bold.

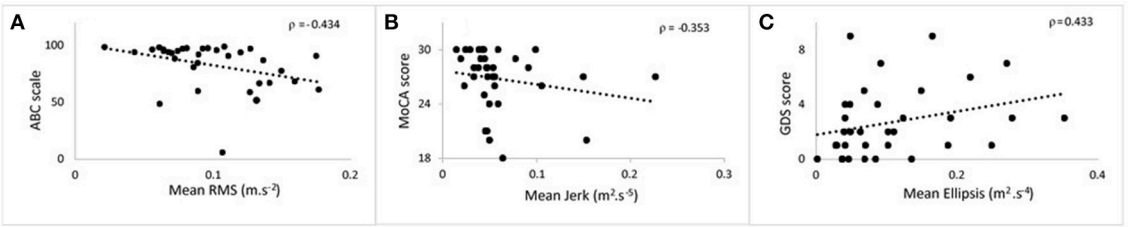


FIGURE 2 | Scatter plots showing the correlation at 36 months between postural parameters and cognitive measures for 120 s phase. **(A)** Mean root mean square against ABC. **(B)** Mean jerk against MoCA. **(C)** Mean ellipsis against GDS. ABC, Activities Balance Self Confidence; MoCA, Montreal Cognitive Assessment; GDS, Geriatric Depression Scale.

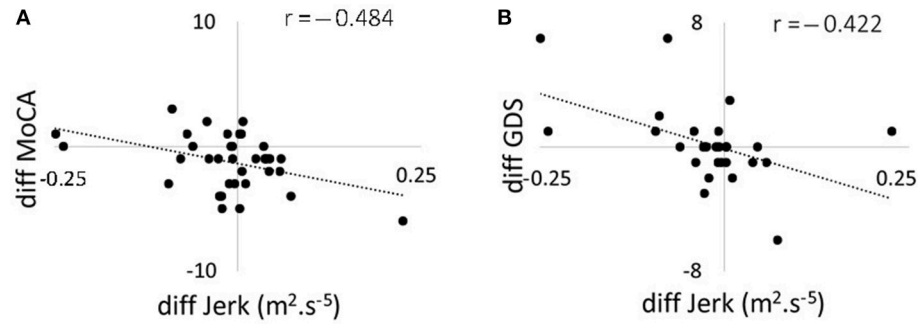


FIGURE 3 | Scatter plots showing the correlation between changes in 120 s jerk from 36 to 54 months and **(A)** changes in MoCA score from 36 to 54 months; **(B)** changes in GDS from 36 to 54 months. MoCA, Montreal Cognitive Assessment; GDS, Geriatric Depression Scale.

Specifically, greater instability has been observed in backward sway when people had normal foot width (57). Axial stiffness increases with PD progression and patients frequently develop a stooped posture (camptocormia) which may also affect AP trunk dynamics (58). However, camptocormia usually presents after 7–8 years of diagnosis, so this is not likely to be a major consideration in our study. The decreased RMS in the AP direction may represent a compensation strategy to maintain stability by keeping movements of the trunk within a smaller, safer range along the AP axis.

We observed negative correlations between postural dynamics with the ABC scale. Greater confidence in standing and a lower fear of falling were associated with lower postural parameters. Reduction in postural dynamics may result from increased lower limb rigidity. Carpenter et al. (59) have reported co-contraction of leg muscles with consequential increased ankle stiffness in people with PD compared to age-matched controls (59). Older adults have also been observed to have increased muscle co-activation compared to young adults with the subgroup of fallers having greater postural sway. Increased co-activation of lower limb agonists and antagonists will result in a more rigid structure, although less reactive to external perturbations. We did not find significant change with disease progression for postural parameters along the ML axis. One study reported increased RMS in the ML direction in people with PD compared to healthy older adults, therefore the RMS value might be expected to increase as the disease progressed (60). However, the observation that there is no longitudinal change may be the result of the interaction of opposing age-related and PD effects on the control of postural dynamics.

We found moderate negative correlations between MoCA and postural dynamics at the 36 months time point with lower cognition associated with increased jerk. Kelly et al. (61) have reported similar findings between lower global cognition and increased postural instability (61). Correlation between postural measures and cognitive tests have also been reported by Nocera et al. (62). Dysfunctions in dopamine networks may to some extent account for this association as impairment in executive function and attention is mediated partially by dopaminergic frontostriatal networks (63). No relationship between postural and cognitive measures was observed at 54 months, which may be due to progression of the pathology, emergence of additional clinical features and effect of medication. Levodopa has been suggested to improve some balance measures but worsen others (64) and in the advanced stages of PD increases postural sway (65). Although both jerk and MoCA decreased on average from 36 to 54 months, we found a moderate negative correlation in the difference between the two time-points for these parameters. The mean change in the MoCA score was 1.23 and reduced the MoCA score at 54 months to 25.54, which is considered clinically to indicate possible cognitive impairment. Our finding suggests there individuals with an increase in postural parameters decrease their cognitive function. This is surprising as mild cognitive impairment is associated with postural instability (66)

and increased rates of cognitive decline have been reported in individuals with postural instability and gait disturbance phenotype (67). Possible different effects of disease progression and aging on postural dynamics and cognitive function may explain the results. Further investigation is however needed.

There were moderate positive correlations between GDS score and postural dynamics. The changes in GDS were however small, and even at 54 months the GDS at 3.11 was below the threshold of 5 which has been reported to indicate mild depression. Previous studies have reported a relationship between depression and gait parameters, which was stronger on dopaminergic medication (68, 69). A review of depression in PD reported contradictory findings regarding postural correlates of depression in PD (29). The association between GDS score and postural instability may be related to the physical constraint on activity imposed by postural instability because of the increased falls risk. However, as depression frequently precedes the motor symptoms, the association is more likely to be due to changes in shared neural circuitry (70).

Limitations

The main limiting factor is that we tested patients in the ON medication state. Postural dynamics will differ in the OFF state compared to the ON state, with motor impairment reported to be greater in the OFF state.

Our standing balance test involved participants self-selecting their foot position. This may from 18 to 54 months consequential decrease in postural dynamics. By contrast, many postural studies adopt a standardized foot position, which restricts patients changing their base of support. However, the purpose of our postural analysis was to examine individual postural dynamics by allowing participants to wear their own comfortable footwear and place their feet in a position they considered would provide them with maximum stability.

CONCLUSION

Postural dynamics decrease over a period of 36 months in people with PD. This may be due to people reducing their postural sway in order to restrict their center of pressure excursions to a smaller "safe" area, as postural instability increases with disease progression. Underlying mechanisms may include co-contraction of agonist and antagonist muscles resulting in increased rigidity. Limiting postural movements may however result in the individual becoming less able to respond to external perturbations and therefore becoming more prone to falls. Postural dynamics are associated at 36 months after diagnosis, with global cognition and depression, emphasizing the interaction between motor and non-motor features, which may reflect shared neural correlates as the locus coeruleus. This study demonstrates the multisystem nature of PD and the need to examine different features as part of a whole unified system.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Newcastle and North Tyneside research ethics committee with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Newcastle and North Tyneside research ethics committee.

AUTHOR CONTRIBUTIONS

AP carried out data analysis, interpreted the data, and wrote the manuscript. PS and LK contributed to data analysis and critically reviewed the manuscript. RM was involved with data collection, reviewed, and commented on manuscript draft. AY was involved with data collection and critically reviewed the manuscript. SD developed code, analyzed data, and critically reviewed the manuscript. LR conceived and designed the study, interpreted the data and critically revised the manuscript.

FUNDING

ICICLE-PD was funded by Parkinson's UK (J-0802, G-1301, G-1507). The research was supported by the Lockhart Parkinson's Disease Research Fund, the National Institute for Health Research (NIHR) Newcastle Biomedical Research Unit based at Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University and a NIHR Biomedical Research Centre award to the University of Cambridge/Addenbrooke's Hospital.

REFERENCES

1. Horsfall L, Petersen I, Walters K, Schrag A. Time trends in incidence of Parkinson's disease diagnosis in UK primary care. *J Neurol*. (2013) 260:1351–7. doi: 10.1007/s00415-012-6804-z
2. Magrinelli F, Picelli A, Tocco P, Federico A, Roncari L, Smania N, et al. Pathophysiology of motor dysfunction in Parkinson's disease as the rationale for drug treatment and rehabilitation. *Parkinsons Dis*. (2016) 2016:9832839. doi: 10.1155/2016/9832839
3. Schrag A, Ben-Shlomo Y, Quinn N. How common are complications of Parkinson's disease? *J Neurol*. (2002) 249:419–23. doi: 10.1007/s004150200032
4. Williams DR, Watt HC, Lees AJ. Predictors of falls and fractures in bradykinetic rigid syndromes: a retrospective study. *J Neurol Neurosurg Psychiatry* (2006) 77:468–73. doi: 10.1136/jnnp.2005.074070
5. Frenklach A, Louie S, Koop MM, Bronte-Stewart H. Excessive postural sway and the risk of falls at different stages of Parkinson's disease. *Mov Dis*. (2009) 24:377–85. doi: 10.1002/mds.22358
6. Karachi C, Francois C. Role of the pedunculopontine nucleus in controlling gait and sleep in normal and parkinsonian monkeys. *J Neural Transm*. (2017) 125:471–83. doi: 10.1007/s00702-017-1678-y
7. Rudzinska M, Bukowczan S, Stozek J, Zajdel K, Mirek E, Chwała W, et al. The incidence and risk factors of falls in Parkinson disease: prospective study. *Neurol Neurochir Pol*. (2013) 47:431–7. doi: 10.5114/ninp.2013.38223
8. Bloem BR, Grimbergen YA, Cramer M, Willemsen M, Zwinderman AH. Prospective assessment of falls in Parkinson's disease. *J Neurol*. (2001) 248:950–8. doi: 10.1007/s004150170047
9. Lord S, Galna B, Yarnall AJ, Coleman S, Burn D, Rochester L. Predicting first fall in newly diagnosed Parkinson's disease: insights from a fall-naive cohort. *Mov Disord*. (2016) 31:1829–36. doi: 10.1002/mds.26742

10. Lord S, Galna B, Yarnall AJ, Morris R, Coleman S, Burn D, et al. Natural history of falls in an incident cohort of Parkinson's disease: early evolution, risk and protective features. *J Neurol*. (2017) 264:2268–76. doi: 10.1007/s00415-017-8620-y
11. Nonnekes J, Goselink R, Weerdesteyn V, Bloem BR. The retropulsion test: a good evaluation of postural instability in Parkinson's disease? *J Parkinson's Dis*. (2015) 5:43–7. doi: 10.3233/JPD-140514
12. Horak FB, Mancini M. Objective biomarkers of balance and gait for Parkinson's disease using body-worn sensors. *Mov Dis*. (2013) 28:1544–51. doi: 10.1002/mds.25684
13. Shumway-Cook A, Woollacott M, Kerns KA, Baldwin M. The effects of two types of cognitive tasks on postural stability in older adults with and without a history of falls. *J Gerontol A Biol Sci Med Sci*. (1997) 52:M232–40. doi: 10.1093/gerona/52A.4.M232
14. Palmerini L, Rocchi L, Mellone S, Valzania F, Chiari L. Feature selection for accelerometer-based posture analysis in Parkinson's Disease. *Trans Info Tech Biomed*. (2011) 15:481–90. doi: 10.1109/TITB.2011.2107916
15. Whitney SL, Roche JL, Marchetti GF, Lin CC, Steed DP, Furman GR, et al. A comparison of accelerometry and center of pressure measures during computerized dynamic posturography: a measure of balance. *Gait Posture* (2011) 33:594–9. doi: 10.1016/j.gaitpost.2011.01.015
16. Mancini M, Salarian A, Carlson-Kuhta P, Zampieri C, King L, Chiari L, et al. ISway: a sensitive, valid and reliable measure of postural control. *J Neuroeng Rehabil*. (2012) 9:59. doi: 10.1186/1743-0003-9-59
17. Del Din S, Godfrey A, Coleman S, Galna B, Lord S, Rochester L. Time-dependent changes in postural control in early Parkinson's disease: what are we missing? *Med Biol Eng Comput*. (2016) 54:401–10. doi: 10.1007/s11517-015-1324-5
18. Lawson RA, Yarnall AJ, Duncan GW, Breen DP, Khoo TK, Williams–Gray CH, et al. Cognitive decline and quality of life in incident Parkinson's disease: the role of attention. *Parkinsonism Relat Disord*. (2016) 27:47–53. doi: 10.1016/j.parkreldis.2016.04.009
19. Uc EY, McDermott MP, Marder KS, Anderson SW, Litvan I, Como PG, et al. Incidence of and risk factors for cognitive impairment in an early Parkinson disease clinical trial cohort. *Neurology* (2009) 73:1469–77. doi: 10.1212/WNL.0b013e3181bf992f
20. Mollenhauer B, Rochester L, Chen-Plotkin A, Brooks D. What can biomarkers tell us about cognition in Parkinson's disease? *Mov Disord*. (2014) 29:622–33. doi: 10.1002/mds.25846
21. Yarnall AJ, Rochester L, Baker MR, David R, Khoo TK, Duncan GW, et al. Short latency afferent inhibition: a biomarker for mild cognitive impairment in Parkinson's disease? *Mov Disord*. (2013) 28:1285–8. doi: 10.1002/mds.25360
22. Morris M, Iansek R, Smithson F, Huxham F. Postural instability in Parkinson's disease: a comparison with and without a concurrent task. *Gait Posture* (2000) 12:205–16. doi: 10.1016/S0966-6362(00)00076-X
23. Ashburn A, Stack E, Pickering RM, Ward CD. A community-dwelling sample of people with Parkinson's disease: characteristics of fallers and non-fallers. *Age Ageing* (2001) 30:47–52. doi: 10.1093/ageing/30.1.47
24. Chen T, Fan Y, Zhuang X, Feng D, Chen Y, Chan P, et al. Postural sway in patients with early Parkinson's disease performing cognitive tasks while standing. *Neurol Res*. (2018) 40:491–8. doi: 10.1080/01616412.2018.1451017
25. Kido T, Tabara Y, Igase M, Ochi N, Uetani E, Nagai T, et al. Postural instability is associated with brain atrophy and cognitive impairment in the elderly: the J-SHIPP study. *Dement Geriatr Cogn Disord*. (2010) 29:379–87. doi: 10.1159/000255106
26. Xu D, Cole MH, Mengersen K, Silburn PA, Qiu F, Graepel C, et al. Executive function and postural instability in people with Parkinson's disease. *Parkinson's Dis*. (2014) 2014:684758. doi: 10.1155/2014/684758
27. Segev-Jacubovski O, Herman T, Yogev-Seligmann G, Mirelman A, Giladi N, Hausdorff JM. The interplay between gait, falls and cognition: can cognitive therapy reduce fall risk? *Expert Rev Neurother*. (2011) 11:1057–75. doi: 10.1586/ern.11.69
28. Rosenberg-Katz K, Herman T, Jacob Y, Mirelman A, Giladi N, Hendler T, et al. Fall risk is associated with amplified functional connectivity of the central executive network in patients with Parkinson's disease. *J Neurol*. (2015) 262:2448–56. doi: 10.1007/s00415-015-7865-6
29. Cummings JL. Depression and Parkinson's disease: a review. *Am J Psychiatry* (1992) 149:443–54. doi: 10.1176/ajp.149.4.443
30. Vermeiren Y, De Deyn PP. Targeting the norepinephrinergic system in Parkinson's disease and related disorders: the locus coeruleus story. *Neurochem Int*. (2017) 102:22–32. doi: 10.1016/j.neuint.2016.11.009
31. Chan-Palay V, Asan E. Quantitation of catecholamine neurons in the locus coeruleus in human brains of normal young and older adults and in depression. *J Comp Neurol*. (1989) 287:357–72. doi: 10.1002/cne.902870307
32. Hassan A, Vallabhajosula S, Zahodne LB, Bowers D, Okun MS, Fernandez HH, et al. Correlations of apathy and depression with postural instability in Parkinson disease. *J Neurol Sci*. (2014) 338:162–5. doi: 10.1016/j.jns.2013.12.040
33. Burn DJ, Landau S, Hindle JV, Samuel M, Wilson KC, Hurt CS, et al. Parkinson's disease motor subtypes and mood. *Mov Disord*. (2012) 27:379–86. doi: 10.1002/mds.24041
34. Khoo TK, Yarnall AJ, Duncan GW, Coleman S, O'Brien JT, Brooks DJ, et al. The spectrum of nonmotor symptoms in early Parkinson disease. *Neurology* (2013) 80:276–81. doi: 10.1212/WNL.0b013e31827deb74
35. Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry* (1988) 51:745–52. doi: 10.1136/jnnp.51.6.745
36. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology* (1967) 17:427–42. doi: 10.1212/WNL.17.5.427
37. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord*. (2008) 23:2129–70. doi: 10.1002/mds.22340
38. Powell LE, Myers AM. The Activities-specific Balance Confidence (ABC) scale. *J Gerontol A Biol Sci Med Sci*. (1995) 50A:M28–34. doi: 10.1093/gerona/50A.1.M28
39. Dalrymple-Alford JC, MacAskill MR, Nakas CT, Livingston L, Graham C, Crucian GP, et al. The MoCA: well-suited screen for cognitive impairment in Parkinson disease. *Neurology* (2010) 75:1717–25. doi: 10.1212/WNL.0b013e3181fc29c9
40. Wechsler D. *WAIS-III: Administration and Scoring Manual*. 3rd ed. San Antonio, TX: Psychological Corporation (1997).
41. Miller GA. The magical number seven plus or minus two: some limits on our capacity for processing information. *Psychol Rev*. (1956) 63:81–97. doi: 10.1037/h0043158
42. Schrag A, Barone P, Brown RG, Leentjens AF, McDonald WM, Starkstein S, et al. Depression rating scales in Parkinson's disease: critique and recommendations. *Mov Disord*. (2007) 22:1077–92. doi: 10.1002/mds.21333
43. Qiu F, Cole MH, Davids KW, Hennig EM, Silburn PA, Netscher H, et al. Effects of textured insoles on balance in people with Parkinson's disease. *PLoS ONE* (2013) 8:e83309. doi: 10.1371/journal.pone.0083309
44. Ladha C, Jackson D, Ladha K, Olivier P. Shaker table validation of OpenMovement AX3 accelerometer. In: *3rd International Conference on Ambulatory Monitoring of Physical Activity and Movement*. Ahmerst (2013).
45. Moe-Nilssen R. Test-retest reliability of trunk accelerometry during standing and walking. *Arch Phys Med Rehabil*. (1998) 79:1377–85. doi: 10.1016/S0003-9993(98)90231-3
46. Mancini M, Horak FB, Zampieri C, Carlson-Kuhta P, Nutt JG, Chiari L. Trunk accelerometry reveals postural instability in untreated Parkinson's disease. *Parkinsonism Relat Disord*. (2011) 17:557–62. doi: 10.1016/j.parkreldis.2011.05.010
47. Godfrey A, Lara J, Del Din S, Hickey A, Munro CA, Wiuff C, et al. iCap: instrumented assessment of physical capability. *Maturitas* (2015) 82:116–22. doi: 10.1016/j.maturitas.2015.04.003
48. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: L. Erlbaum Associates (1988).
49. Mancini M, Carlson-Kuhta P, Zampieri C, Nutt JG, Chiari L, Horak FB. Postural sway as a marker of progression in Parkinson's disease: a pilot longitudinal study. *Gait Posture* (2012) 36:471–6. doi: 10.1016/j.gaitpost.2012.04.010
50. Horak FB, Nutt JG, Nashner LM. Postural inflexibility in parkinsonian subjects. *J Neurol Sci*. (1992) 111:46–58. doi: 10.1016/0022-510X(92)90111-W
51. Duarte M, Sternad D. Complexity of human postural control in young and older adults during prolonged standing. *Exp Brain Res*. (2008) 191:265–76. doi: 10.1007/s00221-008-1521-7

52. Park JH, Mancini M, Carlson-Kuhta P, Nutt JG, Horak FB. Quantifying effects of age on balance and gait with inertial sensors in community-dwelling healthy adults. *Exp Gerontol.* (2016) 85:48–58. doi: 10.1016/j.exger.2016.09.018
53. Perera T, Tan JL, Cole MH, Yohanandan SAC, Silberstein P, Cook R, et al. Balance control systems in Parkinson's disease and the impact of pedunculopontine area stimulation. *Brain* (2018) 141:3009–22. doi: 10.1093/brain/awy216
54. O'Suilleabhain P, Bullard J, Dewey RB. Proprioception in Parkinson's disease is acutely depressed by dopaminergic medications. *J Neurol Neurosurg Psychiatry* (2001) 71:607–10. doi: 10.1136/jnnp.71.5.607
55. Vaugoyeau M, Viel S, Assaiante C, Amblard B, Azulay JP. Impaired vertical postural control and proprioceptive integration deficits in Parkinson's disease. *Neuroscience* (2007) 146:852–63. doi: 10.1016/j.neuroscience.2007.01.052
56. Pantall A, Del Din S, Rochester L. Longitudinal changes over thirty-six months in postural control dynamics and cognitive function in people with Parkinson's disease. *Gait Posture* (2018) 62:468–74. doi: 10.1016/j.gaitpost.2018.04.016
57. Horak FB, Dimitrova D, Nutt JG. Direction-specific postural instability in subjects with Parkinson's disease. *Exp Neurol.* (2005) 193:504–21. doi: 10.1016/j.expneurol.2004.12.008
58. Doherty KM, van de Warrenburg BP, Peralta MC, Silveira-Moriyama L, Azulay JP, Gershanik OS, et al. Postural deformities in Parkinson's disease. *Lancet Neurol.* (2011) 10:538–49. doi: 10.1016/S1474-4422(11)70067-9
59. Carpenter MG, Allum JH, Honegger F, Adkin AL, Bloem BR. Postural abnormalities to multidirectional stance perturbations in Parkinson's disease. *J Neurol Neurosurg Psychiatry* (2004) 75:1245–54. doi: 10.1136/jnnp.2003.021147
60. Mitchell SL, Collins JJ, De Luca CJ, Burrows A, Lipsitz LA. Open-loop and closed-loop postural control mechanisms in Parkinson's disease: increased mediolateral activity during quiet standing. *Neurosci Lett.* (1995) 197:133–6. doi: 10.1016/0304-3940(95)11924-L
61. Kelly VE, Johnson CO, McGough EL, Shumway-Cook A, Horak FB, Chung KA, et al. Association of cognitive domains with postural instability/gait disturbance in Parkinson's disease. *Parkinsonism Relat Disord.* (2015) 21:692–7. doi: 10.1016/j.parkreldis.2015.04.002
62. Nocera JR, Price C, Fernandez HH, Amano S, Vallabhajosula S, Okun MS, et al. Tests of dorsolateral frontal function correlate with objective tests of postural stability in early to moderate stage Parkinson's disease. *Parkinsonism Relat Disord.* (2010) 16:590–4. doi: 10.1016/j.parkreldis.2010.08.008
63. Lord S, Galna B, Coleman S, Yarnall A, Burn D, Rochester L. Cognition and gait show a selective pattern of association dominated by phenotype in incident Parkinson's disease. *Front Aging Neurosci.* (2014) 6:249. doi: 10.3389/fnagi.2014.00249
64. Schoneburg B, Mancini M, Horak F, Nutt JG. Framework for understanding balance dysfunction in Parkinson's disease. *Mov Disord.* (2013) 28:1474–82. doi: 10.1002/mds.25613
65. Rocchi L, Chiari L, Horak FB. Effects of deep brain stimulation and levodopa on postural sway in Parkinson's disease. *J Neurol Neurosurg Psychiatry* (2002) 73:267–74. doi: 10.1136/jnnp.73.3.267
66. Goldman JG, Weis H, Stebbins G, Bernard B, Goetz CG. Clinical differences among mild cognitive impairment subtypes in Parkinson's disease. *Mov Disord.* (2012) 27:1129–36. doi: 10.1002/mds.25062
67. Arie L, Herman T, Shema-Shiratzky S, Giladi N, Hausdorff JM. Do cognition and other non-motor symptoms decline similarly among patients with Parkinson's disease motor subtypes? Findings from a 5-year prospective study. *J Neurol.* (2017) 264:2149–57. doi: 10.1007/s00415-017-8605-x
68. Lord S, Baker K, Nieuwboer A, Burn D, Rochester L. Gait variability in Parkinson's disease: an indicator of non-dopaminergic contributors to gait dysfunction? *J Neurol.* (2011) 258:566–72. doi: 10.1007/s00415-010-5789-8
69. Lord S, Galna B, Coleman S, Burn D, Rochester L. Mild depressive symptoms are associated with gait impairment in early Parkinson's disease. *Mov Disord.* (2013) 28:634–9. doi: 10.1002/mds.25338
70. Borgonovo J, Allende-Castro C, Laliena A, Guerrero N, Silva H, Concha ML. Changes in neural circuitry associated with depression at pre-clinical, pre-motor and early motor phases of Parkinson's disease. *Parkinsonism Relat Disord.* (2017) 35:17–24. doi: 10.1016/j.parkreldis.2016.11.009

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 13 December 2018
doi: 10.3389/fneur.2018.01045

Implementation of a Central Sensorimotor Integration Test for Characterization of Human Balance Control During Stance

Robert J. Peterka[1,2]*, *Charles F. Murchison*[1], *Lucy Parrington*[1], *Peter C. Fino*[1] and *Laurie A. King*[1]

[1] Department of Neurology, Oregon Health and Science University, Portland, OR, United States, [2] National Center for Rehabilitative Auditory Research, VA Portland Health Care System, Portland, OR, United States

OPEN ACCESS

Edited by:
Joyce Fung,
McGill University, Canada

Reviewed by:
Robert Edward Kearney,
McGill University, Canada
Christian Dresel,
University Medical Centre, Johannes Gutenberg University Mainz, Germany

***Correspondence:**
Robert J. Peterka
peterkar@ohsu.edu

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: 12 July 2018
Accepted: 19 November 2018
Published: 13 December 2018

Citation:
Peterka RJ, Murchison CF, Parrington L, Fino PC and King LA (2018) Implementation of a Central Sensorimotor Integration Test for Characterization of Human Balance Control During Stance. Front. Neurol. 9:1045. doi: 10.3389/fneur.2018.01045

Balance during stance is regulated by active control mechanisms that continuously estimate body motion, via a "sensory integration" mechanism, and generate corrective actions, via a "sensory-to-motor transformation" mechanism. The balance control system can be modeled as a closed-loop feedback control system for which appropriate system identification methods are available to separately quantify the sensory integration and sensory-to-motor components of the system. A detailed, functionally meaningful characterization of balance control mechanisms has potential to improve clinical assessment and to provide useful tools for answering clinical research questions. However, many researchers and clinicians do not have the background to develop systems and methods appropriate for performing identification of balance control mechanisms. The purpose of this report is to provide detailed information on how to perform what we refer to as "central sensorimotor integration" (CSMI) tests on a commercially available balance test device (SMART EquiTest CRS, Natus Medical Inc, Seattle WA) and then to appropriately analyze and interpret results obtained from these tests. We describe methods to (1) generate pseudorandom stimuli that apply cyclically-repeated rotations of the stance surface and/or visual surround (2) measure and calibrate center-of-mass (CoM) body sway, (3) calculate frequency response functions (FRFs) that quantify the dynamic characteristics of stimulus-evoked CoM sway, (4) estimate balance control parameters that quantify sensory integration by measuring the relative contribution of different sensory systems to balance control (i.e., sensory weights), and (5) estimate balance control parameters that quantify sensory-to-motor transformation properties (i.e., feedback time delay and neural controller stiffness and damping parameters). Additionally, we present CSMI test results from 40 subjects (age range 21–59 years) with normal sensory function, 2 subjects with results illustrating deviations from normal balance function, and we summarize results from previous studies in subjects with vestibular deficits. A bootstrap analysis was used to characterize

confidence limits on parameters from CSMI tests and to determine how test duration affected the confidence with which parameters can be measured. Finally, example results are presented that illustrate how various sensory and central balance deficits are revealed by CSMI testing.

Keywords: balance, balance control, orientation, sensory integration, sensorimotor, system identification, stance

INTRODUCTION

Human standing balance control is widely understood to be organized as a closed-loop feedback-control system. In a closed loop control system, different subsystems contribute to behavior of the entire system. The various subsystems interact with one another such that it can be problematic to attribute abnormal behavior to a particular subsystem. For balance control, these subsystems include (1) sensory systems (mainly proprioception, vision, and vestibular) that encode body orientation, (2) a sensory integration mechanism that combines sensory cues, (3) a motor activation mechanism that generates joint torques that correct for deviations from a desired orientation, and (4) body and muscle/tendon mechanics. A full appreciation of the feedback control nature of the system has motivated the application of system identification methods that are appropriate for measuring the dynamic properties of a closed-loop system and characterizing subsystems involved in balance control.

Traditional assessment of standing balance monitors spontaneous sway in different conditions that alter the available sensory cues or change the difficulty of making effective control actions [for review see (1)]. Commonly, stance is tested with eyes open, eyes closed, on firm or compliant (foam) surfaces, in different foot placement configurations (e.g., tandem, single leg), or in conditions that are specifically designed to limit the availability of proprioceptive or visual cues (e.g., sway-referencing methods used on EquiTest sensory organization tests, SOT) (2). Performance is monitored using pass/fail criteria or instrumentation is used to record signals related to body sway using, for example, force plate measures of center-of-pressure (CoP) displacements, inertial measurement sensors, or motion capture systems. For instrumented systems, the recorded signals are processed to obtained measures of variability and magnitude of the signals (3). Then the values of sway measures in specific test conditions or changes in sway measures across different test conditions give an indication of standing balance performance in relation to normative measures and provide an indirect indication about the integrity of sensory systems contributing to balance.

There are, however, limitations to assessments based on spontaneous sway measures because sensory and motor system properties cannot be separately evaluated. For example, excessive sway can be due to inadequate motor control (e.g., too little corrective torque generated per unit of body sway) or due to poor quality (low gain or high variability) of sensory systems contributing to balance (4). Another example would be a fall on an eyes closed SOT test condition with surface sway referencing. A fall could occur if (1) subjects have reduced or absent vestibular function, (2) central processing of vestibular information is inadequate (e.g., faulty central integration of semicircular canal and otolith signals), (3) the subject did not transition quickly enough to full reliance on vestibular information for balance from the sensory utilization configuration prior to the start of sway referencing (where subjects use primarily proprioceptive cues for balance control), or (4) the subject did not generate enough corrective torque due to motor control deficiency.

Application of appropriate system identification methods can overcome some of the limitations of balance assessment based on spontaneous sway measures. To disambiguate the cause/effect relationships between sensory processing, motor action, and body sway in a closed-loop control system, an external balance perturbation must be applied and then proper methods must be used to evaluate the relationship between the external perturbation and body sway or other measures (CoP, muscle activations, joint torques) (5). To date, application of these methods has remained primarily in research environments that have specialized equipment needed to apply controlled balance perturbations. Additionally, not all researchers are necessarily familiar with the mathematical methods needed for system identification. To increase access to these methods this report gives a detailed description of a methodology that is becoming more widely used (6–16). Additionally, the test equipment that we used for data collected in this study is commercially available (SMART EquiTest CRS, Natus Medical Inc., Seattle WA). This device includes research module software that allows for the delivery of custom balance perturbations that are needed for application of the methods we describe.

This report describes the methods we have employed in developing and implementing a test battery we refer to as the central sensorimotor integration (CSMI) test. These aspects include (1) modifications of an EquiTest device to obtain calibrated measures of center-of-mass (CoM) body sway, (2) description of our test protocol and the wide-bandwidth stimulus used for balance perturbations, (3) description of the frequency domain analysis methods used to obtain measures of frequency response function (FRFs) that provide a non-parametric representation of dynamic characteristics of the balance control system, and (4) description of two versions of a simple mathematical model of the balance control system. For both models, parameters were adjusted using an optimal estimation procedure to obtain a set of functionally meaningful parameters that separately identify sensory integration and motor control mechanisms.

A primary goal of this report is to encourage wider application of CSMI test methods to facilitate potential clinical applications for improved diagnosis of balance disorders. To this end we (1)

describe the methodology for the CSMI test with accompanying normative data, (2) determine the reliability of parameter estimates as a function of test duration, (3) compare parameters obtained from two versions of balance control models, (4) evaluate whether parameter estimates were significantly affected using measures of CoM sway based on filtering of CoP compared to a more direct measure, and (5) provide supplementary material that includes computer programs to define stimuli and analyze CSMI test results. Finally, we present example CSMI test results from patient populations illustrating applications of these methods to populations with mild traumatic brain injury (mTBI), vestibular deficits, and other balance deficits.

MATERIALS AND METHODS

Participants

This report utilizes a subset of data from a broader investigation into CSMI problems in patients with chronic mTBI (17). Participants included 40 healthy individuals: 13 males, 27 females, age range 21–59 years, 33.7 ± 11.5 years, height 1.69 ± 0.09 m, weight 69.8 ± 15.8 kg (mean ± sd) with no known musculoskeletal or neurological deficits. Data from one subject with mTBI and one additional control subject with unexpected balance behavior were also included to illustrate capabilities of the CSMI test. Further, data from two previous investigations were included to illustrate the effects of vestibular loss. This study was carried out in accordance with a protocol approved by the Joint Institutional Review Board Committee of Oregon Health and Science University and Veterans Administration Portland Health Care System. Additional results illustrating the effects of vestibular deficits were from studies carried out in accordance with a protocol approved by the Institutional Review Board Committee of Oregon Health and Science University. All subjects gave written informed consent prior to the start of experimental procedures in accordance with the Declaration of Helsinki.

Equipment

Standing balance was tested on a modified SMART EquiTest CRS device (Natus Medical Inc, Seattle WA) running software version 8.6.0. This device has motorized drives that allow forward/backward translations or toe up/toe down rotations of the stance surface and sagittal plane rotations of the visual surround. Subjects stand on dual force plates that record 3D forces and moments. Maximum specified surface and visual surround rotational velocities are 50°/s and 15°/s, respectively, which are well above the largest velocites used in this study (2°/s). Maximum accelerations were not specified, but were found to be sufficient to deliver stimuli used in this study.

The EquiTest CRS device includes a Research Module that allows for creation of user-defined tests. We used the Research Module to define a custom protocol that used sampled stimulus waveforms created in Matlab (The Mathworks Inc., Natick MA, USA) to generate continuous surface and/or visual surround rotations that evoke anterior-posterior (AP) body sway in test subjects (see **Supplementary Materials** for Matlab programs that create our stimuli).

The EquiTest device was modified in two ways: (1), a floor and wall-mounted external frame was placed near the EquiTest that supported two "sway rod" devices (described below) that were used to directly measure AP body displacements at hip and shoulder levels, and (2), a plaid-patterned poster (112 cm high × 106 cm wide) with pseudorandomly placed vertical and horizontal black, white, and gray stripes lined the visual surround to provide a rich visual stimulus to enhance responses to visual stimuli (see **Supplementary Figure 1**).

Stimulus Generation and Test Conditions

Subjects were tested in 8 test conditions that included 4 test types (surface-tilt with eyes closed, surface tilt with eyes open viewing a fixed visual surround, visual surround tilt with eyes open with stance on a level surface, and combined surface-tilt and visual-tilt with eyes open) with each test type performed at 2 amplitudes (2 and 4° peak-to-peak). Tests were presented in randomized order.

The surface and visual tilt stimuli were based on a pseudorandom maximal length ternary number sequence consisting of 80 numbers with +1, 0, or −1 values [generated using a 4-stage shift register with feedback; (18)]. The number sequence was transformed into a time series waveform by substituting each number in the sequence with a set of 25 time samples of equal value to create a waveform consisting of 2,000 samples for one stimulus cycle corresponding to a cycle period of 20 s for 100/s sampling. This time series was mathematically integrated and the integrated waveform was scaled to have peak-to-peak values of 2 and 4°. Additionally, the starting point in the number sequence was selected so that the integrated waveform had a non-zero mean such that about 80% of the integrated waveform had positive values giving stimuli that were biased to favor toe-down surface rotations and forward visual surround tilts since subjects can tolerate greater forward than backward sway without loosing balance.

A Fourier transform of the stimulus waveform demonstrates that a waveform created by a maximal length ternary sequence has the property that stimulus energy is only present at the fundamental frequency (fundamental frequency in Hz is 1/cycle duration = 0.05 Hz) and odd harmonic multiples of the fundamental frequency. Additionally, the magnitude of frequency spectral components of the waveform based directly on a maximal length ternary number sequence is approximately flat out to a frequency of about 2 Hz = 1/(2*25 samples per sequence number/100 samples/s) and then diminishes. Since we use the mathematically integrated waveform to control the angular tilt position of the surface or visual surround, the magnitude of spectral components of the integrated stimulus declines in proportion to inverse frequency [see Figure 3 in (19) to see power spectrum representation of a stimulus nearly identical to our stimulus].

Twelve single-cycle waveforms were concatenated to give a final stimulus waveform with a total duration of 246 s that included 2 s no-movement segments at the beginning and 4 s at the end. The stimulus waveform was low-pass filtered at 4.5 Hz to reduced higher frequency components that the EquiTest device could not faithfully deliver. The sample rate for stimulus delivery and data collection was 100/s, the maximum rate allowed by the

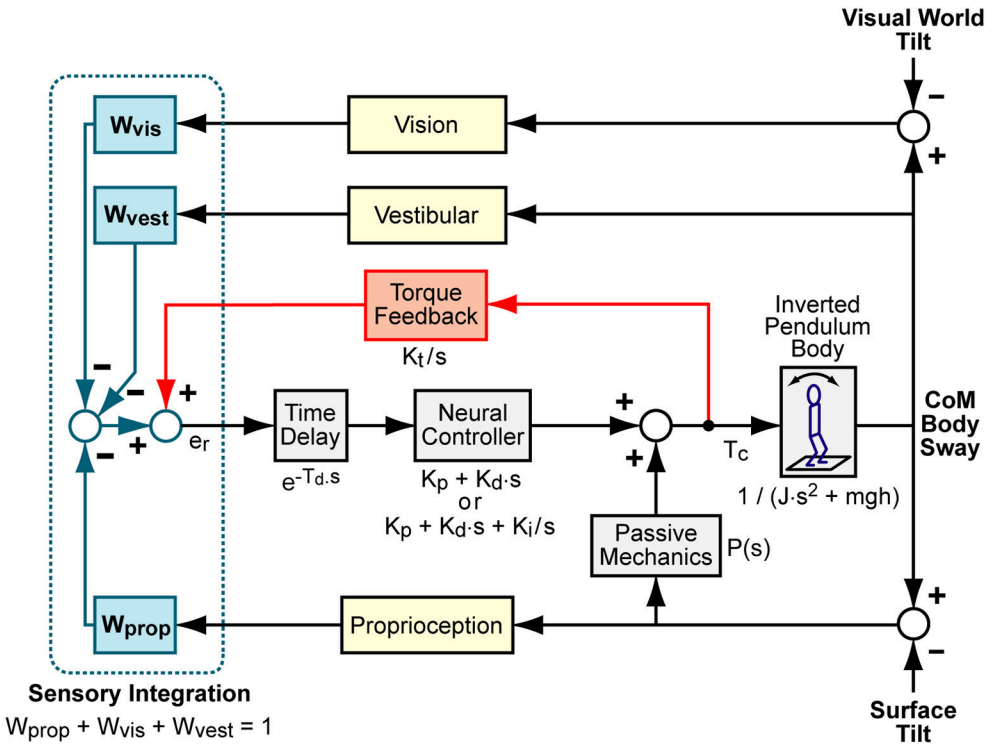


FIGURE 1 | Balance control model block diagram. Visual, vestibular, and proprioception systems provide accurate measures of body orientation relative to the visual scene, earth vertical, and the stance surface, respectively. A weighted combination of these sensory sources provides an internal orientation estimate. This orientation estimate is supplemented with information regarding the mathematical integral of overall corrective ankle torque, T_c, via a positive "Torque Feedback" loop. The signs on the summations within the "Sensory Integration" subsystem indicate whether the sensory information provides negative feedback control (from visual, vestibular, and proprioceptive systems) or positive feedback control (from torque sensors). The sensory information is used to generate time-delayed corrective torque via a "Neural Controller" and corrective torque from the neural controller is supplemented by torque due to passive muscle/tendon mechanics. The overall corrective ankle torque causes a single-segment inverted pendulum body to change orientation. Laplace transform representations of the dynamic properties of various components are shown.

EquiTest research module software. The stimuli were created in Matlab and were saved as ASCII text files that were imported by the EquiTest Research Module software to define experimental tests.

Subjects feet were placed on the stance surface with ankles aligned with the surface rotation axis and at height-dependent stance widths according to EquiTest instructions for performing the clinical SOT. Subjects wore ear protection to mask room and motor sounds.

Following a calibration trial (see below), a warmup test was performed to familiarize subjects with the balance perturbations. The warmup trial was a 4° surface-tilt test that was performed eyes open for the first 120 s and then eyes closed for the remainder of the trial. Then the 8 different tests were performed in randomized order with 3 min breaks given after every 3 trials.

Sway Measurements

Body sway measurements were obtained from measures of whole body CoP displacements from the surface force plates and from measurements of AP body displacements at hip and shoulder level made using a custom "sway rod" system. Each sway rod system consisted of a potentiometer (Midori model CP-2UTN, Midori America Corporation, Irvine CA) attached to an earth-fixed frame located behind and to the subject's left. The potentiometer rotation axis was vertically aligned. The locations of the potentiometers were adjustable in height and in AP depth on the frame and were placed at hip and shoulder heights. A thin 61 cm length aluminum shaft was flexibly attached to the frame-mounted potentiometers to allow free vertical plane rotation of the sway rods without causing potentiometer rotation. The sway rod shafts extended behind the subject with the distal end of the sway rod resting in hip and shoulder hooks mounted on the subject's back at midline. The hip hook was approximately at the hip joint level and the shoulder hook was just below shoulder joint height. Sway rod height above the stance surface and length of the sway rod from the potentiometer to the hook were measured for both hip and shoulder sway rods for use in off-line calculation of body displacements. To facilitate accurate AP placement of the sway rod potentiometer on the frame, each potentiometer module included electronics that lit an LED to signal when the sway rod was parallel to the subject's frontal plane when the subject was standing upright. In this position, the potentiometer registered zero volts. As subjects swayed

forward or backward, the sway rod shaft could slide freely in its hook and rotate the potentiometer producing a voltage change proportional to the potentiometer rotation angle and related, by trigonometry, to AP body displacement at hook levels. The potentiometer electronics module included a scaling amplifier with scaling set to 1 Volt/3 degrees. The potentiometer signals were recorded on auxiliary channels in the EquiTest system that could accept +/−10 V signals that were digitized by a 12-bit A/D converter. Additional description of the sway rod system is included in **Supplementary Figure 1**.

The EquiTest Research Module records various force plate signals, signals encoding surface rotation and translation, and visual surround rotation. Of relevance to the current study are AP CoP displacement, vertical force measures used to measure subject weight, surface rotation angle, visual surround rotation angle, and sway rod potentiometer angles. The EquiTest software encodes data in a proprietary binary format with access to the data provided by exporting test results to ASCII files (from EquiTest software version 8.6.0) or Unicode files (from software version 9.3). One file is created for each test trial.

Estimation of CoM Sway

CoM From Sway Rod Measures

A calibration trial was performed to obtain data used to derive coefficients of an equation that relates hip and shoulder potentiometer signals to a subject's CoM AP displacements and CoM AP rotation angles over the time course of each experimental test. The principle that allows this derivation is that the CoP displacement is equal to the body's horizontal projection of CoM displacement in the case of a static, unmoving body. We approximate this static case by asking the subject to move very slowly in the AP direction over the 120 s duration of a calibration trial while recording the CoP and potentiometer signals. The calibration trial was performed with eyes open on a fixed surface while viewing a stationary visual surround. The subject was directed to assume a variety of upper and lower body orientations (e.g., keeping the body straight while swaying and then with hips slightly flexed or extended while swaying slowly forward and backward).

The potentiometer signals were processed using trigonometric relations to calculate AP displacements at hip and shoulder levels from the sway rod angles measured from the potentiometers:

$$x_h(t) = L_h \tan\theta_h(t) \quad (1)$$

$$x_s(t) = L_s \tan\theta_s(t) \quad (2)$$

where L is the length of the sway rod from the potentiometer to the hook when subjects were in an upright stance position, $\theta(t)$ is the sway rod angle over time measured by appropriately scaling the voltage recorded by the potentiometer, $x(t)$ is the calculated AP displacement of the body, and h and s subscripts indicate hip and shoulder.

A least squared error fit was made to estimate parameters A_h, A_s, and B of an equation relating AP body displacement at hip and shoulder levels to the measured AP CoP displacement, $x_{cop}(t)$, to minimize the squared difference between x_{cop} and x_{cop_fit} defined as:

$$x_{cop\_fit}(t) = A_h \cdot x_h(t) + A_s \cdot x_s(t) + B \quad (3)$$

On subsequent experimental tests, the A_h, A_s, and B parameters derived from the calibration test, was applied to hip and shoulder displacements recorded on experimental tests ($x_{h\_\exp}(t)$ and $x_{s\_\exp}(t)$) to obtain a CoM displacement time series $x_{com}(t) = A_h \cdot x_{h\_\exp}(t) + A_s \cdot x_{s\_\exp}(t) + B$.

The CoM displacement time series was then used to calculate the CoM tilt angle with respect to vertical using the equation:

$$\theta_{com}(t) = \sin^{-1}\left(\frac{x_{com}(t)}{h}\right) \quad (4)$$

where h is the CoM height above the ankle joint. The CoM height estimate was obtained following (20) using measures of leg length (medial malleolus to femoral condyles), thigh length (femoral condyles to greater trochanter), and HAT length (head, arms, trunk segment measured from greater trochanter to glenohumeral joint). Additionally, these body segment length measures along with a body mass measure (obtained from vertical forces measured by the EquiTest device) provided an estimate of the body moment of inertial, J (units: kg m^2), of the legs, thighs, and HAT segments about the ankle joint axis. Along with J, subject mass m, (in kg) and h (in m) were parameters needed in the balance control model that was used to calculate sensory integration and neural control parameters representing each subject's balance performance characteristics.

CoM From Filtered CoP

While the direct measurements of hip and shoulder displacements provide a relatively simple method for measuring CoM displacement using the methods described above, an even simpler method, based on lowpass filtering of CoP, may provide sufficiently accurate CoM displacement measures. An approximate relationship between CoP and CoM displacement is given by Winter et al. (21):

$$x_{cop}(t) = x_{com}(t) - \frac{J}{W \cdot h} \cdot \ddot{x}_{com}(t) \quad (5)$$

Where $\ddot{x}_{com}$ is CoM acceleration, J is body moment of inertia about the ankle joint, and W is body weight excluding the feet. At any given frequency of body motion, x_{com} and $-\ddot{x}_{com}$ are in phase with one another so x_{cop} will also be in phase with x_{com}. Furthermore, the amplitude of $\ddot{x}_{com}$ increases as the square of the frequency of x_{com} and thus makes an increasing contribution to x_{cop} as frequency increases. Because the CSMI methods for quantifying balance control are focused on frequencies below about 1.5 Hz, it may be possible to apply a lowpass filter to the recorded CoP to greatly diminish the CoM acceleration contribution to CoP and obtain a CoM displacement measure (22).

We explored the use of a lowpass filtered CoP to estimate CoM displacement and characterized the extent to which use of this simpler CoM measure affected results in comparison to use of CoM from our sway rod measurement method. We

defined filter coefficients of a 1st order Butterworth filter and applied it using the Matlab "filtfilt" function to provide phaseless 2nd order filtering of the CoP data for each trial in each test condition for each subject. The cutoff frequency was varied in 0.005 Hz increments from 0.25 to 0.65 Hz, the mean squared error (MSE) between the filtered CoP and the CoM from sway rod measures, and the cutoff frequency with the lowest MSE was identified. These best MSE cutoff frequencies were compared across subjects and test conditions. Then a single average best frequency across all subjects and test conditions was calculated and used to process CoP data to obtained CoM displacement, and then CoM sway angles. The CoM data from sway rod and filtered CoP were analyzed as described in the following sections with results compared to determine the extent to which a simpler CoM sway measure could provide comparable results.

Stimulus/Response Analysis

A frequency domain analysis, following the methods of Pintelon and Schoukens (23), was applied to the recorded stimulus tilt angle and the estimated CoM body sway angle of each experimental test to calculate a frequency response function (FRF). An FRF provides a non-parametric description of the dynamic characteristics of the balance control system. The first cycle is ignored to avoid transient responses. Then an FRF is calculated by taking the discrete Fourier transform (using Matlab fft function) of each of the last 11 cycles of the stimulus and CoM sway response time series when the response is assumed to have attained steady state behavior. The assumption of steady state behavior is supported by previous results using similar stimuli that did not reveal evidence for adaptation or habituation over successive cycles on a given trial (6). The experimental FRF, H_e, calculation is:

$$H_e\left(j\omega_k\right) = \frac{\sum_{i=1}^{M} X_{com}^{i}\left(j\omega_k\right)}{\sum_{i=1}^{M} X_{stim}^{i}\left(j\omega_k\right)} \tag{6}$$

where $X_{com}^{i}\left(j\omega_k\right)$ and $X_{stim}^{i}\left(j\omega_k\right)$ are the Fourier transforms of CoM sway response and the stimulus of the *ith* cycle of a total of $M = 11$ cycles, j is the imaginary number $\sqrt{-1}$, and ω_k is radian frequency at the *kth* frequency. Note that a stimulus created by a maximal length ternary sequence has the unusual property that stimulus energy is only present at the fundamental frequency (fundamental frequency in Hz is 1/cycle duration—in this case 0.05 Hz) and odd harmonic multiples of the fundamental frequency. Therefore, all even harmonics of $X_{com}^{i}\left(j\omega_k\right)$ and $X_{stim}^{i}\left(j\omega_k\right)$ were removed prior to the above FRF calculation.

The variability of frequency components of FRFs generally increases with increasing frequency because both the relative responsiveness to the stimulus and the energy of our stimulus declines with increasing frequency. Averaging across stimulus cycles was used to reduce the variability of FRFs, and to further reduce variability, an increasing number of adjacent spectral components were averaged across frequency giving a final distribution of 12 FRF values at frequencies ranging from 0.05 to 1.75 Hz that were approximately equally spaced on a logarithmic frequency scale. The final set of 12 frequencies were at 0.05, 0.1, 0.15, 0.2, 0.3, 0.4, 0.55, 0.7, 0.9, 1.1, 1.35, 1.75 Hz. Higher frequencies were not included since the stimulus energy diminishes rapidly at higher frequencies and body sway behavior becomes increasingly influenced by multi-segment body motions (24) that are not represented by the balance control model used to parameterize the FRFs (see below),

An FRF is a set of complex numbers that vary with frequency but is commonly represented as a gain function, $\left|H_e\left(j\omega_k\right)\right|$, and phase function, $\angle H_e\left(j\omega_k\right)$, given by:

$$|H_e(j\omega_k)| = \sqrt{H\left(j\omega_k\right) \cdot conj\left(H\left(j\omega_k\right)\right)} \tag{7}$$

$$\angle H_e\left(j\omega_k\right) = \tan^{-1}\frac{Im\left(H_e\left(j\omega_k\right)\right)}{Re\left(H_e\left(j\omega_k\right)\right)} \tag{8}$$

where *conj* is the complex conjugate operator, *Im* and *Re* are imaginary and real parts of the complex values of $H_e\left(j\omega_k\right)$, and the subscript *e* refers to the experimental FRF.

Our frequency domain analysis also calculated a coherence function:

$$\gamma^2\left(\omega_k\right) = \frac{\left|\sum_{i=1}^{M} X_{com}^{i}\left(j\omega_k\right) \cdot conj\left(X_{stim}^{i}\left(j\omega_k\right)\right)\right|^2}{\left(\sum_{i=1}^{M}\left|X_{stim}^{i}\left(j\omega_k\right)\right|^2\right) \cdot \left(\sum_{i=1}^{M}\left|X_{com}^{i}\left(j\omega_k\right)\right|^2\right)} \tag{9}$$

where |*| indicates calculation of the magnitude of the complex numbers representing the Fourier components of the stimulus and response spectra, and *conj* is the complex conjugate operation. Coherence function values range from 0 to 1 with higher values indicating larger signal-to-noise conditions in the analysis relating the response to the stimulus. Note that when periodic stimuli are used for system identification, coherence function values only provide an indication of signal-to-noise conditions and do not indicate the presence of non-linearities in the system (23).

Balance Control Model

We represented the balance control as a feedback control system as shown in block diagram form in **Figure 1**. The model represents a system regulated by a continuous, linear, time-invariant control mechanism. Previous work found no evidence for non-linear control mechanisms regulating balance in response to sustained, steady-state stimuli (25). The **Figure 1** model has five major components that include (1) body mechanics of an inverted pendulum, (2) sensory integration provided by a weighted summation of orientation information from proprioceptive, visual, and vestibular systems, (3) time delayed neural controller that transforms the weighted sensory information into corrective ankle torque, (4) a torque positive feedback component that contributes to control by feeding back information related to the time integral of the corrective torque applied at the ankles, and (5) a passive component that generates ankle torque as a function ankle angle and/or angular velocity with no time delay (26). As others have demonstrated (27, 28), it is problematic to obtain reliable estimates of parameters associated with the passive component since other neural controller parameters have a very similar influence over the

shape of FRFs predicted by this model. We also found it difficult to obtain reliable estimates of passive parameters. Therefore, we do not present results that include estimates of the passive component contribution, but the passive component is given in the model equations given below to illustrate its potential influence on FRFs.

The model, H_m, can be expressed as a differential equation in the Laplace domain that predicts the CoM response, $X_{com}(s)$, for a given surface stimulus, $X_{surf}(s)$, visual stimulus, $X_{vis}(s)$, or combined surface plus visual stimuli. The Laplace equations for surface, visual, or combined stimuli are:

$$H_{surf}(s) = \frac{X_{com}(s)}{X_{surf}(s)} = \frac{W_{prop} \cdot NC \cdot TD \cdot B + P \cdot B}{1 - TF \cdot NC \cdot TD + P \cdot B + NC \cdot TD \cdot B} \quad (10)$$

$$H_{vis}(s) = \frac{X_{com}(s)}{X_{vis}(s)} = \frac{W_{vis} \cdot NC \cdot TD \cdot B}{1 - TF \cdot NC \cdot TD + P \cdot B + NC \cdot TD \cdot B} \quad (11)$$

$$H_{surf+vis}(s) = \frac{X_{com}(s)}{X_{surf+vis}(s)} = \frac{\left(W_{prop} + W_{vis}\right) \cdot NC \cdot TD \cdot B + P \cdot B}{1 - TF \cdot NC \cdot TD + P \cdot B + NC \cdot TD \cdot B} \quad (12)$$

where s is the Laplace variable, $NC = K_p + K_d \cdot s$ is the neural controller (a proportional-derivative, PD, neural controller), $TD = e^{-T_d \cdot s}$ is the time delay component, B is a linearized equation representing inverted pendulum body mechanics given by $\frac{1}{(J \cdot s^2 - mgh)}$ with m equal to body mass minus mass of the feet and g the gravity constant, TF is the torque feedback component given by $\frac{K_t}{s}$, and $P(s)$ is the passive component. Simple forms of P can include only a simple stiffness factor, $P = K_{pas}$ or a combination of stiffness and damping $P = K_{pas} + B_{pas} \cdot s$.

The torque feedback mechanism assumes that the balance control system has available to it a measure of corrective ankle torque derived from sensory sources. This torque signal is processed to eliminate higher frequency components and is added (positive feedback) to the sensory error signals derived from the other sensory systems. The combined sensory error signal is, in turn, processed to generate additional ankle torque (29). Functionally, torque feedback influences low frequency sway behavior such that the body moves toward an orientation where corrective torque is minimal (typically the upright orientation, but also can be toward orientation aligned with the gravito-inertial vector in an accelerating environment such as an accelerating train).

An alternative neural control structure used a neural controller with an integration factor $NC = K_p + K_d \cdot s + K_i/s$ (a proportional-integral-derivative, PID, neural controller) rather than PD control with torque feedback (6, 13, 15). A model with PD control plus torque feedback has a similar, but not identical, ability to account for features of experimental FRFs as a model with PID control and no torque feedback. Because both neural control structures have been used to describe experimental results, it is of interest to understand whether the estimate of parameters shared between the two models depends on which of these two neural control structures are used in the model.

By substituting $s = j\omega$ into the above equations, model predicted FRFs can be calculated for a given set of parameter values at the same set of k frequencies as the experimental FRFs. Model parameters can be adjusted to optimally match the experimentally determined FRFs, thereby providing a parametric representation of the non-parametric experimental FRFs.

Model Parameter Estimation

For each subject's FRF for each of the 8 test conditions, model parameters were estimated by adjusting the parameters to minimize an error function. This minimization was performed using the Matlab "fmincon" function from the Optimization toolbox. This function requires definition of an error function that calculates a value with each call to the error function. Our error function was:

$$E = \sum_{k=1}^{N} \frac{\left|H_m\left(j\omega_k\right) - H_e\left(j\omega_k\right)\right|}{\left|H_m\left(j\omega_k\right)\right|} \quad (13)$$

where $N = 12$ was the number of frequency components in the FRFs and the subscripts e and m indicate the experimental and model-predicted FRF, respectively. The "fmincon" function adjusts parameters beginning with initial values to minimize the error using search criteria constraints that limit the parameters to specified ranges. The optimization procedure is not guaranteed to find a parameter set associated with a global minimum error. To overcome this, the optimization can be repeated multiple times beginning with different initial values. This is necessary when fitting more complex models (28). For the simple model applied in this study, we have found reliable convergence to the same parameter values independent of initial values. In practice and for results presented in this report, five repeated optimizations were performed and parameters associated with the lowest error were selected to represent the best fit.

On tests with very low signal-to-noise as indicated by low coherence values, the identified parameter set can be invalid in that the parameters define a system that is unstable. For example, the neural control stiffness parameter K_p must be greater than mgh (with g the gravity constant) for the system to be stable. Therefore, the K_p lower constraint is set to mgh. If the optimization finds a K_p value equal to mgh, the identified parameter set is obviously invalid.

For the 2 test conditions that simultaneously presented surface-tilt and visual-tilt stimuli, experimental FRFs were calculated separately relating the individual stimuli to the recorded CoM sway, model parameter estimates were obtained for each experimental FRF, and the model parameters were averaged to give a final set of parameters characterizing system properties.

Model Quality

The ability of the model and identified parameters to account for the stimulus-evoked body sway was assessed by a variance

accounted for (VAF) measure:

$$VAF = 100 \cdot \left(1 - \frac{\sum_{i=1}^{N} \left(\overline{\theta_{com}}(t_i) - \overline{\theta_{sim}}(t_i)\right)^2}{\sum_{i=1}^{N} \overline{\theta_{sim}}(t_i)^2}\right) \quad (14)$$

where $\overline{\theta_{com}}$ is the experimental CoM body sway averaged across the last 11 stimulus cycles, $\overline{\theta_{sim}}$ is the corresponding mean CoM body sway obtained from simulations of the **Figure 1** model using Matlab Simulink (version 8.6). VAF values were calculated for each subject and on each of the 8 test conditions using the identified parameters. VAF values for both the PID and PD plus torque feedback models were calculated.

Bootstrap Analysis

A bootstrap analysis was used (1) to characterize the distribution and range of parameter values associated with normal sensorimotor control and (2) to investigate the extent to which the accuracy and reliability of parameter estimates are influenced by reducing the number of stimulus/response cycles included in the analysis.

For each subject and each test condition the Fourier transformed stimulus/response data of M cycles were randomly selected (with replacement) from the 11 available cycles of experimental data. An FRF was calculated from these M cycles of data and model parameters were obtained. This random selection and fitting process was repeated 10,000 times and parameter sets from each of these analyses were saved for subsequent analysis. Five different bootstrap selections were made with different numbers of sampled cycles with M = 3, 6, 9, 11, 15, and 20. Thus, for each subject and each test condition we obtained 10,000 parameter sets at each of the 5 different cycle counts.

Then a second bootstrap was performed by randomly sampling (with replacement) parameters sets from the 10,000 parameters sets of the 40 subjects from the previously saved bootstrap samples for each of the 5 different cycle counts. This yielded for each model parameter a set of 10,000 samples for the 5 different cycle counts that were then statistically summarized by calculating mean and median values, and 90 and 95 percentile confidence ranges.

RESULTS

Calibration Procedure

Data from a 2 min calibration test were used to estimate linear regression coefficients needed to transform measures of AP body displacements at hip and shoulder levels to measures of CoM displacement (Equation 3). An example of data from a calibration trial showing hip and shoulder level displacements (Equations 1, 2), the regression fit of these displacements to the AP CoP, and the fit error are provided in **Figure 2**. Because the subject begins the trial in an upright position, the value of the first data point in the potentiometer signal is subtracted from remainder of the points so that the calculated AP displacement represent deviations from the upright position. The regression fit accounts well for slowly varying CoP changes that are indicative of the displacement of the CoM as a function of sway-rod measured hip and shoulder displacements but not the rapid oscillations of CoP that reflect the torque corrections used by the subject to maintain the displaced CoM position. The fit error shows no obvious bias and only small rapid oscillations about a constant offset value accounted for by the B term in Equation 3. These small oscillations are indicative of the transient corrective torques generated to maintain the slowly moving CoM displacements. The particular values of the A_h and A_s regression coefficients depend on subject body mass distributions and the specific heights of the sway rods and B depends on foot placement on the surface. Across all 40 subjects, the values of the Equation 3 coefficients were $A_h = 0.581 \pm 0.056$ (Mean $\pm$ SD) and $A_s = 0.345 \pm 0.035$. The value of B is not relevant to FRF analysis since B only affects the mean value CoM displacement which is not used in the FRF analysis.

Example Stimulus-Evoked Sway Analysis

For each subject, the calibration coefficients for that subject are applied to the hip and shoulder displacement data on each stimulus trial to calculated AP CoM displacement, and then, using the estimate of the subject's CoM height above the ankle joint axis, Equation 4 was applied to calculate the AP CoM sway angle. An example of CoM sway data from a single subject and the corresponding 12-cycle surface-tilt stimulus that evoked this sway is shown in **Figure 3A**. There is cycle-to-cycle variability that partially obscures the relationship between the stimulus and CoM response. Averaging of CoM across the last 11 cycles clarifies the stimulus-response relationship and shows that the subject's CoM sway angle tends to track the surface tilt angle (**Figure 3B**) and often the sway is greater than the stimulus. For reference, if a subject was able to fully compensate for the balance perturbation caused by the rotating surface, CoM sway would not deviate from upright and the sway trace in **Figures 3A,B** would be flat. The focus of this paper is on the frequency domain analysis of sway responses, but time domain

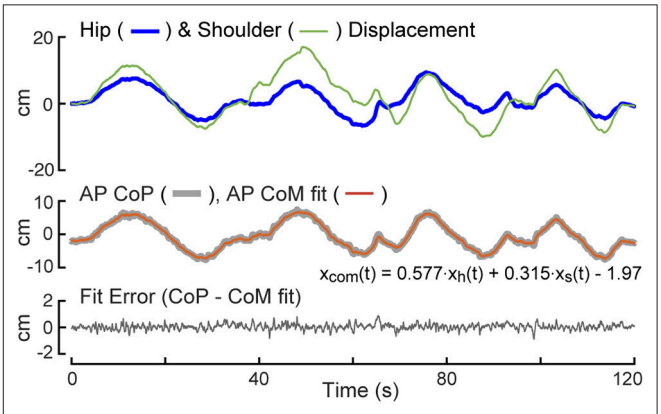


FIGURE 2 | Calibration example. The test subject is instructed to sway slowly forward and backward while recording anterior-posterior (AP) center-of-pressure (CoP) displacement, and body displacements at hip, $x_h(t)$, and shoulder, $x_s(t)$, levels. A least squared error fit of a linear combination of hip and shoulder displacements to CoP provides coefficients for use in measuring center-of-mass (CoM) displacement on subsequent tests.

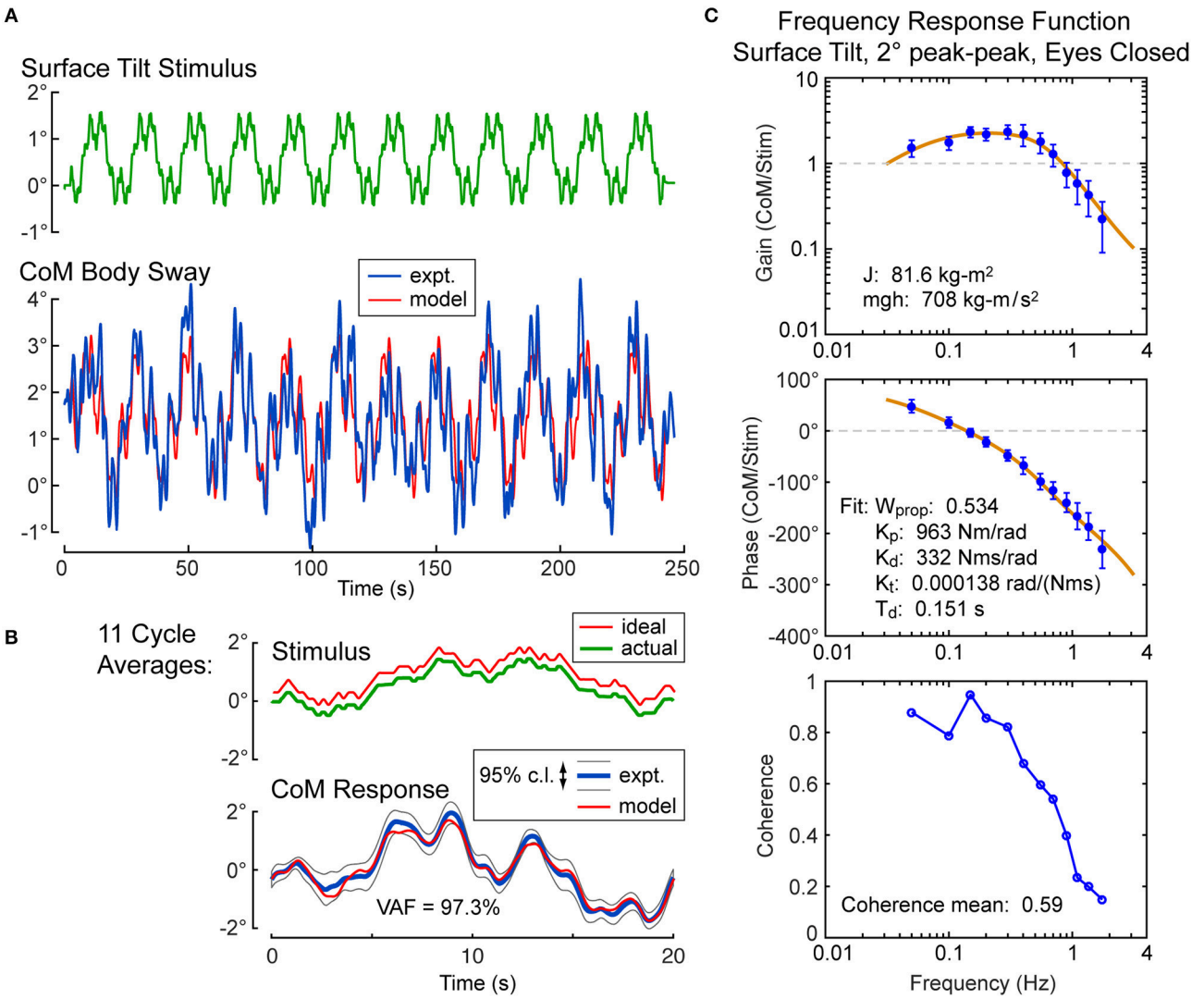


FIGURE 3 | Example single-subject data and data analysis of center-of-mass (CoM) sway evoked by a surface-tilt stimulus with 2° peak-to-peak amplitude during eyes closed stance. Twelve cycles of the surface-tilt stimulus and the corresponding evoked CoM sway are shown **(A)**. Averaging across the last 11 cycles of the stimulus and sway response reveal the close correspondence between stimulus and response **(B)**. A frequency response function represented by gain and phase functions [mean values ±95% confidence limits; see (30)] characterize the balance control dynamics of this individual on this particular test with a coherence function providing information on signal-to-noise quality **(C)**. The solid lines through the frequency response data are based on model parameter estimates. Model-predicted CoM sway based on identified parameters is shown in **(A,B)** with a variance accounted for (VAF) measure showing that the model accounts for most of the experimental stimulus evoked sway. Comparison of the actual and ideal stimulus (ideal is offset from the actual for comparison) in **(B)** demonstrates the accurate delivery of the desired stimulus.

analyses are also performed in the analysis programs included in the **Supplemental Material**.

An FRF derived by application of Equation 6 to the CoM sway data is shown in **Figure 3C** along with the associated coherence function derived using Equation 9. The FRF is represented by gain and phase functions (Equations 7, 8) with each gain value indicating the ratio of CoM sway amplitude to the stimulus amplitude at individual frequencies and the phase indicating the relative timing between the stimulus and response. If the test subject had been a rigid mannequin whose feet were glued to the tilting surface, the mannequin's body would remain perpendicular to the surface throughout testing. The FRF analysis of the mannequin's CoM response would show gains of unity and phases of zero across all frequency components of the surface-tilt stimulus and the coherence function values would be unity (assuming no measurement noise in recording of body sway and surface tilt) indicating perfect correlation between stimulus and response. Actual human FRFs differ from the ideal mannequin behavior in several ways. CoM response gains vary with frequency. Typically gains are highest at mid-frequencies (~0.1–0.8 Hz) with values often greater than one, indicating subject sway amplitude is greater than the stimulus amplitude,

and decrease for both lower and higher frequencies. Phase values cross zero at ∼0.1 Hz and typically show phase leads at low frequencies and increasing phase lags at higher frequencies. Coherence values are less than one and tend to decrease with increasing frequency consistent with overall reduced signal-to-noise as sway response magnitude relative to stimulus declines with increasing frequency.

Also shown in **Figure 3C** is the optimization fit to the experimental FRF obtained by adjusting model parameters to minimize the Equation 13 error criterion. The model accounts well for the experimental FRF and provides a set of parameters that characterize the dynamic properties of the balance control system for each individual subject in each test condition.

Effect of Stimulus Duration on Parameter Estimates

Shorter test durations are desirable in clinical applications, but too short a test duration likely will compromise the accuracy of parameter estimates and increase their variance. A bootstrap analysis was used to investigate the tradeoff between test duration and accuracy of parameter estimation. The results of the analysis for the sensory weight parameter on the 8 test conditions are provided in **Figure 4**. For each test condition there are five vertical bars showing 95th (thin bar) and 90th (thick bar) percentile confidence limits, and mean and median values corresponding to the five bootstrap analyses that included 3, 6, 9, 11, 15, and 20 cycles of data (arranged in left to right order). The percentile bars show that the distributions generally become narrower with increasing cycle counts but the narrowing diminishes with increasing cycle counts. The mean and median parameter values were greatest at the lowest cycle count suggesting bias in the parameter estimate at the lowest cycle count and indicating that 3 cycles are not sufficient to accurately estimate parameter values. The bias was largest for the visual stimulus conditions (5 and 6), which are also the conditions where the sensory weights were lowest and coherence values were lowest (see below) indicating low signal-to-noise in response to visual stimuli. Trends in narrowing distributions and reduced bias with increasing cycles counts were similar for the other model parameters.

Our conclusion is that for most test conditions, 6 stimulus cycles are adequate for the purpose of obtaining accurate parameter estimates. This judgment is based on the observation that, for most test conditions, 6 cycles were sufficient to achieve a stable variance of the parameter distribution and mean and median values showed minimal changes when cycle counts were further increased (**Figure 4**). However, an exception applied to the visual test conditions where the responsiveness to the stimulus and signal-to-noise were low. For these low response conditions, 11 cycles should be considered as a lower limit of test cycles. Additionally, our conclusions specifically apply to the 2 and 4° stimulus amplitudes we used. It is evident in **Figure 2** that the parameter bias was greater and parameter distributions became wider for all 2° compared to 4° stimulus amplitudes suggesting that studies that use even lower stimulus amplitudes will likely need to use a greater number of stimulus cycles to avoid bias and reduce variability of parameter measures.

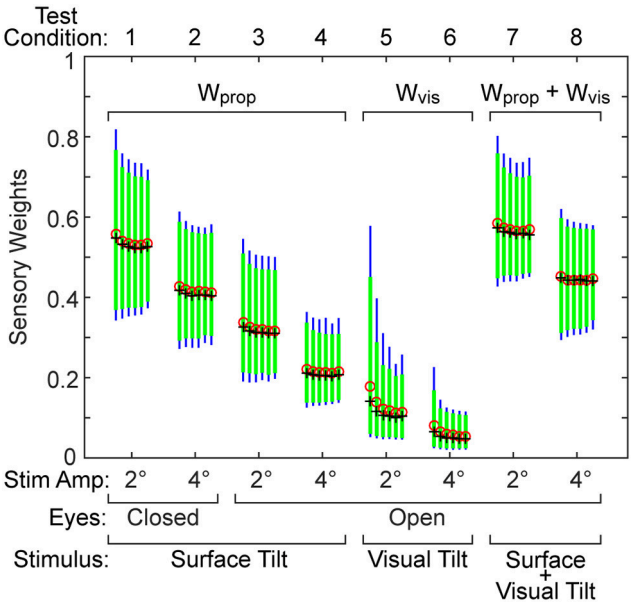


FIGURE 4 | Results from a bootstrap analysis used to investigate how test duration affects the distribution of the sensory weight parameter in the eight test conditions. The five vertical bars for each test condition represent the 90th percentile (thick green bar) and 95th percentile (thin blue bar) range of the parameter when results were derived from tests that included either 3, 6, 9, 11, 15, and 20 stimulus-response cycles (arranged left to right for each condition). Mean (red o) and median (black +) values of each distribution are shown.

Identified Balance Model Parameters

Parameters of the balance control model that included torque feedback were obtained for each of the 40 subjects on each of the 8 test conditions (**Table 1**). Only one subject's parameters on 1 test condition were incompatible with stability and were not include in summary statistics. Specifically, on the 2° visual stimulus condition the neural controller stiffness parameter K_p for this subject converged to the lower bound of *mgh* set for this parameter. The K_p value must be greater than *mgh*, the gravity stiffness constant, for the system to be stable. The FRF data on this individual test showed very low and variable gains and phases consistent with the low measured coherence values (mean = 0.087).

Parameters and mean coherence values for all subjects on each test condition are shown in **Figure 5**. The figure includes boxplots that show median parameter values for each test condition and summarize the parameters distributions. The figure also shows parameter values of individual subjects.

The sensory weight measures showed consistent changes across test amplitude. In each of the 4 test types, the sensory weights on 4° trials were, on average, lower than on 2° trials of corresponding test types. This was the case for all but one individual in 1 test type. Because the model assumed that a sensory weight represents the relative contribution of a particular sensory system to overall balance control, a decrease

TABLE 1 | Parameters derived using balance control model with PD neural control plus torque feedback.

Condition	Parameter	Mean (SD)	5%tile	25%tile	50%tile	75%tile	95%tile
1	W_{prop}	0.509 (0.079)	0.367	0.461	0.512	0.557	0.676
	K_p/mgh	1.51 (0.133)	1.31	1.42	1.50	1.56	1.79
	K_d/mgh	0.517 (0.067)	0.421	0.465	0.521	0.565	0.627
	$K_f \times 10{,}000$	1.27 (0.46)	0.64	0.92	1.21	1.51	2.11
	T_d	0.144 (0.015)	0.119	0.133	0.143	0.157	0.168
2	W_{prop}	0.396 (0.070)	0.298	0.351	0.390	0.442	0.534
	K_p/mgh	1.61 (0.144)	1.37	1.52	1.59	1.70	1.90
	K_d/mgh	0.542 (0.085)	0.406	0.473	0.554	0.598	0.670
	$K_f \times 10{,}000$	1.17 (0.50)	0.48	0.77	1.13	1.52	2.21
	T_d	0.120 (0.013)	0.098	0.111	0.117	0.128	0.145
3	W_{prop}	0.299 (0.057)	0.209	0.265	0.294	0.327	0.426
	K_p/mgh	1.61 (0.272)	1.34	1.41	1.56	1.71	2.51
	K_d/mgh	0.523 (0.072)	0.397	0.476	0.521	0.570	0.640
	$K_f \times 10{,}000$	1.23 (0.56)	0.52	0.76	1.11	1.56	2.45
	T_d	0.126 (0.023)	0.091	0.110	0.126	0.139	0.164
4	W_{prop}	0.207 (0.046)	0.137	0.168	0.204	0.238	0.297
	K_p/mgh	1.74 (0.341)	1.41	1.53	1.64	1.84	2.53
	K_d/mgh	0.543 (0.095)	0.334	0.475	0.548	0.612	0.705
	$K_f \times 10{,}000$	1.35 (0.79)	0.32	0.68	1.29	1.83	3.06
	T_d	0.092 (0.021)	0.056	0.076	0.094	0.104	0.129
5	W_{vis}	0.117 (0.050)	0.051	0.086	0.107	0.135	0.216
	K_p/mgh	1.24 (0.103)	1.12	1.19	1.22	1.28	1.53
	K_d/mgh	0.496 (0.045)	0.412	0.467	0.501	0.524	0.596
	$K_f \times 10{,}000$	0.802 (0.894)	0.000	0.010	0.062	0.116	0.167
	T_d	0.210 (0.025)	0.173	0.187	0.212	0.229	0.256
6	W_{vis}	0.055 (0.026)	0.025	0.038	0.048	0.069	0.121
	K_p/mgh	1,24 (0.113)	1.11	1.17	1.23	1.30	1.51
	K_d/mgh	0.494 (0.066)	0.397	0.444	0.496	0.526	0.606
	$K_f \times 10{,}000$	0.88 (1.32)	0.00	0.11	0.47	1.06	5.11
	T_d	0.202 (0.029)	0.146	0.178	0.211	0.226	0.240
7	$W_{prop}+W_{vis}$	0.556 (0.071)	0.435	0.511	0.553	0.590	0.689
	K_p/mgh	1.50 (0.137)	1.30	1.40	1.49	1.56	1.81
	K_d/mgh	0.482 (0.077)	0.354	0.423	0.468	0.546	0.610
	$K_f \times 10{,}000$	1.19 (0.43)	0.46	0.92	1.17	1.38	1.98
	T_d	0.132 (0.021)	0.090	0.122	0.133	0.148	0.160
8	$W_{prop}+W_{vis}$	0.431 (0.064)	0.345	0.377	0.424	0.497	0.531
	K_p/mgh	1.55 (0.120)	1.39	1.45	1.52	1.62	1.82
	K_d/mgh	0.492 (0.085)	0.342	0.435	0.486	0.563	0.623
	$K_f \times 10{,}000$	1.05 (0.47)	0.34	0.73	1.00	1.47	1.92
	T_d	0.104 (0.018)	0.072	0.093	0.104	0.121	0.127

Mean, standard deviation (SD) and distribution percentile values are based on 40 subjects except for Condition five where one subject's parameters were excluded. Units on K_p, K_d, K_f, and T_d are Nm/rad, Nms/rad, rad/(Nms), and s, respectively. K_p and K_d values for each subject were normalized by the subject's mgh (mass × gravity × center of mass height; units Nm/rad) value.

in one weight must be associated with an increase in the contribution of a different sensory system. Specifically, for eyes closed surface-tilt tests (conditions 1 and 2 where only proprioception and vestibular cues contribute to balance), W_{prop} is the identified parameter and then the vestibular contribution is given by $W_{vest} = 1-W_{prop}$. Vision also contributes to balance on conditions 3 and 4 so the combined contribution of visual and vestibular to balance is given by $W_{vis} + W_{vest} = 1-W_{prop}$. The identified sensory weight in the visual stimulus conditions (conditions 5 and 6) is W_{vis} so the combined contribution of vestibular and proprioception is $W_{vest} + W_{prop} = 1-W_{vis}$. Finally, in combined surface and visual stimulus conditions (conditions 7 and 8), the identified sensory weight is the combined visual and proprioceptive contribution $W_{vis} + W_{prop}$, so the vestibular contribution is $W_{vest} = 1-(W_{vis} + W_{prop})$.

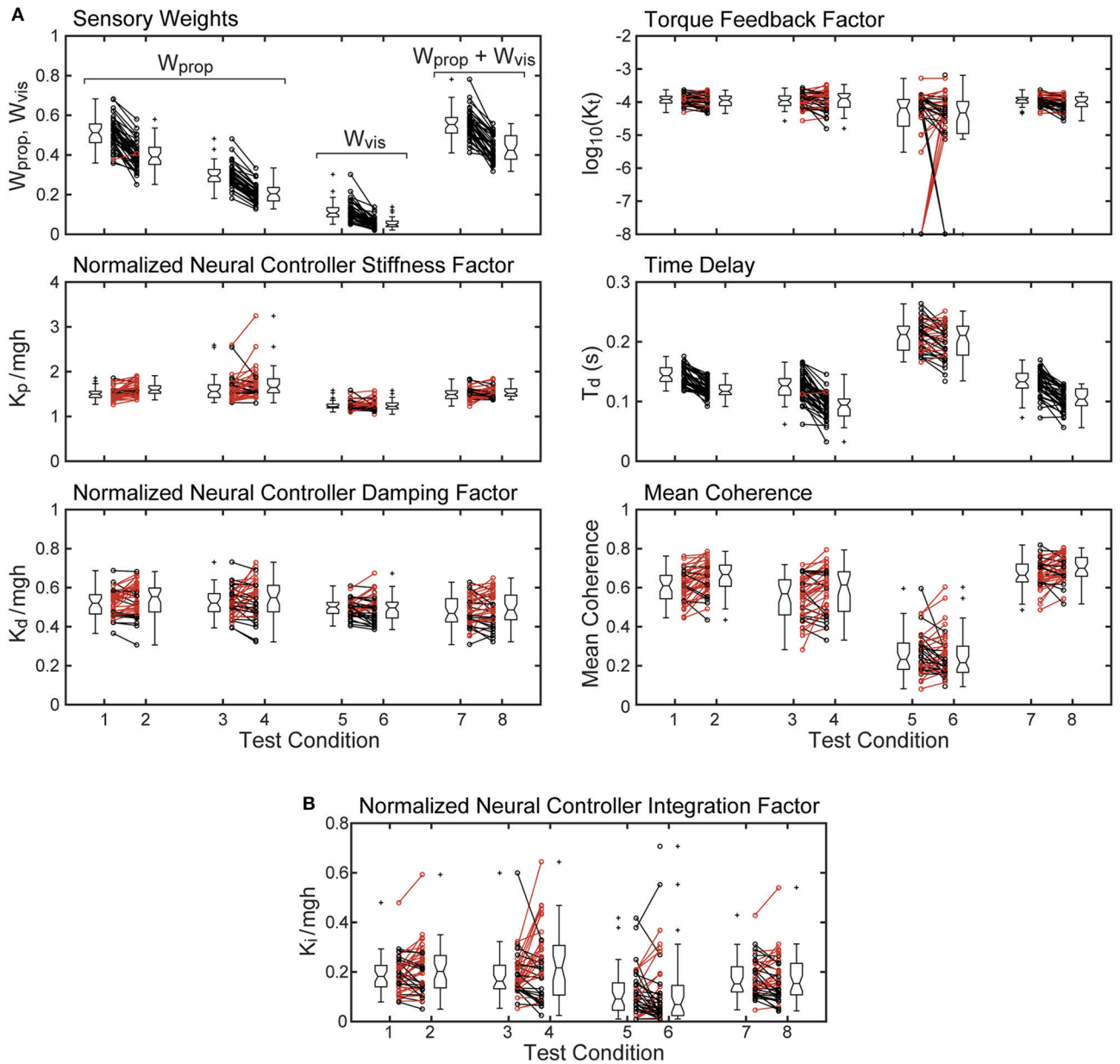


FIGURE 5 | Mean coherence and identified parameter values for the 8 test conditions from 40 subjects whose stimulus-response behavior was modeled using a proportional-derivative neural controller plus torque feedback are shown in **(A)**. Subject data points from 2 and 4° stimulus-amplitude tests for the 4 test types are connected by lines with black lines and points indicating smaller parameter values on the 4° tests compared to the 2° tests and red lines indicating larger parameter values on the 4° tests. Boxplots next to the individual points show median values (center horizontal line), lower and upper 25th and 75th percentile values (lower and upper edges of the box), approximate 95% confidence limits on the median values (notches on the box), error bars (spanning smallest to largest individual values that are not considered to be outliers), and outlying data points (+'s). **(B)** shows values of the normalized integration control factor derived from model fits using a proportional-integral-derivative neural controller. Parameters from the single subject whose model fit for test condition five was not compatible with stability are not included.

The time delay parameter was consistently smaller on 4° vs. 2° amplitude tests on 3 of the 4 test types (surface-tilt eyes open and closed, and combined surface + visual tilt stimuli). On these same 3 test types, the time delays were notably smaller (mean = 0.120 s across the 3 test types) than on the visual stimulus conditions (mean = 0.206 s).

The neural controller parameters K_p and K_d shown in **Figure 5** were normalized by dividing by *mgh* to account for the high correlation of these neural controller parameters with body mechanics parameters (**Figure 6A**). The high correlation was expected since larger subjects must generate a larger corrective torque to compensate for the larger balance disturbance caused

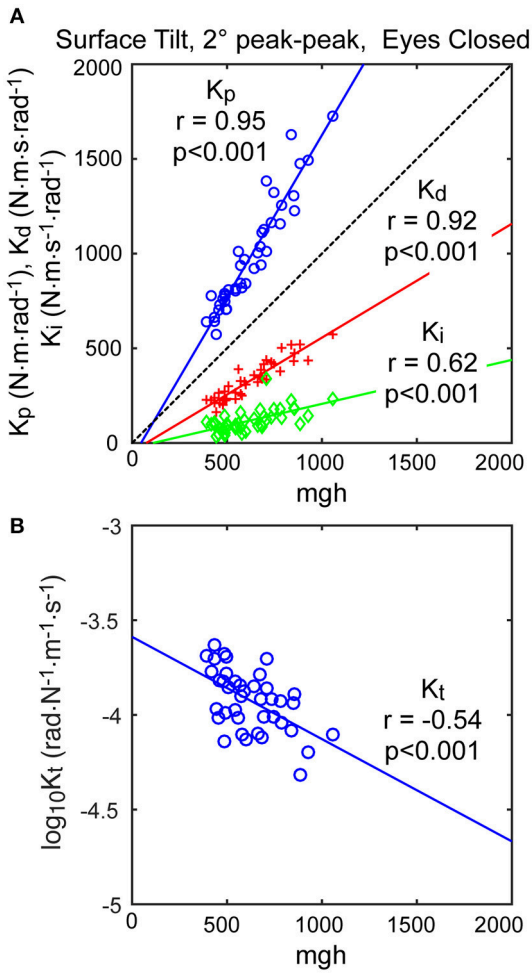


FIGURE 6 | Correlation of neural controller and torque feedback parameters with *mgh* (body mass excluding feet x gravity constant × center of mass height above ankle joints). Individual values are shown for 40 subjects from the surface-tilt, eyes closed, 2° tests. In **(A)**, the K_p and K_d parameters are from the model with proportional-derivative control plus torque feedback and K_i is from the model with proportional-integral-derivative control. **(B)** shows a negative correlation between the torque feedback parameter K_t and *mgh*.

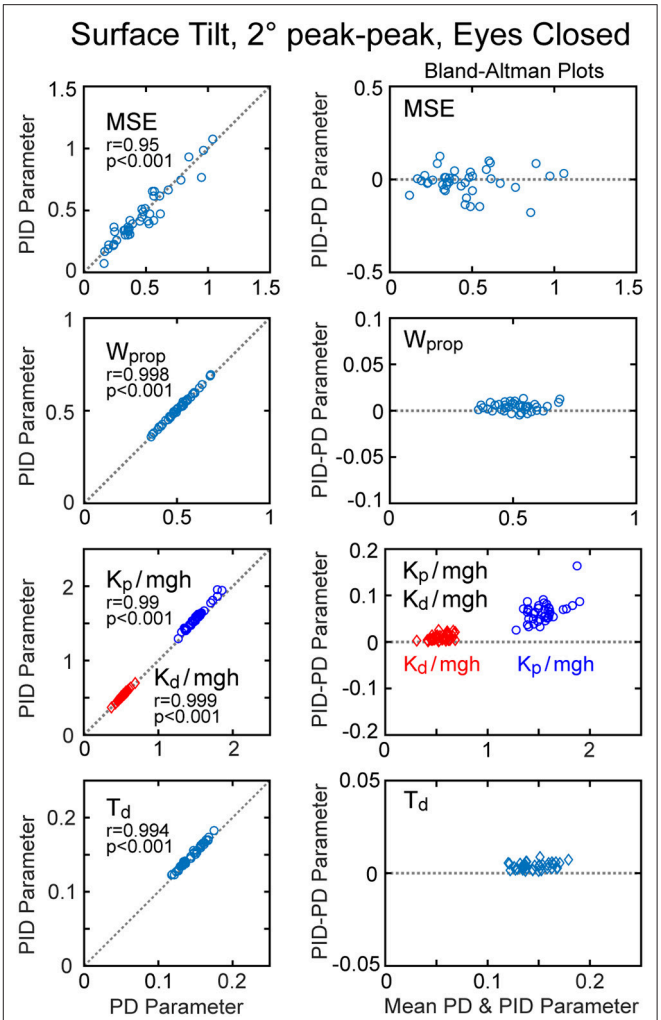


FIGURE 7 | Correlation and Bland-Altman plots comparing model fit mean square error (MSE) and parameters from the model with PD (proportional-derivative control) plus torque feedback with parameters from a PID (proportional-integral-derivative) model. Comparisons are shown for results from 40 subjects on the surface-tilt, eyes closed, 2° amplitude test.

by gravity with *mgh* being the disturbance torque due to gravity. Similarly, the damping parameter K_d was also highly correlated with *mgh*. The normalized K_p values were generally larger for the 3 test types that include surface-tilt simulation (mean = 1.58 across conditions 1–4, 7, 8) than on the visual stimulus conditions (mean = 1.24 across conditions 5, 6). Both normalized K_p and K_d values were slightly larger on the 4° tests than the 2° tests for the 3 test types that include surface-tilt stimulation.

Notably there were several outlying values of normalized K_p on the surface-tilt eyes open tests (conditions 3 and 4). There was no indication that these outlying values were due to poor quality parameter estimates or that these subjects had abnormal balance control systems. A possible explanation is that a few subjects under these test conditions used a strategy that maintained a stiffer balance control system by using co-contraction to increase a passive contribution to overall corrective torque production. Because our model did not separately represent a passive component, the model fit attributed the increased overall stiffness to a higher value of K_p. Consistent with this explanation, the shortest time delay parameters identified on test conditions 3 and 4 were associated with the same subjects who had the largest normalized K_p values. This is consistent because torque generated by passive stiffness acts without time delay whereas, the sensorimotor contribution to torque generation has a finite time delay. Therefore, time delay values from subjects who made greater use of co-contraction would be expected to have shorter values since there was only one time-delay parameter in the model that represents an overall effective time delay. Additionally, the generally shorter time delay values on 4° vs. 2° tests across all test conditions could also be attributed a greater contribution of passive torque. However, other explanations are also plausible, such as there being different time delays associated

with the different sensory contributions to balance. For example, if the time delay of the vestibular contribution to balance was shorter than other sensory systems, then an up-weighting of the vestibular contribution at the higher stimulus amplitude could also cause an apparent overall reduction in time delay.

The torque feedback parameter, K_t, modifies the contribution of the neural controller to the generation of corrective torque. Because of the association of torque feedback with overall torque generation, one might expect that K_t would also scale with increasing *mgh*. K_t did show a weak correlation with *mgh*, however it was a negative correlation (**Figure 6B**). The reason for this becomes evident if the frequency dependent relationship between sensory error and overall corrective torque generation is considered. Specifically, torque feedback only affects the magnitude of torque generation at frequencies below about 0.1 Hz such that larger values of K_t result in a greater reduction in torque. If K_p and K_d are increased without changing K_t, the relative influence of K_t increases and there is relatively less corrective torque generated below 0.1 Hz. This effect can be countered if K_t is decreased when K_p and K_d are increased. The net effect is that dynamic characteristics of the balance control system can remain invariant across subjects with different values of *mgh* if K_t is lower in subjects with larger *mgh*.

An alternative version of the balance control model with a PID neural controller rather than a PD controller with torque feedback also provided a good representation of the balance control system (parameters summarized in **Supplementary Table 1**). The estimates of parameters that are common to the two models were very similar and the overall MSE was nearly identical. Parameters common to the two model versions are compared in **Figure 7** by showing correlation plots (left column) and Bland-Altman plots (right column). These parameter comparisons include sensory weights, neural controller parameters K_p and K_d, and time delay for the two model versions for the eyes closed 2° surface-tilt condition. Although correlations were uniformly high, the Bland Altman plots reveal small biases between parameter measures from the two different models. Across all test conditions the mean differences between parameters from the model with PID control and the model with PD plus torque feedback were 0.0025, 0.059, 0.0085, and 0.0034 for sensory weight, normalized K_p, normalized K_d, and time delay, respectively, corresponding to percent differences of 0.77, 3.8, 1.7, and 2.4%. Positive differences and percentages indicate that the parameters from PID model were greater than from the PD plus torque feedback model. Unlike the K_t parameter, the integral control parameter K_i of the PID controller does scale with *mgh* (**Figure 6A**). **Figure 6A** plots the normalized K_i values of the 40 subjects for test condition 1.

Table 2 summarizes the VAF measures from the 8 test conditions and the 2 model configurations (PID and PD plus torque feedback). Both model configurations were equally effective in accounting for the experimental evoked sway. The VAF values were notably smaller on the visual stimulus conditions compared to all other conditions consistent with low sensitivity to visual stimulation (i.e., low W_{vis} values) and low coherence.

TABLE 2 | Variance accounted for (VAF) measures expressed as percentages obtained from comparisons of experimental and model simulated responses to balance perturbations in the 8 test conditions.

Test condition	VAF PD + torque feedback model	VAF PID model
1: Surf Stim 2°, Eyes Closed	95.1 (2.9)	94.9 (3.6)
2: Surf Stim 4°, Eyes Closed	94.7 (3.2)	95.1 (4.3)
3: Surf Stim 2°, Eyes Open	94.2 (5.6)	92.4 (11.0)
4: Surf Stim 4°, Eyes Open	94.0 (5.8)	89.2 (14.1)
5: Vis Stim 2°, Eyes Open	73.2 (22.3)	74.9 (23.2)
6: Vis Stim 4°, Eyes Open	75.1 (19.9)	76.3 (20.9)
7: Surf+Vis Stim 2°, Eyes Open	97.3 (1.3)	96.2 (2.6)
8: Surf+Vis Stim 4°, Eyes Open	96.2 (2.3)	96.7 (2.2)

Mean and standard deviation (SD) values are based on 40 subjects except for Condition five where one subject's parameters were not consistent with a stable system and were excluded.

Results From Lowpass Filter Estimates of CoM

Lowpass filtering of the recorded CoP provided a measure of CoM displacement that corresponded closely to sway rod measures of CoM displacement (**Figure 8A**). Across all subjects and tests, the cutoff frequency that provided the best fit to sway rod CoM was tightly distributed with mean 0.469 Hz ± 0.0261 SD (**Figure 8B**). This mean cutoff frequency was used to filter CoP across all tests. Then this lowpass filter derived CoM sway was used to calculate FRFs and the parameters were estimated for the model using PD plus torque feedback. There was a close correspondence between model parameters derived using CoM sway rod measures and lowpass filtering (**Figures 8C,D**). Across all test conditions, the mean difference between model parameters from sway rod CoM vs. lowpass CoM was −0.015, −0.048, −0.0062, 0.005, and -7.9×10^{-6} for sensory weight, normalized K_p, normalized K_d, time delay, and K_t, respectively, corresponding to percent differences of −4.7, −3.2, −1.2, 3.5, and −7.3%. Negative differences and percentages indicate that the parameters from sway rod CoM results were greater than from lowpass CoM. Descriptive statistics of parameters derived using CoM from lowpass filtered CoP are given in the **Supplemental Table S2**.

Examples From Subjects With Balance Deficits

The methods related to those described in this paper have been used to investigate how various disorders affect balance control. Here we present some examples from previous and ongoing studies that illustrate how application of CSMI testing can be used to better understand how balance control is influenced by specific deficits and to characterize mechanisms that compensate (or not) for deficits. The examples include results from subjects with bilateral vestibular loss, unilateral vestibular loss, and mTBI. An addition example demonstrates the ability of CSMI tests to identify normal balance function in an individual apparently intent on disrupting the test procedure.

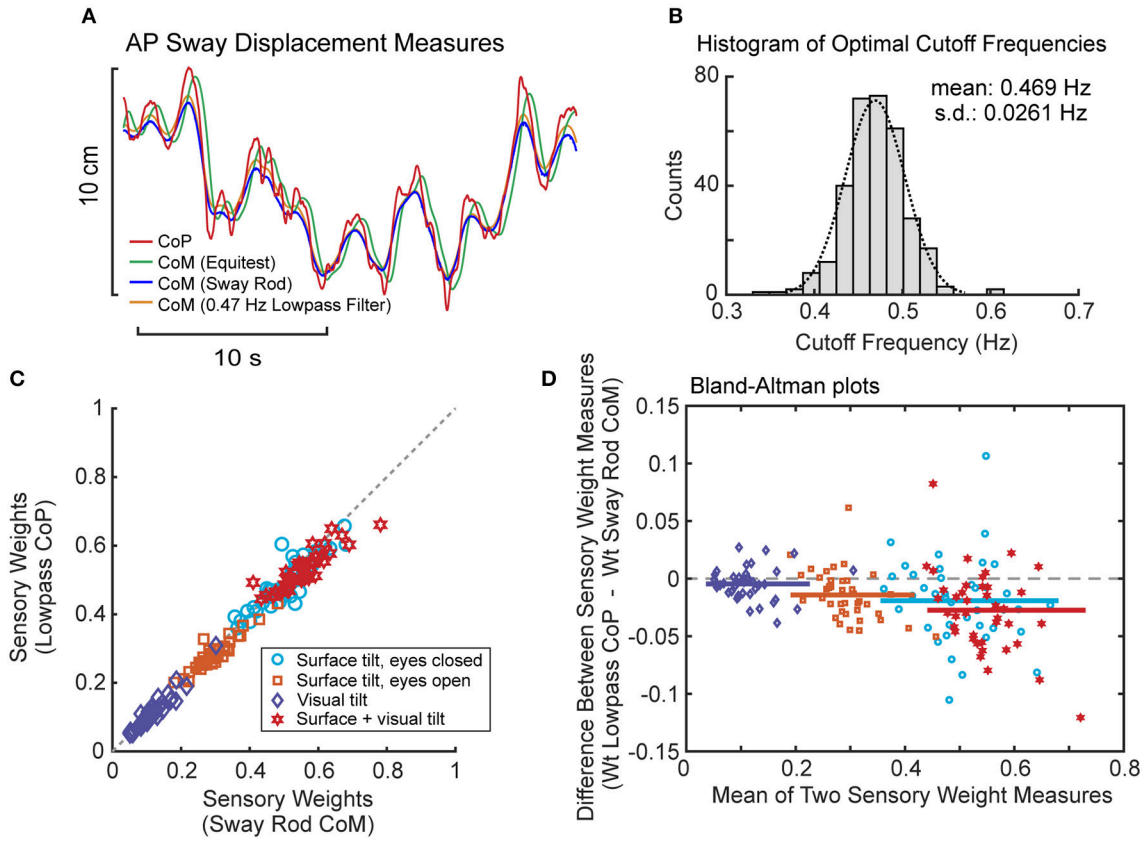


FIGURE 8 | Results associated with phaseless lowpass filtering of center-of-pressure (CoP) to estimate center-of-mass (CoM) displacement. **(A)** Example traces of CoP and CoM displacement measures from EquiTest recordings, sway rod estimates, and phaseless lowpass filtering. **(B)** Distribution of cutoff frequencies that minimized errors between CoM derived from phaseless lowpass filtering and sway rod estimates. **(C)** Comparison of sensory weights based on sway rod and lowpass filtered CoP measures of CoM from 40 subjects on the 4 test conditions with 2° amplitudes. Gray dashed line shows 1:1 slope. Significance values on all comparisons in **(C)** are $p < 0.001$. **(D)** Bland Altman plots comparing the sensory weight measures shown in **(C)**.

Proprioceptive sensory weights from 4 subjects with severe bilateral vestibular loss tested with eyes closed using a pseudorandom surface-tilt stimulus (peak-to-peak amplitudes ranging from 0.5 to 4°) that evoked AP sway are shown in **Figure 9A** and are compared to mean results from 8 subjects with normal sensory function from the same study (6). The results confirm the expectation that orientation information from proprioception and the vestibular system are the primary contributors to balance control when visual cues are not available. The vestibular loss subjects compensate for the loss by becoming 100% reliant of proprioceptive information as indicated by the identified proprioceptive weights equal to unity across all stimulus amplitudes. With increasing stimulus amplitude, subjects with normal vestibular function decrease their reliance on proprioceptive information as indicated by the decrease in proprioceptive weights. The model-based interpretation of this decreasing reliance on proprioception is that subjects are increasing their reliance on vestibular cues ($W_{vest} = 1 - W_{prop}$) with increasing stimulus amplitude. The inability of vestibular loss subjects to modify their proprioceptive sensory weight with increasing stimulus amplitude confirms the model-based interpretation of the sensory integration constraint that the sum of the sensory weights of systems contributing to balance control equals unity, and confirms the ability of the CSMI methods to identify sensory weights. Additional confirmation of sensory integration assumptions has been obtained from experiments the independently perturbed the vestibular system using galvanic vestibular stimuli during eyes-closed surface-tilt stimuli (7).

Mean proprioceptive sensory weights as a function of stimulus amplitude from 11 subjects with well-compensated complete unilateral vestibular loss in comparison to results from age matched controls are shown in **Figure 9B** (11). Tests were performed eyes closed using a surface-tilt stimulus that evoked medial-lateral body sway. Head movements evoked by CSMI tests are of rather small magnitude compared to the range over which vestibular receptors can encode head motion. One might assume that subjects with unilateral vestibular loss could fully compensate for their loss by relying on accurate vestibular information from their functioning ear and, therefore, would give CSMI test results that are indistinguishable from controls. However, this was not the case since unilateral vestibular loss subjects showed a consistent bias toward increased reliance

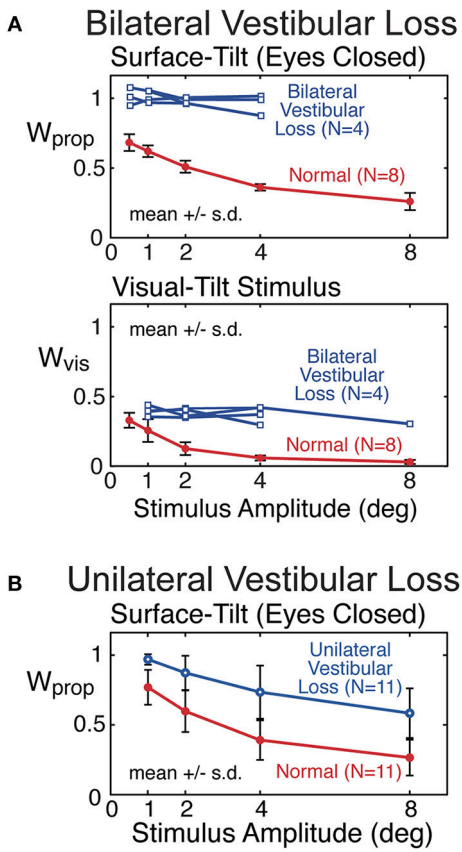


FIGURE 9 | Example results from previous studies showing sensory weight measures in subjects with bilateral vestibular loss **(A)** and well compensated unilateral vestibular loss **(B)** in comparison to subjects with normal vestibular function. Bilateral vestibular loss results from Peterka (6) and unilateral loss results from Peterka (11).

of proprioceptive cues. In particular, at the lowest stimulus amplitude the unilateral vestibular loss subjects resembled bilateral loss subjects in their essentially 100% reliance on proprioception. However, larger stimulus amplitudes could distinguish between unilateral and bilateral loss subjects since unilateral loss subjects were able to utilize their remaining vestibular function, although results from individual subjects showed wide variations in this ability.

Our ongoing study of mTBI subjects with chronic balance complaints has identified deficits primarily in the sensory-to-motor mechanism of balance control (i.e., neural controller) in a few subjects. An example from one mTBI subject is shown in **Figure 10** together with a control subject whose identified proprioceptive sensory weight on an example test (eyes open, 2° surface-tilt; condition 3) was the same as the mTBI subject (both had $W_{prop} = 0.42$ which were near the high end of the range for control subjects in condition 3). The FRFs of the mTBI and control subject were quite different with the mTBI subject having ~2 times larger gains in the low frequency region below ~0.15 Hz, and greater phase lags at low to mid frequencies (**Figure 10A**). The solid lines show that the model fits accounted well for the experimental FRF data.

The mTBI subject's increased sensitivity to the surface-tilt stimulus in comparison to the control subject was obviously not attributed to differences in sensory weights since the mTBI subject and control subject were selected to have the same sensory weight. The higher sensitivity in the mTBI subject was largely due to low neural controller stiffness (normalized $K_p = 1.18$—a value below that of all control subjects). While this value was only 13% lower than the normalized stiffness of the control subject (normalized $K_p = 1.36$), a low stiffness control has an exaggerated influence on overall response sensitivity due to the feedback nature of the balance control system. Specifically, the equations that define dynamic characteristics of the balance control system predict that the peak mid-frequency FRF gain is approximately:

$$Peak\ Gain = W_{prop} \frac{\frac{K_p}{mgh}}{\frac{K_p}{mgh} - 1} \tag{15}$$

Substituting the values for the mTBI subject and the control subject into this equation give peak gain values of 2.8 and 1.6, respectively, which correspond well to the peak FRF gains shown in **Figure 10A**. The 1.75 times greater sensitivity of the mTBI subject to the stimulus is largely attributed to the mTBI subject's reduced stiffness, but a second factor also contributed to the increasing divergence between the mTBI and control subject's FRF gain values at the lowest frequencies. Specifically, the mTBI subject's torque feedback factor ($K_t = 2.7 \times 10^{-5}$) was 3.8 times smaller than that of the control subject, and was smaller than all but one K_t value of the 40 control subjects in this study in test condition 3. The torque feedback mechanism contributes to balance control by moving the body toward an upright position (even if the surface is tilted) to reduce the overall magnitude of corrective torque generation. But this torque feedback mechanism has an influence on sway behavior only at frequencies below about 0.1 Hz and it is the mechanism that accounts for the low frequency decline in FRF gains. If K_t is very small, the subject's low frequency sway response to the tilting surface is determined by Equation 15. The combination of low stiffness, relatively high sensory weight, and greatly reduced torque feedback left this mTBI subject with overall poor balance control—the functional consequences of which were evident in the sway responses to the stimulus (**Figure 10B**). The control subject's sway was similar in magnitude to the surface-tilt stimulus, but the mTBI subject's sway was much larger with peak sway amplitudes very close to the limits of stance stability. In fact, only the first 5 cycles are shown because the mTBI subject fell later in the test.

A final example shown in **Figure 11** is from a nominal control subject whose body sway showed very large oscillatory motions throughout all trials. But note that the large sway oscillations are not correlated with the stimulus. Thus, the CSMI analysis was not greatly affected by the large sway and was able to calculate FRFs from the stimulus/response data (but with reduced coherence). Parameter estimates were consistent with parameters from other control subjects. Although we cannot rule out some organic

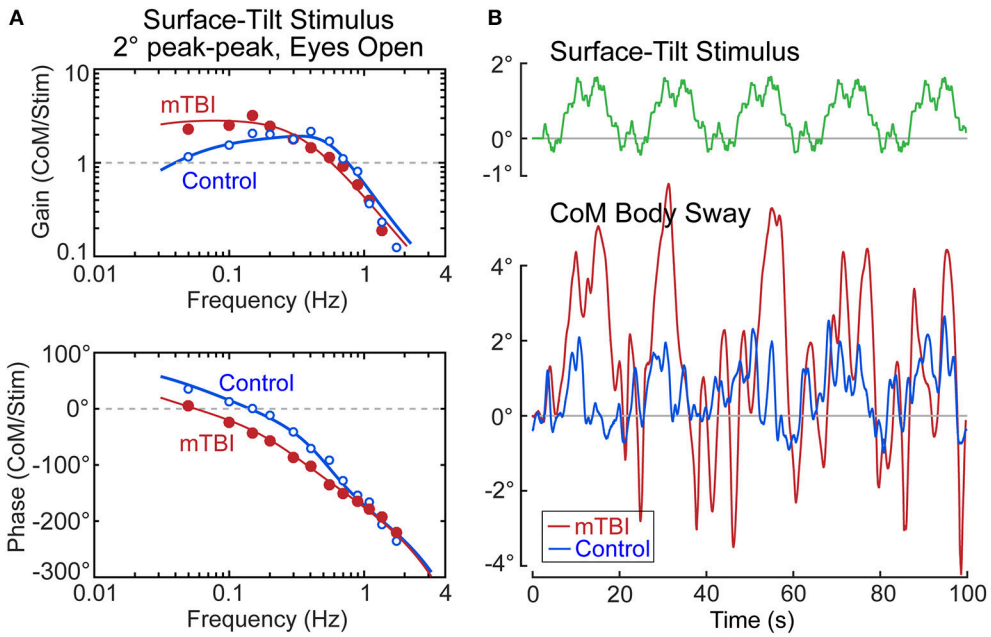


FIGURE 10 | Example results from a subject with chronic balance complaints following mild traumatic brain injury (mTBI) in comparison to a control subject. Model fits (solid lines) to the frequency response function data in **(A)** identified equal sensory weight measures of $W_{prop} = 0.42$ for both subjects. The divergence between the mTBI and control results are accounted for by the mTBI subject having a lower value of the neural controller proportional gain parameter, K_p, and lower value of the torque feedback parameter, K_t. The functional consequences of these differences are that the surface-tilt stimulus evoked much larger sway in the mTBI subject **(B)**.

dysfunction causing this highly usual sway pattern, a plausible interpretation, based on the normal parameter measures, is that this subject was purposely interfering with the testing procedure. This subject's results were not included with the other control subjects.

DISCUSSION

This report provides detailed information on how to implement and interpret results from a CSMI test of balance control. Test results from 40 subjects provided sufficient information to establish preliminary normative values for parameters that characterize the normal performance of sensory integration and sensory-to-motor mechanisms contributing to balance control under a variety of test conditions. The CSMI test relies on a model-based approach to interpret body sway responses to sustained rotations of the stance surface and/or visual surround. Many practical decisions were made to successfully implement CSMI testing, but the decisions imposed limitations that are discussed below.

Considerations and Limitations

Simplification of Body Mechanics

The CSMI analysis relates CoM body sway angle to a rotational stimulus that evokes that sway with the body mechanics represented by a one-segment inverted pendulum while, in reality, the body is a multi-segment system. Although methods exist to experimentally identify dynamic properties of multi-segment body systems (14, 31–33), the complexity of the identified system escalates rapidly with each added segment. If a model-based approach is used to estimate system parameters, reliability of parameter measures can suffer, and the proliferation of parameters makes the interpretation of results more complex (28).

Despite the complexity of multi-segment body motions, physics dictates that CoM must remain within the base of support for stability during sustained stance. Therefore, an analysis that focuses on CoM motion is justified. Additionally, upper and lower body segments tend to move in phase with one another at frequencies below about 1 Hz, further justifying the relevance of a one-segment body representation and focus on CoM motion if perturbing stimuli remain below about 1.5 Hz. However, if measurements of body motion are made at different segmental levels (e.g., measures of lower and upper body motion), FRFs can still be calculated relating the stimulus to body segment motion with interpretations made that mainly consider features of the FRFs, such as peak gains (13), thus bypassing a model-based interpretation.

Choice of Balance Control Model

We investigated two versions of the model shown in **Figure 1**. One used a neural controller with PD properties and torque feedback, and the other used a PID controller. An early study employed PID control (34) and a later study using methods very similar to the current study also choose PID control (6). However, this later study demonstrated that the PID control model did not account well for FRF data below about 0.05 Hz because the predicted phase of the model with PID control converges to zero

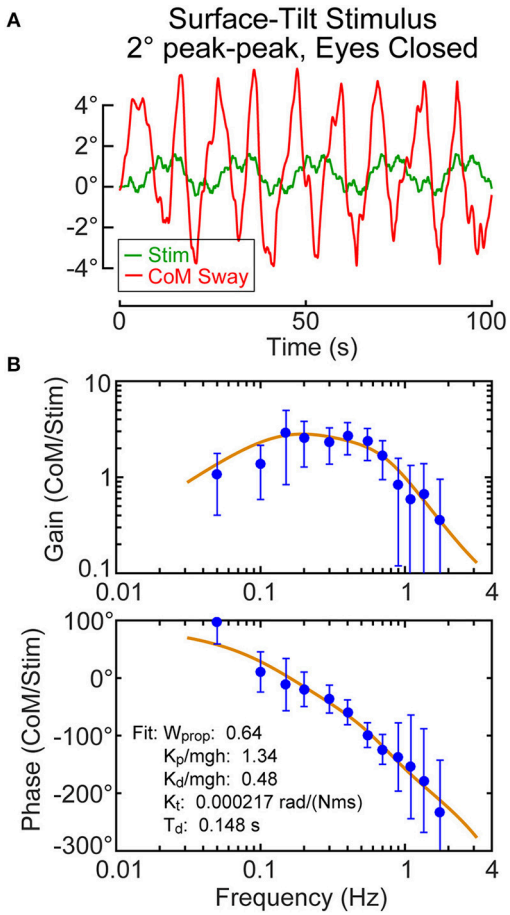


FIGURE 11 | Example results from a subject with no known physiological deficits but who showed large oscillatory sway patterns **(A)**. The frequency response function data and parameters identified from the model fit **(B)** are compatible with normal balance control suggesting the possibility that the subject was purposely trying to disrupt testing.

degrees at very low frequencies, while actual FRF data shows low frequency phase leads. Thus, later studies favored a model based on PD control with torque feedback that does predict low frequency phase leads (7, 26). Additionally, the earlier models that used torque feedback assumed first order lowpass filter properties (i.e., a leaky integrator) for the torque feedback instead of the current model that assumes pure integration. However, the time constant of the leaky integrator was fairly long (about 8 s or more) meaning that quite low frequency FRF data is needed to obtain estimates of this time constant. Because the current study used stimulus periods of 20 s, the lowest FRF frequency of 0.05 Hz was not low enough to accurately estimate the torque feedback time constant, so a simpler pure integrator was used instead.

Neither version of the model included any parameter that represents the passive/intrinsic mechanical contribution to corrective torque generation due to muscle/tendon properties [P(s) in **Figure 1**]. A previous study identified passive stiffness and damping parameters that contributed 10–15% of the overall corrective torque (6) consistent with a recent study showing a relatively low contribution of passive properties under similar conditions (35). The previous study by Peterka (6) used a backboard to constrain the body to have one-segment inverted pendulum mechanics and used wider bandwidth pseudorandom stimuli. These test conditions forced a close correspondence between the model and the actual body mechanics, possibly facilitating reliable estimates of passive properties. In the current study, we investigated applying model structures that included passive stiffness and/or damping parameters but found that we were not able to reliably estimate passive properties and therefore chose to not include passive components in the final models. In particular, in models that included passive and active stiffness, the passive and active stiffness parameters could vary widely across subjects, but the sum of passive plus active stiffness parameters was typically equal to the value of the active stiffness identified using a model without passive stiffness. A recent sensitivity analysis of this type of model supports the notion that there is considerable interaction among parameters, making unique identification difficult among parameters, such as passive and active stiffness, that have similar effects on the FRFs (27). The addition of EMG recordings of leg muscles can apparently enhance the capabilities of parameter identification by making identification of passive parameters more reliable as well as allowing for identification of additional parameters related to muscle activation (36). However, for clinical applications, the additional complexity of EMG recording may not be justified unless there are specific patient populations were it would be beneficial to distinguish between passive and active contributions.

The effect of the choice to exclude a passive component is that other parameters, mainly neural controller stiffness and damping, and the time delay parameter, could be affected. That is, a simple model of passive properties could include a stiffness factor representing length-tension properties of muscles and tendons, and a damping factor representing force-velocity properties. Because these passive properties have very similar dynamic characteristics as the active neural controller parameters, except that the actively generated corrective torque is delayed in time, it is likely that parameter identification procedure would effectively include the passive contributions in the neural controller parameters. Because there is no time delay between muscle stretch and generation of passive torque, a subject whose system had a relatively large contribution from passive mechanical properties (possibly modulated by co-contraction) would likely bias the overall time delay estimate toward lower values. Indeed, a few subjects on eyes open surface tilt test (conditions 3 and 4) had large, outlying stiffness (K_p) values (**Figure 5**). These were the same subjects with corresponding short time delays (T_d) on these test conditions.

Although we were not able to reliably identify passive muscle/tendon contributions, a recent study (13) using very similar methods reported identifying passive stiffness and damping values similar to those reported in Peterka (6).

Additional motivations for investigating the two model versions were that the PID model continues to be used (13, 15) and that the PID model may be entirely adequate for quantifying and parameterizing balance control properties. Practical stimuli

for clinical applications favor shorter tests. To maintain enough cycles to allow for adequate across cycle averaging, the cycle durations of the pseudorandom stimuli need to be shorter. The shorter cycle durations limit the lowest frequencies of the FRFs, and it is only at low frequencies where torque feedback provides a better accounting for FRF data than PID control. The VAF results (**Table 2**) indicate that both model versions can accurately represent the available data.

Results shown in **Figure 7** illustrate that parameters shared by the two model versions (sensory weights, K_p, K_d, and T_d) gave very similar results. However, there were some differences between parameters from the two model versions. The largest difference was in normalized K_p where the K_p values from PID model were on average 3.8% larger across all test conditions than from the PD plus torque feedback model. Differences were smaller in the other parameters but with values from the PID model always being slightly larger.

The time delay parameter was consistently identified as having a larger value in the visual stimulus conditions compared to the surface stimulus conditions (**Figure 6**). This could reflect an inadequacy of the **Figure 1** model where only one time delay parameter is included. Effectively this assumes that time delays associated with the sensing and processing of proprioceptive, vestibular, and visual systems are all the same. The longer overall time delay identified with visual stimuli could be consistent with there being a longer time delay in visual contribution to balance control compared to other sensory systems.

Choice of Stimuli

For a clinical test, there is a tradeoff between test duration and accuracy/bias of estimated parameters. Bootstrap analysis was used to investigate this tradeoff using data available from the 40 participants to estimate the changes in parameter distributions and mean and median values of parameters assuming tests had included cycle averages ranging from 3 to 20 cycles (**Figure 4**). Parameter distributions narrowed with increasing cycles with results showing that results based on 3 cycle averages were undesirable due to larger biases in parameters estimates. In most test conditions, measures based on 6 cycle averages were likely adequate for clinical application based on reduced bias and shorter test times. However, tests based on an 11 cycle averages are a better choice for the visual tests (conditions 5 and 6) where sway responses were lower and signal-to-noise of the data were lower (see coherence results in **Figure 5A**).

The 4 different test types were each performed at 2 different stimulus amplitudes. The motivation for performed the same type of test at 2 amplitudes was to have a basis for identifying sensory re-weighting abnormalities as seen in previous results from bilateral vestibular loss subjects (**Figure 9A**). Our choice of 2 and 4° peak-to-peak stimulus amplitudes was based on concern over mechanical limitations of the EquiTest device that showed gear backlash problems in the surface rotation motor that affected stimulus repeatability, with the repeatability being poorer at lower stimulus amplitudes. In retrospect, a stimulus with an amplitude smaller than 2° would have been a better choice since a 2° stimulus can cause falls in subjects with abnormally low neural controller stiffness and torque feedback (**Figure 10**). Other similar recent studies have used lower amplitudes (0.5 and 1°) (13, 15, 19). Lower amplitudes have the additional potential benefit that subjects may not even perceive that their balance is being perturbed, and yet they respond reliably even to a 0.5° stimulus (6). However, longer stimulus durations should be used to avoid measurement bias due to low signal-to-noise (**Figure 4**).

The desire to limit the total duration of clinical testing also impacts the decision about which tests to include in a test battery. Of the 4 test types we investigated, one might argue that little additional information was gained by including both eyes-closed surface stimulation and dual surface and visual stimulation since parameters from these tests were quite similar. One might also question the utility of visual stimulus tests since results were less reliable compared to other tests. However, before deciding on a final test battery, more results are needed from patients with a broad range of pathologies to determine which tests are best able to distinguish normal from abnormal balance function.

Simplified Measures of Body Sway for CSMI Analysis

We investigated the possible use of a simple method for measuring AP CoM sway based on offline lowpass filtering of CoP. Brenière (22) suggested that CoM could be recovered from CoP by what amounts to appropriate symmetric (phaseless) lowpass filtering. When 0.47 Hz lowpass filter estimates of CoM were used for FRF calculations and then for model parameter estimation, there was good correspondence between parameters obtained using sway rod and lowpass filtered CoM measures. The close correspondence suggests that clinical tests can be based on the lowpass filter method for measuring CoM. However, differences were large enough that parameter norms should not be considered to be fully equivalent to those using more direct estimates of CoM motion. Nonetheless, implementation of the lowpass filter method is easier to perform, potentially making it a more practical tool for clinical use. This method reduces the overall test duration and requires less expertise in setting up and performing tests.

Also of note is that the EquiTest system provides CoM displacement measures. As shown in **Figure 8A**, this measure lags CoM sway rod measures and is larger in amplitude indicating that it is derived by filtering the CoP using a conventional (not a phaseless) filter with a cutoff frequency higher than our optimal 0.47 Hz cutoff frequency. Thus, FRFs derived using the EquiTest CoM measures would not provide comparable results.

Implementation

One goal of this study was to make available a detailed explanation of the methods to perform CSMI testing. To this end, Matlab programs used to create stimuli, analyze data to obtain FRFs, and identify model parameters that optimally account for the FRF data are provided in the **Supplementary Material**.

DATA AVAILABILITY STATEMENT

Datasets are available on request. The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

RP contributed to the conception and design of the study, analysis, interpretation, drafted and revised manuscript. CM contributed to analysis and interpretation of data. LP contributed to analysis, interpretation of data, and revised manuscript. PF contributed to the design of the study, data acquisition, and revised manuscript. LK contributed to the conception and design of the study, and revised manuscript. All authors approved the final manuscript.

FUNDING

This work was supported by the Assistant Secretary of Defense for Health Affairs under award numbers W81XWH-15-1-0620 and W81XWH-17-1-0424. Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the Department of Defense. Example results from bilateral and unilateral vestibular loss subjects were from work supported by NASA grant NAG5-7869, NIH NIA grant R01AG17960, and NIH NIDCD grant DC04082.

ACKNOWLEDGMENTS

The authors would like to acknowledge the contributions of the research assistants involved in data collection for this project, including Clayton Swanson, Heather Belding, Merissa Walls, Emily Sippel, Alexa Beeson, and Nicholas Kreter.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2018.01045/full#supplementary-material

REFERENCES

1. Pasma JH, Engelhart DE, Schouten AC, van der Kooij H, Maier AB, Meskers CGM. Impaired standing balance: the clinical need for closing the loop. *Neuroscience* (2014) 267:157–65. doi: 10.1016/j.neuroscience.2014.02.030
2. Shepard NT, Janky K. Background and technique of computerized dynamic posturography. In: Jacobson GP, Shepard NT, editors. *Balance Function Assessment and Management.* San Diego, CA: Plural Publishing, Inc (2008). p. 339–57.
3. Prieto TE, Myklebust JB, Hoffman RG, Lovett EG, Myklebust BM. Measures of postural steadiness: differences between healthy young and elderly adults. *IEEE Trans Biomed Eng.* (1996) 43:956–66. doi: 10.1109/10.532130
4. Maurer C, Mergner T, Peterka RJ. Abnormal resonance behavior of the postural control loop in Parkinson's disease. *Exp Brain Res.* (2004) 157:369–76. doi: 10.1007/s00221-004-1852-y
5. van der Kooij H, van Asseldonk E, van Der Helm FCT. Comparison of different methods to identify and quantify balance control. *J Neurosci Methods* (2005) 145:175–203. doi: 10.1016/j.jneumeth.2005.01.003
6. Peterka RJ. Sensorimotor integration in human postural control. *J Neurophysiol.* (2002) 88:1097–118. doi: 10.1152/jn.2002.88.3.1097
7. Cenciarini M, Peterka RJ. Stimulus-dependent changes in the vestibular contribution to human postural control. *J Neurophysiol.* (2006) 95:2733–50. doi: 10.1152/jn.00856.2004
8. Kiemel T, Elahi AJ, Jeka JJ. Identification of the plant for upright stance in humans: multiple movement patterns from a single neural strategy. *J Neurophysiol.* (2008) 100:3394–406. doi: 10.1152/jn.01272.2007
9. Cenciarini M, Loughlin PJ, Sparto PJ, Redfern MS. Stiffness and damping in postural control increase with age. *IEEE Trans Biomed Eng.* (2010) 57:267–75. doi: 10.1109/TBME.2009.2031874
10. Kiemel T, Zhang Y, Jeka JJ. Identification of neural feedback for upright stance in humans: Stabilization rather than sway minimization. *J Neurosci.* (2011) 31:15144–53. doi: 10.1523/JNEUROSCI.1013-11.2011
11. Peterka RJ, Statler KD, Wrisley DM, Horak FB. Postural compensation for unilateral vestibular loss. *Front Neurol.* (2011) 2:57. doi: 10.3389/fneur.2011.00057
12. Pasma JH, Engelhart D, Maier AB, Schouten AC, van der Kooij H, Meskers CGM. Changes in sensory weighting of proprioceptive information during standing balance with age and disease. *J Neurophysiol.* (2015) 114:3220–33. doi: 10.1152/jn.00414.2015
13. Wiesmeier IK, Dalin D, Maurer C. Elderly use proprioception rather than visual and vestibular cues for postural motor control. *Front Aging Neurosci.* (2015) 7:97. doi: 10.3389/fnagi.2015.00097
14. Engelhart D, Pasma JH, Schouten AC, Aarts RG, Meskers CG, Maier AB, et al. Adaptation of multijoint coordination during standing balance in healthy young and healthy old individuals. *J Neurophysiol.* (2016) 115:1422–35. doi: 10.1152/jn.00030.2015
15. Wiesmeier IK, Dalin D, Wehrle A, Granacher U, Muehlbauer T, Dietterle J, et al. Balance training enhances vestibular function and reduces overactive proprioceptive feedback in elderly. *Front Aging Neurosci.* (2017) 9:273. doi: 10.3389/fnagi.2017.00273
16. van Kordelaar J, Pasma JH, Cenciarini M, Schouten AC, van der Kooij H, Maurer C. The reliance on vestibular information during standing balance control decreases with severity of vestibular dysfunction. *Front Neurol.* (2018) 9:371. doi: 10.3389/fneur.2018.00371
17. Fino PC, Peterka RJ, Hullar TE, Murchison C, Horak FB, Chestnut JC, et al. Assessment and rehabilitation of central sensory impairments for balance in mTBI using auditory biofeedback: a randomized clinical trial. *BMC Neurol.* (2017) 17:41. doi: 10.1186/s12883-017-0812-7
18. Davies WDT. *System Identification for Self-Adaptive Control.* London: Wiley-Interscience (1970).
19. Pasma JH, Assländer L, van Kordelaar J, de Kam D, Mergner T, Schouten AC. Evidence in support of the independent channel model describing the sensorimotor control of human stance using a humanoid robot. *Front Comput Neurosci.* (2018) 12:13. doi: 10.3389/fncom.2018.00013
20. Winter DA. *Biomechanics and Motor Control of Human Movement*. New York, NY: John Wiley & Sons, Inc (2005).
21. Winter DA, Patla AE, Prince F, Ishac M, Gielo-Perczak K. Stiffness control of balance in quiet standing. *J Neurophysiol.* (1998) 80:1211–21. doi: 10.1152/jn.1998.80.3.1211
22. Brenière Y. Why we walk the way we do. *J Motor Behav.* (1996) 28:291–8. doi: 10.1080/00222895.1996.10544598
23. Pintelon R, Schoukens J. *System Identification: A Frequency Domain Approach.* Hoboken, NJ: John Wiley & Sons, Inc (2012). doi: 10.1002/9781118287422
24. Goodworth AD, Peterka RJ. Influence of stance width on frontal plane postural dynamics and coordination in human balance control. *J Neurophysiol.* (2010) 104:1103–18. doi: 10.1152/jn.00916.2009
25. van der Kooij H, de Vlugt E. Postural responses evoked by platform perturbations are dominated by continuous feedback. *J Neurophysiol.* (2007) 98:730–43. doi: 10.1152/jn.00457.2006
26. Peterka RJ. Simplifying the complexities of maintaining balance. *IEEE Eng Med Biol Mag.* (2003) 22:63–8. doi: 10.1109/MEMB.2003.1195698
27. Pasma JH, Boonstra TA, van Kordelaar J, Spyropoulou VV, Schouten AC. A sensitivity analysis of an inverted pendulum balance control model. *Front Comput Neurosci.* (2018) 11:99. doi: 10.3389/fncom.2017.00099

28. Goodworth AD, Peterka RJ. Identifying mechanisms of stance control: a single stimulus multiple output model-fit approach. *J Neurosci Methods* (2018) 296:44–56. doi: 10.1016/j.jneumeth.2017.12.015
29. Peterka RJ. Sensory integration for human balance control. In: Day BL, Lord SR, editors. *Handbook of Clinical Neurology,* Vol. 159 (3rd series) *Balance, Gait, and Falls*. Elsevier (in press).
30. Otnes RK, Enochson LD. *Digital Time Series Analysis.* New York, NY: Wiley (1972).
31. Goodworth AD, Peterka RJ. Sensorimotor integration for multisegmental frontal plane balance control in humans. *J Neurophysiol.* (2012) 107:12–28. doi: 10.1152/jn.00670.2010
32. Boonstra TA, Schouten AC, van der Kooij H. Identification of the contribution of the ankle and hip joints to multi-segmental balance control. *J Neuroeng Rehabil.* (2013) 10:23. doi: 10.1186/1743-0003-10-23
33. Engelhart D, Schouten AC, Aarts RG, van der Kooij H. Assessment of multi-joint coordination and adaptation in standing balance: A novel device and system identification technique. *IEEE Trans Neural Syst Rehabil Eng.* (2015) 23:973–82. doi: 10.1109/TNSRE.2014.2372172
34. Johansson R, Magnusson M, Akesson M. Identification of human postural dynamics. *IEEE Trans Biomed Eng.* (1988) 35:858–69. doi: 10.1109/10.7293
35. Sakanaka TE, Lakie M, Reynolds RF. Sway-dependent changes in standing ankle stiffness caused by muscle thixotropy. *J Physiol.* (2016) 594:781–93. doi: 10.1113/JP271137
36. Pasma JH, van Kordelaar J, de Kam D, Weerdesteyn V, Schouten AC, van der Kooij H. Assessment of the underlying systems involved in standing balance: the additional value of electromyography in system identification and parameter estimation. *J Neuroeng Rehabil.* (2017) 14:97. doi: 10.1186/s12984-017-0299-x

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer RK and handling Editor declared their shared affiliation at the time of the review.

frontiers in Neurology

ORIGINAL RESEARCH
published: 04 January 2019
doi: 10.3389/fneur.2018.01132

Supplementary Motor Area and Superior Parietal Lobule Restore Sensory Facilitation Prior to Stepping When a Decrease of Afferent Inputs Occurs

Olivia Lhomond[1], *Normand Teasdale*[2], *Martin Simoneau*[2,3] *and Laurence Mouchnino*[1]*

[1] Aix Marseille Univ, CNRS, Laboratoire de Neurosciences Cognitives, Marseille, France, [2] Faculté de médecine, Département de kinésiologie, Université Laval, Québec, QC, Canada, [3] Centre Interdisciplinaire de Recherche en Réadaptation et Intégration Sociale, Québec, QC, Canada

The weighting of the sensory inputs is not uniform during movement preparation and execution. For instance, a transient increase in the transmission to the cortical level of cutaneous input ∼700 ms was observed before participants initiated a step forward. The sensory facilitation occurred at a time when feet cutaneous information is critical for setting the forces to be exerted onto the ground to shift the center of mass toward the supporting side prior to foot-off. Despite clear evidence of task-dependent modulation of the early somatosensory signal transmission, the neural mechanisms are mainly unknown. One hypothesis suggests that during movement preparation the premotor cortex and specifically the supplementary motor area (SMA) can be the source of an efferent signal that facilitates the somatosensory processes irrespectively of the amount of sensory inputs arriving at the somatosensory areas. Here, we depressed mechanically the plantar sole cutaneous transmission by increasing pressure under the feet by adding an extra body weight to test whether the task-dependent modulation is present during step preparation. Results showed upregulation of the neural response to tactile stimulation in the extra-weight condition during the stepping preparation whereas depressed neural response was still observed in standing condition. Source localization indicated the SMA and to a lesser extent the superior parietal lobule (SPL) areas as the likely origin of the response modulation. Upregulating cutaneous inputs (when mechanically depressed) at an early stage by efferent signals from the motor system could be an attempt to restore the level of sensory afferents to make it suitable for setting the anticipatory adjustments prior to step initiation.

Keywords: step movement, somatosensory evoked potential, body representation in brain, supplementary motor area (SMA), balance control

OPEN ACCESS

Edited by:
Joyce Fung,
McGill University, Canada

Reviewed by:
Pedro Ribeiro,
Universidade Federal do Rio de Janeiro, Brazil
W. Geoffrey Wright,
Temple University, United States

***Correspondence:**
Laurence Mouchnino
laurence.mouchnino@univ-amu.fr

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *28 June 2018*
Accepted: *10 December 2018*
Published: *04 January 2019*

Citation:
Lhomond O, Teasdale N, Simoneau M and Mouchnino L (2019) Supplementary Motor Area and Superior Parietal Lobule Restore Sensory Facilitation Prior to Stepping When a Decrease of Afferent Inputs Occurs. Front. Neurol. 9:1132. doi: 10.3389/fneur.2018.01132

INTRODUCTION

Anticipatory postural adjustments (APAs) precede different voluntary lower limb movements [leg flexion: (1, 2); lateral leg raising: (3); gait initiation: (4, 5). For example, in gait initiation, the leg movement is always preceded by a shift of the center of mass (CoM) toward the supporting side and forward to create the condition for proper step movement execution.

Part of these APAs are aimed at unloading the leg to be moved and preserving balance during the movement. It has been demonstrated by Massion (6) that the APAs are centrally preprogrammed and prepared from at least 1,400 ms before step execution as reported by Mackinnon et al. (7). During gait initiation, monitoring the initial standing condition is a prerequisite for setting of the APAs [e. g., (8–11)]. For instance, Timmann and Horak (10) showed that the anticipatory phase that propels the body forward is reduced when a backward platform displacement is triggered during the planning phase of the stepping movement. This suggests that sensory inputs regarding the new standing conditions are controlled online and can be rapidly processed to alter the APAs based on visual, vestibular, proprioceptive, tactile information related to body current position relative to the support. Among the sensory receptors that convey information concerning balance, plantar sole tactile receptors are well suited to detect the mere transient changes in the contact forces between the feet and the ground to alter the forthcoming APAs. For example in the absence of any vestibular and visual inputs, the amplitude of the APAs is changed according to the current body position in space on the basis of cutaneous cues with at least some contribution of proprioceptive information (12). In addition, Lin and Yang (13) showed a decrease of the mediolateral APAs after desensitization of the plantar sole cutaneous receptors by immersion in cold water; the greater the desensitization the smaller the APAs amplitude. This is not the case, however, when some sensory inputs remained from one of the feet (14), that is, after unilateral tibial nerve block. Altogether, these results indicate that plantar cutaneous and intrinsic foot muscle proprioceptive inputs (15) provide information for shaping the centrally programmed APAs.

In support of these behavioral studies, we have recently demonstrated using electrophysiological techniques, that the early transmission of cutaneous inputs from the periphery to the cortex was facilitated during the planning phase of gait initiation [about 700 ms before any muscular activity for motor execution, (16)]. Such variation was observed as early as 55 ms after an electrical stimulation of the cutaneous receptors of the plantar sole (16) or the fingers (17). This observation was interpreted as reflecting the activity of the primary somatosensory cortex (SI) (18–20). These authors and others [for example, (21)] have shown that this early sensory process is related to the incoming sensory inputs and is representative of the stimulus characteristics (e.g., intensity, frequency). In addition, Duysens at al. (22) have reported an increase of the perception of tactile stimuli when sensory transmission is increased. Therefore, the sensitivity of the sensory cortex to afferents is supported by an attenuation or a facilitation of the somatosensory evoked potentials (22, 23). A "task-related facilitation" mechanism might therefore contribute to enhance perception of tactile inputs when sensory information is relevant for performing the task. This is in line with Bolton et al.'s study (24) which demonstrated that when the somatosensory information coming from the hand is used to control balance, the somatosensory evoked potential following the median nerve stimulation is increased. This process referred to as "task-related sensory facilitation" presumably serves to optimize the monitoring of equilibrium during quiet upright standing (24) as well as during the planning phase of gait initiation (16). During movement preparation the premotor cortex and specifically the supplementary motor area (SMA) can be the source of an efferent signal prompting sensory facilitation. Indeed, during movement preparation, various authors have observed a specific preparatory cortical activity known as the movement-related contingent negative variation [CNV; (25–28)]. During the final stage of the CNV, an increase in the SMA activity was reported (25) possibly to set the APAs timing (29). In addition, an increase activity of the SPL (an important node for sensorimotor integration) was noted when somatosensory afferents were stimulated (30). The SMA is recognized to have direct connections with the sensorimotor cortex (31, 32) and is also interconnected to the SPL (33). The link from the SMA to the sensory mechanism can be indirectly revealed by source localization analysis. For instance, activation of the SMA and pre-motor areas were time-locked to somatosensory facilitation following tactile stimulation (16). Such increase in the activation of the SMA was also observed when the demands of locomotor tasks require increased processing of sensory information even when the tasks were imagined [imagining walking, initiating gait, walking with obstacles, (34)].

Despite clear evidence of the effect of sensorimotor tasks on the response to cutaneous stimulation, the neural mechanisms underlying sensory facilitation are mainly unknown. One hypothesis proposes that the responsiveness of afferent nerve is increased at spinal level to improve the transmission of information to the supraspinal center (35). Alternatively, the specific facilitation of the response might be evoked by an efferent signal from premotor areas. This is in line with the SMA modulatory function of somatosensory activity used by other cortical areas during self-generated movements (36).

In the present study, we developed a paradigm to determine if motor preparation can evoke a cortico-cortical facilitation during the planning phase of the stepping movement even when the amount of plantar sole afferent is attenuated. To do so, the afferent input from the plantar sole cutaneous mechanoreceptors were decreased by having participants wearing a 20 kg weighted-vest (37). We compared the somatosensory-evoked potentials (SEPs) of healthy participants during upright standing or the preparation of a stepping movement. We expected the SEPs to be larger during the planning phase of the stepping movement in the extra-weight condition.

METHODS

Fifteen healthy participants performed the experiment [8 male, mean age: 25 ± 3 years; mean body mass index (BMI): 23.9 ± 2.9 kg/m^2]. Informed consent was obtained from all participants, and all procedures were approved by the Ethics Committee at Laval University. In the task hereafter referred to as the Stepping task, participants were instructed to step forward with the right leg in response to an auditory signal (a 100-ms tone) keeping their eyes closed **(Figure 1A)**. This auditory Go step signal was preceded 1 s earlier with a pre-cueing tone. This pre-cue signal served as a warning stimulus allowing

participants to have a period of preparation (7). During the stepping task, the plantar sole of the forthcoming supporting foot was stimulated twice during the preparation phase of the step that is 600 ms (early preparation, St1) and 100 ms (late preparation, St2) before the Go step signal (see below for the stimulation technique). A control task (hereafter referred to as the Standing task) was performed with a similar design (i.e., 2 auditory signals and 2 electrical stimulations, St0) where participants adopted an upright quiet standing position. In both tasks the participants were standing upright and loading symmetrical. At the start of a task, the participants looked at a fixation point positioned at eye level, ∼2 m directly in front of them. One second before the pre-cue signal, participants were asked to close their eyes and receive verbal instruction on the nature of the upcoming task. The Standing and Stepping tasks were randomly presented across the experimental session to prevent preparation of a stepping movement long before task instruction. No more than 2 Standing trials were presented in succession. For both tasks, the same sequence of two tones and two stimulations as in the Stepping task were delivered.

Each participant performed 50 stepping movements (i.e., 100 stimulations). In the Standing task 50 stimulations were delivered. Participants were asked to stand quietly in two conditions: (i) Loaded, participants were standing while wearing a 20-kg weight-vest representing an increased weight of 25 ± 4% (**Figure 1A**, right panel) and (ii) Control, without extra-weight.

Stimulation Procedure

The electrical stimulus was delivered by an isolated bipolar constant current stimulator (DS5 Digitimer, Welwyn Garden City, UK). On the supporting foot, the cathode was located under the metatarsal region and the anode underneath the heel (5 × 9 cm electrodes, Platinium Foam Electrodes). The stimulation consisted of a single rectangular 10-ms pulse (16, 37). The stimulation intensity was set to avoid any cutaneous reflexes. The electrical stimulation of the plantar sole activates all nerve fibers associated with the mechanoreceptors including free nerve endings. These mechanoreceptors respond to mechanical skin deformation while electrical stimulus rather activates all the sensory nerves in absence of skin deformation. Due to the position of the electrodes and direction of the current flow between the electrodes, the sensation did not mimic displacement in center of pressure, that is a mechanical stimulation. For instance, the electrical stimulation did not evoke a specific percept of pressure change on the foot plantar sole leading to a postural reaction. For each participant, while in a quiet upright standing position, we determined the lowest intensity leading to constant perception of the stimulation (mean amplitude of 6.9 ± 1 mA). This stimulation was determined as the baseline value. For each participant, the stimulation intensity was set at

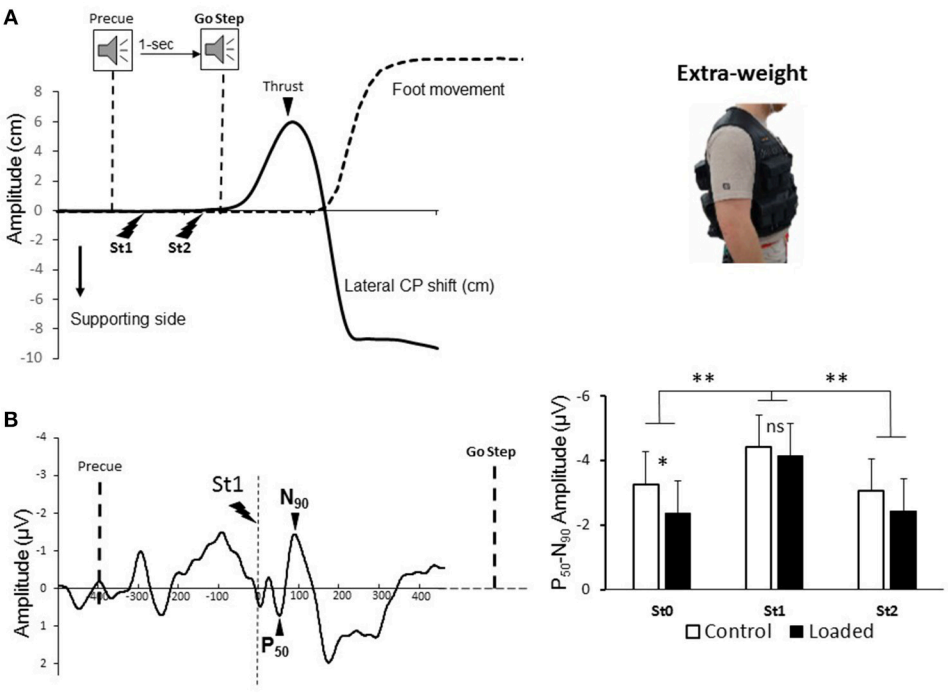


FIGURE 1 | (**A,** left panel) Behavioral recordings during the Stepping task for one representative participant: mediolateral center of pressure, and foot movement in dotted line. Electric stimulations during motor preparation was identified. (**A**, right panel) The 20 kg weight was distributed on the front and back of the vest. (**B**, left panel) Grand average somatosensory-evoked potential (SEP). Dashed line indicates the moment of the stimulation. Note that the first potential observed −300 ms prior to the electrical stimulus was an auditory potential evoked by the pre-cue tone. (**B**, right panel) Mean amplitude for 15 participants of the averaged P_{50}-N_{90} SEP evoked by the electrical stimulation and recorded over Cz electrode during Standing (St0) and movement preparation (St1 and St2). (*$p < 0.05$ and **$p < 0.01$).

25% higher than their perceptual threshold value (but below their motor threshold). The interval between each electrical stimulus was designed to avoid the "interference phenomenon" which is a reduction of the somatosensory evoked potentials when two stimulations are too close in time (38). An interval longer than 300 ms would be sufficient to avoid the interference phenomenon according to Morita et al. (39).

Behavioral Recordings and Analyses

Ground reaction forces and moments were recorded at a sampling rate of 1,000 Hz through a force platform (AMTI model OR-6-6, Watertown, MA, USA). The APAs were measured by computing lateral center of pressure (CP) (**Figure 1A**, left panel). First, the lateral CP shift is directed toward the side of the stepping movement: this corresponds to a vigorous thrust onto the ground exerted mainly by the forthcoming moving leg while still on the ground (6). This force shifts the center of mass toward the supporting side to unload the leg performing the stepping movement. After removing the mean of the signal (computed during 1 s from the recording onset), we computed the mean of the trials of each participant and condition. The amplitude of the thrust was defined as the difference between the initial position and the peak toward the stepping side. An electromagnetic sensor located on the top of the right foot recorded the kinematics of the stepping movements (sampling frequency 100 Hz, model Flock of Birds, Ascension Technology Corporation, VT, USA).

Electroencephalography Recordings and Analyses

Participants were fitted with an EEG system (Geodesic 64-channel EEG sensor net GSN64; Electrical Geodesics Inc., Eugene) sampled at 1,000 Hz. The electrodes were referenced to the vertex (Cz), and then re-referenced to the net average. Data pre-processing was performed with BrainVision Analyzer 2 (Brain Products, Germany). The EEG signals were filtered off-line with 45 Hz (high cut-off) filters (digital filters, 24 dB/octave) and 0.1 Hz (low cut-off) filters (digital filters, 12 dB/octave). Vertical electrodes were recorded bipolarly with electrodes placed above and below the left eye; horizontal electrodes were recorded bipolarly with electrodes positioned near the outer canthus of each eye. The EEG signals were corrected for eye blinking according to the statistical method of Gratton et al. (40).

Somatosensory evoked potentials (SEPs, **Figure 1B**) were obtained by averaging, for each participant and condition, all synchronized epochs relative to the electrical stimulus. The average amplitude of the 60-ms pre-stimulus epoch served as a baseline. We measured the SEPs over the Cz electrode as this electrode overlays the sensorimotor cortices and, on the homunculus, the feet are located on the inner surface of the longitudinal fissure. The earliest discernible positive (P_{50}) and negative (N_{90}) peaks after each stimulus were identified. These peak latencies are comparable to latencies measured by Duysens et al. (22) and Altenmüller et al. (23) evoked by stimulating the sural nerve. The fact that the sural nerve is mainly a cutaneous nerve (41) suggests that P_{50}-N_{90} originates from cutaneous input. The amplitude of the P_{50}-N_{90} waveform was measured peak-to-peak (**Figure 1B**, left panel).

To estimate the neural sources of the SEPs, we used dynamic statistical parametric mapping (dSPM) implemented in the Brainstorm software [(42), freely available at http://neuroimage.usc.edu/brainstorm]. We used the data from all sensors processed and averaged for each participant, condition and electrode. The forward model was computed using a 3D-shell sphere boundary element model (BEM) on the anatomical MRI brain MNI Colin27 template (15,000 vertices), a predominant volume conductor model (43, 44). The cortical sources were analyzed during 2-time windows that encompass and follow the P_{50}-N_{90} SEP (i.e., [50–90 ms] and [90–130 ms]) to find the source of the facilitation observed during motor preparation.

Statistical Analyses

The SEPs amplitude and latencies recorded at Cz were submitted to repeated measures analysis of variance (ANOVA) with condition (i.e., Loaded and Control) and epoch (St0, St1, and St2) as factors. *Post-hoc* analysis was performed through Newmann–Keuls test. The Standing task was included as a level (i.e., St0) along with St1 and St2 epochs of the Stepping task in a one-way ANOVA. We also conducted paired *t*-test for the statistical source estimation maps for contrasts (i.e., Stepping minus Standing tasks). The behavioral data (i.e., step kinematics and forces) were analyzed using paired *t*-test. All dependent variables (EEG and behavioral data) showed normal distributions (i.e., $Ps > 0.05$, Kolmogorov–Smirnov test). The level of significance was set at 5% for all analyses.

RESULTS

Somatosensory Evoked Potential

The results for the amplitude of the P_{50}-N_{90} SEPs showed a main effect of epoch [**Figure 1B** right panel, $F_{(2,28)} = 9$; $p < 0.001$]. The amplitude of the P_{50}-N_{90} SEPs was greater during the early preparation of the stepping movement (i.e., epoch St1) than during standing (St0) or late preparation of the stepping movement (i.e., epoch St2). The amplitude of the P_{50}-N_{90} SEPs was also altered by the loading [$F_{(1,14)} = 4.88$; $p < 0.05$]. This attenuation was due to the standing condition [St0, $t_{(14)} = -2.4$; $p = 0.02$] as previously reported by Lhomond et al. (37). It is worth noting, however, that the amplitude of the SEPs was similar in the loaded and control conditions during the early preparation [St1, $t_{(14)} = -0.66$; $p = 0.51$] of the stepping movement. This result suggests that despite sensory attenuation during the standing epoch, it seems that neural mechanisms related to stepping movement preparation alleviate sensory attenuation probably to ascertain proficient APAs. Overall the latencies of the P_{50} did not differ with loading [$F_{(1,14)} = 1.14$; $p = 0.3$]. The latencies were slightly longer during the early and late epochs of stepping movement preparation (overall means of St1 and St2: 55 ± 11 ms) than for the standing epoch (st0) (overall mean of St0: 50 ± 9 ms) [$F_{(2,28)} = 4.8$; $p = 0.015$].

Source Localization

Source analysis localized SMA and superior parietal lobule (SPL) as the generators of the increase in amplitude of the P_{50}-N_{90} SEPs observed in the early preparation of the stepping movement (St1)

in loading condition. Significant differences between the absolute mean activity computed in the Loaded condition is depicted in **Figure 2**. Starting during the P_{50}-N_{90} period [50–90 ms], the SPL shows greater activity during the later temporal window [90–130 ms] during stepping preparation than when solely standing still. We observed marked significant increase in the activation of the primary sensorimotor areas in the later temporal window [90–130 ms].

Behavioral Results During the APAs

Variables related to motor execution (Stepping movement) were analyzed to verify whether the APAs (i.e., latency, amplitude, duration) varied across the conditions. The APAs onset occurred, on average 120 ± 50 ms after the Go step signal and this value did not differ between conditions [$t_{(14)} = 1.48$; $p = 0.15$]. This short latency attests that participants attempted to synchronize step onset with the Go signal and did not react to it. To further test whether modifications of the APAs occurred due to loading, we analyzed the duration and amplitude of the CP thrust (**Figure 1A**). The results showed that thrust duration is unchanged by loading [overall mean: 314 ± 31 ms; $t_{(14)} = 1.25$; $p = 0.22$]. The maximal amplitude of the thrust, however, was smaller in the loaded condition [means of 3.7 ± 1.1 and 4.2 ± 1.2 cm for the loaded and control condition, $t_{(14)} = 3.66$; $p = 0.002$]. This result indicates that the amplitude of the APAs is altered according to the loading condition.

DISCUSSION

By adding an extra-weight on the body to increase the pressure on the plantar sole mechanoreceptors, we have shown that the neural response to the same somatosensory stimulus evoked a decrease of the early P_{50}-N_{90} neural response when standing still and an increase of this neural response when preparing for a stepping movement. In the loaded condition during standing, the fact that the P_{50}-N_{90} neural response to the stimulation was decreased is consistent with the hypothesis of a depressed transmission of cutaneous inputs arriving at the cortical level (37). This is likely the result of an increase pressure of the foot plantar sole where the mechanoreceptors are embedded (15, 45–49). By contrast, when preparing for a stepping movement the depressed transmission did not prevent the facilitation of sensory processing to occur. This upregulation is consistent with the hypothesis of an efferent signal coming from the premotor areas. The SMA and to a lesser extent the superior parietal lobule (SPL) areas are the likely sources of sensory processing facilitation.

During the early preparation of the stepping movement (i.e., some 720 ms before the APAs execution), efferent signals from the frontal cortex could restore a certain level of sensory processing to ascertain proficient setting of the APAs prior to step initiation. Indeed, motor preparation of the transition from stance to stepping movement requires an estimation of the body's orientation relative to gravity (50). Although several sensors contribute to that "prior knowledge" of body orientation, it can be determined from foot plantar sole cutaneous receptors

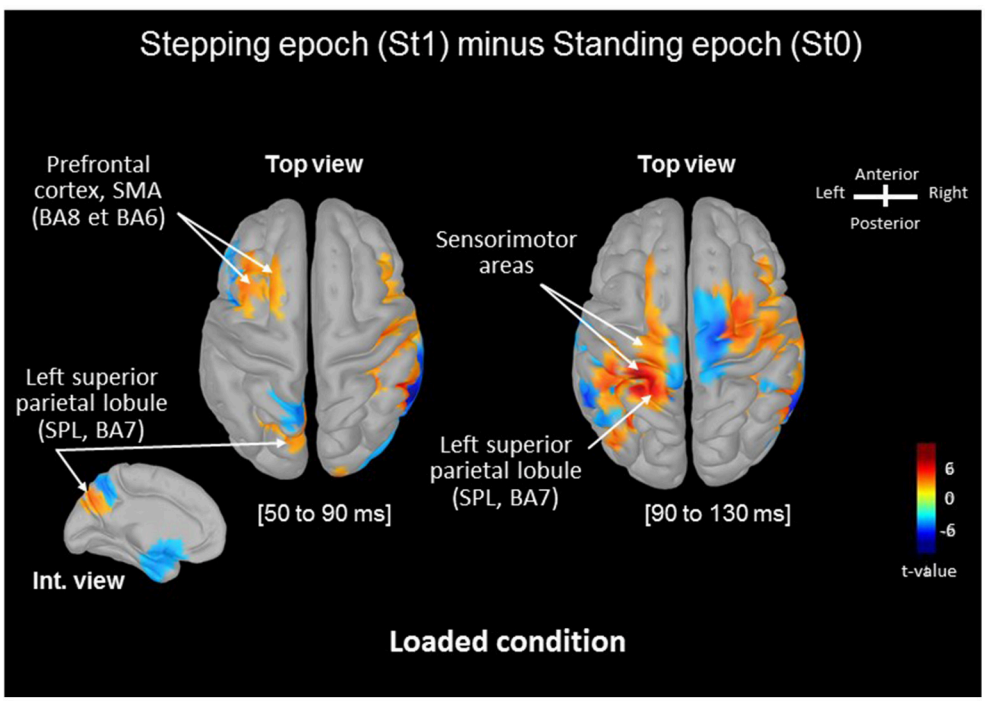


FIGURE 2 | Statistical source estimation maps for St1vs. St0 contrast (i.e., Stepping minus Standing tasks) in the Loaded condition. Significant *t*-values ($p \leq 0.05$, $n = 15$) of the source localization during the [50–90 ms] and [90–130 ms] time windows projected on a cortical template (MNI's Colin 27). For both windows we display the top cortical view and the internal view of the left hemisphere for the P_{50}-N_{90} SEP. The red color represents a higher activity in St1 relative to St0.

and intrinsic foot muscle proprioception in absence of visual, vestibular or proprioceptive inputs (12, 15). Depressed afferents reaching the cortical level may have prompted the SMA to provide an efferent signal to the somatosensory regions (31, 32, 36). This is supported by the fact that SMA neurones are sensitive to somatosensory stimuli (here depressed) (51) and that SMA is connected to SI [with no direct connection from the thalamus, for a review (52)]. These interconnections to SI are compatible with the idea that this area may in turn have facilitated the sensory processing during the early motor preparation. In line with this suggestion is the fact that the SMA is known to be activated specifically during movement preparation as it has been reported in studies assessing cortical network related to motor imagery (34, 53). It has been suggested, by Jeannerod (54), that motor imagery is functionally equivalent to movement preparation. For instance, when demands of the locomotor tasks require increasing cognitive and sensory information processing, the left SMA becomes progressively engaged (34).

The increased SPL activity for St1 relative to St0 observed from the P_{50} component and strengthened after N_{90}, suggests that this region contributed to the sensory facilitation via thalamocortical projections. Indeed, a large proportion of thalamic neurons directly project to the SPL (55–58). The increase of the SPL region could entail that the sensorimotor integration mechanisms were updating the current body representation to adapt the feedforward setting of the APAs as evidenced later with the smaller thrust peak in the Loaded compared to the Control conditions. In the Loaded condition, a crucial update of the body representation was likely needed as loading increases sensory and motor noise (59). This is in line with the proposition that to update body representation, simultaneous integration of sensory and motor signals overtime is required (10, 60). A key region for this process would be the SPL as it has been demonstrated that a patient with a lesion of the SPL failed to maintain a constant grip force or to perform accurate slow reaching movement in absence of vision (61). The authors suggested that, for this patient, the storage mechanism was damaged thus stored state estimate of body representation decayed over time.

During the later stage of the preparation process (St2) the sensory transmission did not remain as high as in the early stage of the preparation phase (St1) likely because at that time the APAs preparation was almost finished thus online change was not possible. For instance, MacKinnon et al. (7) reported that when a startle-like acoustic stimulus was delivered to release the planned movement 100 ms before the go cue signal for step initiation, the muscles activation sequence was like control voluntary step in duration and amplitude. The fact that St2 P_{50}-N_{90} magnitude was like St0 (Standing only) confirms that no further down- or up-regulation of somatosensory transmission occurred as it was reported in a previous study (16).

In conclusion, sensory facilitation is restored at an early stage of the preparation process, that is, when participants needed to perform proficient APAs before executing stepping movements. This action occurs regardless of the quantity of afferents arriving at the cortical level. Specifically, when plantar sole cutaneous afferents were attenuated, sensory processing could involve both interconnections between the primary somatosensory cortex and SMA and an indirect thalamic connection to PPC which bypass primary somatosensory cortex. Restoration of sensory facilitation in SPL and SMA regions prior to stepping is consistent with the involvement of these two sensorimotor areas in body representation and motor preparation.

AUTHOR CONTRIBUTIONS

OL, NT, MS, and LM contributed to the conception and design of the study, organized the database. OL performed the statistical analysis. OL and LM wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

ACKNOWLEDGMENTS

This research was supported by grants from the NSERC Discovery program to MS and NT.

REFERENCES

1. Rogers MW, Pai Y-C. Dynamic transitions in stance support accompanying leg flexion movements in man. *Exp Brain Res.* (1990) 81:398–402. doi: 10.1007/BF00228132
2. Rogers MW, Pai Y-C. Organization of preparatory postural responses for the initiation of lateral body motion during goal directed leg movements. *Neurosci Lett.* (1995) 187:99–102. doi: 10.1016/0304-3940(95)11351-7
3. Mouchnino L, Aurenty R, Massion J, Pedotti A. Coordination between equilibrium and head-trunk orientation during leg movement: a new strategy build up by training. *J Neurophysiol.* (1992) 67:1587–98. doi: 10.1152/jn.1992.67.6.1587
4. Brenière Y, Do MC. Control of Gait Initiation. *J Motor Behav.* (1991) 23:235–40. doi: 10.1080/00222895.1991.9942034
5. Malouin F, Richards CL. Preparatory adjustments during gait initiation in 4–6-year-old children. *Gait Posture* (2000) 11:239–53. doi: 10.1016/S0966-6362(00)00051-5
6. Massion J. Movement, posture and equilibrium: interaction and coordination. *Prog Neurobiol.* (1992) 38:35–56. doi: 10.1016/0301-0082(92)90034-C
7. Mackinnon CD, Bissig D, Chiusano J, Miller E, Jager C, Zhang Y, et al. Preparation of anticipatory postural adjustments prior to stepping. *J Neurophysiol.* (2007) 97:4368–79. doi: 10.1152/jn.01136.2006
8. Mille M, Mouchnino L. Are human anticipatory postural adjustments affected by a modification of the initial position of the center of gravity? *Neurosci Lett.* (1998) 242:61–4. doi: 10.1016/S0304-3940(98)00047-0
9. Ruget H, Blouin J, Teasdale N, Mouchnino L. Can prepared anticipatory postural adjustments be updated by proprioception. *Neuroscience* (2008) 155:640–8. doi: 10.1016/j.neuroscience.2008.06.021
10. Timmann D, Horak F. Perturbed step initiation in cerebellar subjects: 2. Modification of anticipatory postural adjustments. *Exp Brain Res.* (2001) 141:110–20. doi: 10.1007/s002210100858
11. Timmann D, Horak FB. Perturbed step initiation in cerebellar subjects. *Exp Brain Res.* (1998) 119:73–84. doi: 10.1007/s002210050321
12. Mouchnino L, Blouin J. When standing on a moving support, cutaneous inputs provide sufficient information to plan the anticipatory postural adjustments for gait initiation. *PLoS ONE* (2013) 8:e55081. doi: 10.1371/journal.pone.0055081

13. Lin SI, Yang WC. Gait and Posture Effect of plantar desensitization on postural adjustments prior to step initiation. *Gait Posture* (2011) 34:451–6. doi: 10.1016/j.gaitpost.2011.06.016
14. Fiolkowski P, Brunt D, Bishop M, Woo R. Does postural instability affect the initiation of human gait ? *Neurosci Lett.* (2002) 323:167–70. doi: 10.1016/S0304-3940(02)00158-1
15. Wright WG, Ivanenko YP, Gurfinkel VS. Foot anatomy specialization for postural sensation and control. *J Neurophysiol.* (2012) 107:1513–21. doi: 10.1152/jn.00256.2011
16. Mouchnino L, Fontan A, Tandonnet C, Perrier J, Saradjian AAH, Blouin J, et al. Facilitation of cutaneous inputs during the planning phase of gait initiation. *J Neurophysiol.* (2015) 114:301–8. doi: 10.1152/jn.00668.2014
17. Desmedt JE, Robertson D. Differential enhancement of early and late components of the cerebral somatosensory evoked potentials during forced-paced cognitive tasks in man. *J Physiol.* (1977) 271:761–82. doi: 10.1113/jphysiol.1977.sp012025
18. Chapman CE, Meftah EM. Independent controls of attentional influences in primary and secondary somatosensory cortex. *J Neurophysiol.* (2005) 94:4094–107. doi: 10.1152/jn.00303.2005
19. Hämäläinen H, Kekoni J, Sams M, Reinikainen K, Näätänen R. Human somatosensory evoked potentials to mechanical pulses and vibration: contributions of SI and SII somatosensory cortices to P50 and P100 components. *Electroencephalogr Clin Neurophysiol*. (1990) 75:13–21. doi: 10.1016/0013-4694(90)90148-D
20. Hari R, Reinkainen K, Kaukoranta E, Hämäläinen M, Ilmoniemi R, Penttinen A, et al. Somatosensory evoked cerebral magnetic fields from SI and SII in man. *Electroencephalogr Clin Neurophysiol.* (1984) 57:3399–401. doi: 10.1016/0013-4694(84)90126-3
21. Lin YY, Shih YH, Chen JT, Hsieh JC, Yeh TC, Liao KK, et al. Differential effects of stimulus intensity on peripheral and neuromagnetic cortical responses to median nerve stimulation. *NeuroImage*. (2003) 20:909–17. doi: 10.1016/S1053-8119(03)00387-2
22. Duysens J, Tax AAM, Nawijn S, Berger W, Prokop T, Altenmuller E. Gating of sensation and evoked-potentials following foot stimulation during human gait. *Exp Brain Res.* (1995) 105:423–31.
23. Altenmüller E, Berger W, Prokop T, Trippel M, Dietz V. Modulation of sural nerve somatosensory evoked potentials during stance and different phases of the step-cycle. *Electroencephalogr Clin Neurophysiol.* (1995) 96:516–25. doi: 10.1016/0013-4694(95)00093-E
24. Bolton DAE, McIlroy WE, Staines WR. The impact of light fingertip touch on haptic cortical processing during a standing balance task. *Exp Brain Res.* (2011) 212:279–91. doi: 10.1007/s00221-011-2728-6
25. Bonnet M, Chiambretto M, Decety J, Vidal F. Laplacian ERPs for planning to imagine a learned motor sequence. *Curr Psychol Cogn.* (1998) 17:685–98.
26. Caldara R, Deiber MP, Andrey C, Michel CM, Thut G, Hauert CA. Actual and mental motor planning and execution: a spatiotemporal ERP study. *Exp Brain Res.* (2004) 159:389–99. doi: 10.1007/s00221-004-2101-0
27. Cunnington R, Iansek R, Bradshaw JL, Phillips JG. Movement-related potentials associated with movement planning and motor imagery. *Exp Brain Res.* (1996) 111:429–36. doi: 10.1007/BF00228732
28. Stippich C, Ochmann H, Sartor K. Somatotopic mapping of the human primary sensorimotor cortex during motor imagery and motor execution by functional magnetic resonance imaging. *Neurosci Lett.* (2002) 331:50–4. doi: 10.1016/S0304-3940(02)00826-1
29. Viallet F, Massion J, Massarino R, Khalil R. Coordination between posture and movement in a bimanual load lifting task: putative role of a medial frontal region including the supplementary motor area. *Exp Brain Res.* (1992) 88:674–84. doi: 10.1007/BF00228197
30. Saradjian AH, Teasdale N, Blouin J, Mouchnino L. Independent early and late sensory processes for proprioceptive integration when planning a step. *Cereb Cortex.* (2018). doi: 10.1093/cercor/bhy104. [Epub ahead of print].
31. Arai N, Lu M-K, Ugawa Y, Ziemann U. Effective connectivity between human supplementary motor area and primary motor cortex: a paired-coil TMS study. *Exp Brain Res.* (2012) 220:79–87. doi: 10.1007/s00221-012-3117-5
32. Jurgens U. The efferent and afferent connections of the supplementary motor area. *Brain Res.* (1984) 300:63–81. doi: 10.1016/0006-8993(84)91341-6
33. Bakola S, Gamberini M, Passarelli L, Fattori P, Galletti C. Cortical connections of parietal field PEc in the macaque: linking vision and somatic sensation for the control of limb action. *Cereb Cortex* (2010) 20:2592–604. doi: 10.1093/cercor/bhq007
34. Malouin F, Richards CL, Jackson PL, Dumas F, Doyon J. Brain activations during motor imagery of locomotor-related tasks: a PET study. *Hum Brain Mapp.* (2003) 19:47–62. doi: 10.1002/hbm.10103
35. Confais J, Kim G, Tomatsu S, Takei T, Seki K. Nerve-specific input modulation to spinal neurons during a motor task in the monkey. *J Neurosci.* (2017) 37:2561–2516. doi: 10.1523/JNEUROSCI.2561-16.2017
36. Haggard P, Whitford B. Supplementary motor area provides an efferent signal for sensory suppression. *Cog Brain Res.* (2004) 19:52–8. doi: 10.1016/j.cogbrainres.2003.10.018
37. Lhomond O, Teasdale N, Simoneau M, Mouchnino L. Neural consequences of increasing body weight: evidence from somatosensory evoked potentials and the frequency-specificity of brain oscillations. *Front Human Neurosci.* (2016) 10:1–10. doi: 10.3389/fnhum.2016.00318
38. Burke D, Gandevia SC. Interfering cutaneous stimulation and the muscle afferent contribution tocortical potentials. *Electroencephalogr Clin Neurophysiol.* (1988) 70:118–25. doi: 10.1016/0013-4694(88)90112-5
39. Morita H, Petersen N, Nielsen J. Gating of somatosensory evoked potentials during voluntary movement of the lower limb in man. *Exp Brain Res.* (1998) 120:143–52. doi: 10.1007/s002210050388
40. Gratton G, Coles MG, Donchin E. A new method for off-line removal of ocular artifact. *Clin Neurophysiol.* (1983) 55:468–84. doi: 10.1016/0013-4694(83)90135-9
41. Burke D, Skuse NF, Lethlean AK. Cutaneous and muscle afferent components of the cerebral potential evoked by electrical stimulation of human peripheral nerves. *Electroencephalogr Clin Neurophysiol.* (1981) 51:579–88. doi: 10.1016/0013-4694(81)90202-9
42. Tadel F, Baillet S, Mosher JC, Pantazis D, Leahy RM. Brainstorm: a user-friendly application for MEG/EEG analysis. *Comput Intell Neurosci.* (2011) 2011:1–13. doi: 10.1155/2011/879716
43. Huang Y, Parra LC, Haufe S. The New York Head—a precise standardized volume conductor model for EEG source localization and tES targeting. *NeuroImage* (2016) 140:150–62. doi: 10.1016/j.neuroimage.2015.12.019
44. Mosher JC, Leahy RM, Lewis PS. EEG and MEG: forward solutions for inverse methods. *IEEE Trans Biomed Eng.* (1999) 46:245–59. doi: 10.1109/10.748978
45. Bandholm T, Boysen L, Haugaard S, Zebis MK, Bencke J. Foot medial longitudinal-arch deformation during quiet standing and gait in subjects with medial tibial stress syndrome. *J Foot Ankle Surg.* (2008) 47:89–95. doi: 10.1053/j.jfas.2007.10.015
46. McPoil TG, Cornwall MW, Medoff L, Vicenzino B, Fosberg KK, Hilz D. Arch height change during sit-to-stand: alternative for the navicular drop test. *J Foot Ankle Res.* (2008) 1:3. doi: 10.1186/1757-1146-1-3
47. Wu X, Madigan ML. Impaired plantar sensitivity among the obese is associated with increased postural sway. *Neurosci Lett.* (2014) 583:49–54. doi: 10.1016/j.neulet.2014.09.029
48. Kennedy PM, Inglis JT. Distribution and behaviour of glabrous cutaneous receptors in the human foot sole. *J Physiol.* (2002) 538:995–1002. doi: 10.1113/jphysiol.2001.013087
49. Strzalkowski NDJ, Peters RM, Inglis JT, Bent LR. Cutaneous afferent innervation of the human foot sole: what can we learn from single-unit recordings? *J Neurophysiol.* (2018) 120:1233–46. doi: 10.1152/jn.00848.2017
50. Massion J. Postural control system. *Curr Opin Neurobiol.* (1994) 4:877–87. doi: 10.1016/0959-4388(94)90137-6
51. Picard N, Strick PL. Motor areas of the medial wall: a review of their location and functional activation. *Cereb Cortex* (1996) 6:342–53. doi: 10.1093/cercor/6.3.342
52. Allison T, McCarthy G, Luby M, Puce A, Spencer DD. Localization of functional regions of human mesial cortex by somatosensory evoked potential recording and by cortical stimulation. *Electroencephalogr Clin Neurophysiol.* (1996) 100:126–40. doi: 10.1016/0013-4694(95)00226-X
53. Lotze M, Montoya P, Erb M, Hülsmann E, Flor H, Klose U, et al. Activation of cortical and cerebellar motor areas during executed and imagined hand movements: an fMRI study. *J Cogn Neurosci.* (1999) 11:491–501. doi: 10.1162/089892999563553

54. Jeannerod M. The representing brain: neural correlates of motor intention and imagery. *Behav Brain Sci.* (1994) 17:187–245. doi: 10.1017/S0140525X00034026
55. Pearson RC, Brodal P, Powell TP. The projection of the thalamus upon the parietal lobe in the monkey. *Brain Res.* (1978) 144:143–8. doi: 10.1016/0006-8993(78)90440-7
56. Pons TP, Kaas JH. Connections of area 2 of somatosensory cortex with the anterior pulvinar and subdivisions of the ventroposterior complex in macaque monkeys. *J Comp Neurol.* (1985) 240:16–36. doi: 10.1002/cne.902400103
57. Padberg J, Cerkevich C, Engle J, Rajan AT, Recanzone G, Kaas J, et al. Thalamocortical connections of parietal somatosensory cortical fields in macaque monkeys are highly divergent and convergent. *Cereb Cortex* (2009) 19:2038–64. doi: 10.1093/cercor/bhn229
58. Impieri D, Gamberini M, Passarelli L, Rosa MGP, Galletti C. Thalamo-cortical projections to the macaque superior parietal lobule areas PEc and PE. *J Comp Neurol.* (2018) 526:1041–56. doi: 10.1002/cne.24389
59. Simoneau M, Teasdale N. Balance control impairment in obese individuals is caused by larger balance motor commands variability. *Gait Posture* (2015) 41:203–8. doi: 10.1016/j.gaitpost.2014.10.008
60. Wolpert DM, Ghahramani Z, Jordan MI. An internal model for sensorimotor integration. *Science* (1995) 269:1880–2. doi: 10.1126/science.7569931
61. Wolpert DM, Goodbody SJ, Husain M. Maintaining internal representations: the role of the human superior parietal lobe. *Nat Neurosci.* (1998) 1:529–33. doi: 10.1038/2245

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 09 January 2019
doi: 10.3389/fneur.2018.01131

Revisiting the Relationship Between Internal Focus and Balance Control in Young and Older Adults

Victoria W. K. Chow[1]*, *Toby J. Ellmers*[2,3], *William R. Young*[2,3], *Toby C. T. Mak*[1] and *Thomson W. L. Wong*[1]

[1] Li Ka Shing Faculty of Medicine, School of Public Health, The University of Hong Kong, Hong Kong, China, [2] Department of Clinical Sciences, Brunel University London, London, United Kingdom, [3] Institute for Environment, Health and Societies, Brunel University London, London, United Kingdom

Research highlights the detrimental effect that directing too much conscious attention toward movement can have on postural control. While this concept has received support from many studies, recent evidence demonstrates that this principle does not always translate to aging clinical populations. Given the increasing clinical interest in this topic, the current study evaluated if the original notion (that an internal focus results in compromised balance performance) is upheld in young and older adults during a challenging balance task where we are able to objectively corroborate changes in attentional focus; using an electroencephalography (EEG) method previously identified as an objective indicator of conscious movement control. This method assesses the neural coherence, or "communication," between T3 (verbal-analytical) and Fz (motor-planning) regions of the brain. Thirty-nine young and 40 older adults performed a challenging balance task while holding a 2-meter pole under two randomized conditions: Baseline and Internal focus of attention (directing attention internally toward movement production). Results showed that young adults demonstrated increased EEG T3-Fz coherence in conjunction with increased sway path during the Internal focus condition. However, no significant differences were observed in older adults between conditions for any measure. The current study provides supporting evidence for the detrimental effect that adopting an Internal focus can have on postural control—especially in populations able to govern these processes in a relatively "automatic" manner (e.g., young adults). However, this work illustrates that such observations may not readily translate between populations and are not robust to age-related changes. Further work is necessary to examine mechanisms underlying this clear translational issue.

Keywords: attention, internal focus, EEG, T3-Fz coherence, balance, aging

OPEN ACCESS

Edited by:
Joyce Fung,
McGill University, Canada

Reviewed by:
Maayan Agmon,
University of Haifa, Israel
Ruey-Meei WU,
National Taiwan University, Taiwan

***Correspondence:**
Victoria W. K. Chow
u3511810@connect.hku.hk

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *30 July 2018*
Accepted: *10 December 2018*
Published: *09 January 2019*

Citation:
Chow VWK, Ellmers TJ, Young WR, Mak TCT and Wong TWL (2019) Revisiting the Relationship Between Internal Focus and Balance Control in Young and Older Adults. Front. Neurol. 9:1131. doi: 10.3389/fneur.2018.01131

INTRODUCTION

Traditional conceptualizations have viewed postural control as a largely automatic process requiring minimal conscious involvement. However, recent decades have seen this notion become increasingly discredited, largely based on observations made in dual-tasking paradigms, where poorer performance on a range of different balance tasks are observed when carrying out a simultaneous cognitive task [for reviews see (1, 2)]. While dual-task related breakdown in postural

control is often reported in young adults [e.g., (3, 4)], these decrements appear to be particularly pronounced in older adults (1). This observation has led researchers to propose the existence of an age-related increase in the minimum amount of controlled (conscious) processing required to effectively regulate postural stability (1). Therefore, while older adults *can* maintain similar levels of postural stability (compared to young adults) during conditions of single-task, doing so will likely require increased attentional resources necessary for such controlled processing—resources less available during dual-task conditions.

These findings illustrate that postural control, particularly in older adults, requires some level of conscious, attentional input. However, other lines of research highlight the detrimental effect that directing *too* much conscious attention toward movement can have on postural control. For example, seminal work published by Wulf and colleagues describes enhanced postural stability when performers direct attention externally (e.g., toward ensuring markers placed on a stabilometer remain horizontal), rather than internally (e.g., toward minimizing movement in the ankles) (5, 6). These findings have since been replicated during other experimental conditions designed to similarly limit the amount of conscious attention directed toward postural control in both young and older adults (7–9). This has led researchers to suggest that stability may be enhanced during balance tasks by promoting the use of more automatic control mechanisms (6, 7, 9). It would, therefore, appear that while the control of posture and gait does require some level of cognitive input (1, 2), these processes may typically be governed using largely automatic processes. As such, it has been suggested that adopting an internal focus of attention may disrupt the "automatic" processes typically used to regulate posture, leading to superfluous muscle activity and constrained motor outputs (10).

This perspective has received support from research carried out in various contexts, especially skilled sports performance [e.g., (10–12)]. However, recent evidence demonstrates that this principle does not always translate between contexts as expected and that the behavioral (e.g., performance) consequences of adopting an internal focus may depend on several factors, including the performer's level of skill/movement proficiency (13–16). For example, Castaneda and Gray (14) found that highly skilled baseball players benefited from an external focus during a batting simulation, whereas novices performed best when adopting an internal focus. In the context of rehabilitation after Stroke, compared to an external focus condition, adopting an internal focus has also been shown to enhance movement proficiency (17, 18), thus seemingly contradicting basic assumptions established through observations in young healthy adults completing identical tasks [e.g., (19)]. Kal et al. (18) argued that, similar to when novice performers attempt to learn a sporting skill for the first time, in situations where automatic processes lack the requisite "knowledge" to proficiently carry out the given task, it may be necessary to allocate attention toward the conscious control of a skill in order to avoid gross performance errors. In other words, in the absence of adequate automatic control processes, motor tasks that were once completed with relative ease now present a formidable challenge and command significant cognitive resources during their execution. As such, one might argue that changes in task difficulty are sufficient to determine whether the adoption of an internal focus represents an adaptive or maladaptive strategy.

When attempting to translate the above-described notions proposed by Wulf and colleagues (6, 10) to different clinical groups, this issue of task difficulty/increased reliance on conscious control processes is rarely noted and could explain discrepancies in findings observed between young healthy adults and clinical populations [e.g., (18, 19)]. Furthermore, in the absence of a validated method for objectively measuring the degree to which a performer is focussing internally, previous research on this topic has almost exclusively relied solely on experimental manipulations of, and/or self-reported changes in, attentional focus to rationalize observed changes in performance. Utilizing an objective, real-time measure would allow for further investigation into the mechanisms through which these aforementioned discrepancies may occur. For example, if certain clinical populations do, in fact, benefit from adopting an internal focus, then we would expect objective measures to record heightened levels of conscious movement processing at baseline.

Considering the above, and given the ever-increasing interest (from both researchers and clinicians) in this topic, the current study aimed to address two fundamental issues. First, we evaluated if the original notion proposed by Wulf and colleagues (5, 6, 10) is upheld in young adults during a challenging balance task where we are able to objectively corroborate changes in attentional focus using an electroencephalography (EEG) method capable of objectively measuring changes in conscious control processes (described below). Second, given discrepancies in observations made between young healthy adults and older adults with neurological conditions [e.g., (18, 19)], we aimed to evaluate if our observations in young adults are robust simply to age-related changes (i.e., without the added complexity of co-morbidities and neurological complexities). This was achieved by inviting an active and healthy cohort of older adults to complete the same protocol as the young adults, while attempting to normalize the difficulty of the balance task to account for age-related changes in balance control. Based on this task-difficulty normalization process, we predicted to observe similar patterns of behavioral outcomes in both the young and older adults—whereby the adoption of an internal focus results in disrupted regulation of postural stability. Furthermore, as this previous research tends to contrast conditions of internal focus with an external focus of attention, rather than exploring how directing attention internally alters postural control when compared to a baseline no-instruction condition [e.g., (5–8)], it is difficult to isolate the effects of adopting an internal focus. As such, the present research compared the effects of adopting an internal focus of attention to a baseline no-instruction condition.

Research suggests that EEG coherence, or "communication," between T3 (verbal-analytical) and Fz (motor-planning) regions of the brain may provide an objective, real-time measure of attentional focus during postural control tasks. For example, Ellmers et al. (20) reported significantly higher T3-Fz coherence during a postural sway task when young adults consciously controlled their swaying movements ("internal focus" condition), compared to when attention was directed toward either an external auditory cue ("external focus" condition) or a baseline

(no instruction) condition. Similarly, T3-Fz coherence when regulating postural stability has also been shown to increase in line with task difficulty (21). These findings suggest that consciously processing postural control may be characterized by increased conscious verbal-analytical or cognitive processes, thus supporting previous research which implicates verbal processes in the conscious control of posture and gait (22). These findings are also in line with the predictions presented in the Theory of Reinvestment [for a review, see (23)], which posits that conscious motor processing is characterized by an increased reliance on explicit verbal cues/rules. As such, while the regulation of postural stability typically occurs with low levels of explicit verbal-analytical processes, attempts to consciously control or monitor posture results in an increased reliance on such explicit processes. These results describing increased T3-Fz coherence during conditions of heightened conscious postural control also support those presented previously during other motor tasks (24, 25). For example, Zhu et al. (25) observed greater T3-Fz coherence during a golf putting task performed by individuals reporting a greater propensity for consciously controlling their movements. In a second experiment, the authors similarly reported increased T3-Fz coherence in individuals performing a golf putt under conditions designed to promote heightened conscious, cognitive involvement. Taken together, these findings suggest that conscious, controlled motor processing (including during postural control tasks) can be characterized by heightened EEG T3-Fz coherence—indicating increased verbal-analytical involvement during motor planning and control.

In the present study, healthy young and older adults completed a challenging postural control task under conditions of Baseline and Internal focus, while measuring changes in EEG T3-Fz coherence. We predicted to observe the following results in young adults: (1) Increased EEG T3-Fz coherence during Internal focus; (2) Decreased postural stability (i.e., increased sway) during Internal focus; (3) Significant positive associations between the change in T3-Fz coherence and postural sway between Baseline and Internal focus; (4) Significant positive associations between a trait propensity to consciously control and monitor movement, and both T3-Fz coherence and body sway during Baseline. Furthermore, as attempts were made to normalize the difficulty of the postural task for older adult participants, we predicted to observe the same patterns of results in a group of healthy older adults with high levels of functional balance, deemed to be at a low risk of falling.

METHODS

Participants

Thirty-nine young adults (20 men and 19 women) aged between 18 and 39 years of age ($M = 23.5$ years, $SD = 5.2$ years), and forty older adults (12 men and 28 women) aged between 65 and 83 years ($M = 69.7$ years, $SD = 3.8$ years), participated in the research. Young adults were recruited from undergraduate and post-graduate courses in London and Hong Kong, while older adults were recruited from different elderly community centers in Hong Kong. The inclusion criteria for young adults were: (i) aged 18 or above and below 40 years; (ii) ability to provide written informed consent; (iii) ability to stand independently without any walking aid, and; (iv) no history of cerebral vascular disease, Parkinson's or any other neurological impairments. Inclusion criteria were identical for older adults, but with the following amendments/additions: (i) participants were aged 65 years or above; (ii) a score of 24/30 or above in the Chinese version of Mini-Mental State Examination [MMSE-C (26, 27)], and; (iii) a score of 45/56 or higher on the Berg Balance Scale [BBS (28)]. The older adult participants had a mean MMSE-C score of 29.23 ($SD = 0.92$) out of 30, and a mean BBS score of 54.88 ($SD = 1.52$) out of 56. These variables were not assessed in the young adult participants, given that young adults typically score 100% on both assessments. Two (out of 40) older adults reported that they did not engage in weekly exercise (compared to 5/39 young adults), and all but one older adult reported their health status as fair–excellent (compared to 38/39 young adults reporting their health status as fair–excellent).

Participants had no prior experience with the specific tasks utilized in the current protocol. The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB).

Task and Procedure

For young adults, the balance task required participants to stand as still as possible in tandem stance on a $19.7'' \times 16.1'' \times 2.4''$ foam-pad (Balance Pad Elite, AIREX, Switzerland), while horizontally holding a 2-m pole. Participants held the pole with their hands facing upwards and elbows tucked against their body. Older adults undertook an identical procedure, the only difference being that they performed the balance task while standing with a narrow base of support (standing with their feet together), rather than in tandem stance. This methodological alteration was deemed necessary to ensure a comparable level of task difficulty between young and older adult participants, as pilot testing revealed that many older adult participants were unable to complete a 20s trial standing in tandem stance. As narrow-based standing is ranked as the next most challenging standing position, after tandem standing [according to the BBS (28)], this was deemed the most appropriate modified balance task for older adults to complete.

All participants performed two 20s trials under conditions of: Baseline (no instructions, other than to "stand as still as possible"), and; Internal focus (instructed to focus explicitly on lower limb movement: "Try to focus on your lower limb movement while performing the task"). Trials were presented in a randomized order. Participants fixated a point on a featureless wall 2-meters in front of them, with approximate head-pitch and general gaze fixation monitored and noted by the experimenter during each trial to ensure consistency between conditions[1]. The

[1]Participants also completed an additional two 20s trials under conditions of External focus, whereby they were instructed to keep the pole as stable and level as possible. However, as these instructions often resulted in participants visually fixating the pole (unlike the fixations made toward the distant wall during Baseline and Internal focus), we deemed that these between-condition differences in gaze distance would likely confound results. Consequently, data from the External focus condition have not been included in the analysis.

balance task and attentional focus instructions were derived from those previously used by Wulf et al. (6).

Apparatus

Electroencephalographic activity was recorded using a wireless EEG device (Brainquiry PET 4.0, Brainquiry, The Netherlands) at a sample rate of 200 Hz. EEG data were recorded using real-time biophysical data acquisition software (BioExplorer 1.5, CyberEvolution, US). EEG activity was recorded from two scalp locations [T3 [verbal-analytical] and Fz [motor planning]; see Ellmers et al. (20)] referenced to the right mastoid and grounded to the left mastoid using disposable electrodes (ARBO H124SG Ø 24 mm, Kendall, US), in accordance with the standard international 10–20 system (29). An impedance test was conducted to ensure a sufficient signal-to-noise ratio before each measurement. EEG signals were pre-processed (low-pass filter: 42 Hz, high-pass filter: 2 Hz) to remove potential biologic artifacts. T3-Fz coherence was calculated in 1 Hz frequency bins throughout each trial, using algorithms previously described by Zhu et al. (25). Previous research (20) has demonstrated that alpha2 (10–12 Hz) T3-Fz coherence is sensitive at detecting within-subject changes in conscious movement processing/attentional focus during a postural sway task (while no such changes were observed for alpha1(8–10 Hz) T3-Fz coherence). Similar results were also presented by Chu and Wong (21), whereby only alpha2 T3-Fz coherence was sensitive at detecting increases in task difficulty during a postural stability task. These findings support those presented by Zhu et al. (25) which highlight T3-Fz coherence as being sensitive to detecting differences in conscious movement processing during a golf-putting task. Consequently, the main EEG variable of interest was alpha2 T3-Fz coherence, with alpha2 T3-Fz coherence averages calculated for each trial, and then averaged across the relevant conditions. EEG pre-processing and coherence calculations were conducted using custom scripts in a biophysical data processing and analysis software (BioReviewer 1.6, CyberEvolution, US).

Body sway data were collected using 3-D motion capture with a minimum capture frequency of 100 Hz, using reflective markers placed on participants' sternum. Postural sway was obtained by calculating the root-mean-square of sternum co-ordinates in the horizontal (X–Z) plane throughout the 20-s trial. Raw data were passed through a low-pass Butterworth filter with a cut-off frequency of 5 Hz and analyzed using custom Matlab (R2015B Mathworks Inc., Natick, USA) scripts to calculate the variable of total body sway (mm).

Questionnaires

Participants' trait propensity to consciously process their movement was assessed using the Movement Specific Reinvestment Scale [MSRS; Masters et al. (30)]. This 10-item questionnaire consists of two 5-item subscales: conscious motor processing ("movement control"; e.g., *"I am always trying to think about my movements when I carry them out"*) and movement self-consciousness ("movement monitoring"; e.g., *"I'm self-conscious about the way I look when I am moving"*). Items are rated on a 6-point Likert scale (1 = *strongly disagree*; 6 = *strongly agree*). Both subscales range from 5–30, with higher scores reflecting a higher propensity for reinvestment. Both subscales have good internal validity and test-retest reliability (30).

Data Analysis

Baseline-Internal Focus Changes

As the majority of the variables were non-normally distributed, it was not possible to run a 2 × 2 (Young/Older adults × Condition) ANOVA. Furthermore, while attempts were made to normalize the difficulty of the balance task between groups, we cannot ensure parity in the task difficulty. Therefore, we treated the young and older adult data as two separate datasets and analyzed them as such. For young adults, a paired-samples *t*-test was used to explore any differences in T3-Fz coherence between Baseline and Internal focus. For older adults, between-condition changes in T3-Fz coherence were examined using a Wilcoxin test. The use of a non-parametric test was deemed necessary here, and elsewhere, as data were non-normally distributed. Separate Wilcoxon tests were used to determine the Baseline-Internal focus change in total body sway for both young and older adults. For all statistical comparisons, effect sizes are reported as Cohen's *d*, unless the assumption of normality is violated, where effect sizes are reported as $r = Z/\sqrt{N}$ (31).

Correlations

Separate bivariate correlations were used to investigate the association between the Baseline-Internal focus percentage change in both T3-Fz coherence and total body sway, in young and older adults. Separate bivariate correlations were also used to explore any associations between MSRS scores and either Baseline T3-Fz coherence or Baseline total body sway, in both young and older adults. All analyses were conducted with Spearman's non-parametric correlations (given the failures to meet parametric assumptions), aside from the correlation exploring MSRS scores and Baseline T3-Fz coherence in young adults.

RESULTS

Young Adults

There was a significant increase in T3-Fz coherence from Baseline ($M = 0.327$, $SD = 0.12$) to Internal ($M = 0.366$, $SD = 0.12$), $t_{(38)} = -2.07$, $p = 0.023$, $d = 0.33$ (see **Figure 1**). Increased coherence was accompanied by significantly greater total body sway during Internal ($M = 30.48$ mm, $SD = 22.68$), compared to Baseline ($M = 24.46$ mm, $SD = 11.50$), $Z = -1.76$, $p = 0.040$, $r = 0.28$ (see **Figure 2**). Percentage change data for both analyses are presented in **Figure 3**.

Older Adults

There was no significant change in T3-Fz coherence observed from Baseline ($M = 0.333$, $SD = 0.13$) to Internal ($M = 0.331$, $SD = 0.14$), $Z = -0.36$, $p = 0.36$, $r = 0.06$ (see **Figure 1**). There was a similar lack of significant change in total body sway observed between Baseline ($M = 29.08$ mm, $SD = 7.98$) and Internal ($M = 28.06$ mm, $SD = 9.58$), $Z = -0.83$, $p = 0.20$,

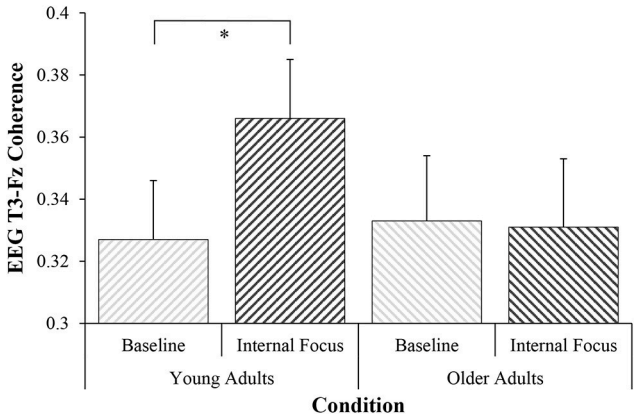


FIGURE 1 | Electroencephalographic alpha2 (10–12 Hz) T3-Fz coherence during conditions of Baseline and Internal focus (mean ± standard error), *$p < 0.05$.

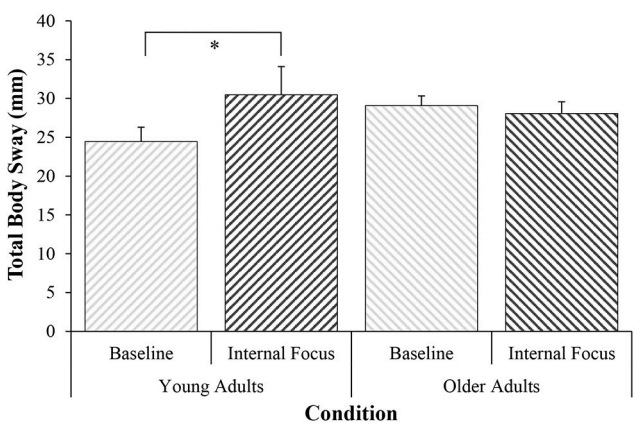


FIGURE 2 | Total body sway (mm) during conditions of Baseline and Internal focus (mean ± standard error), *$p < 0.05$.

$r = 0.13$ (see **Figure 2**). Percentage change data for both analyses are presented in **Figure 3**.

Correlations

Percentage Change

There were no significant correlations observed between the percentage change in T3-Fz coherence and total body sway from Baseline to Internal in either young ($r = 0.09$, $p = 0.30$) or older adults ($r = 0.13$, $p = 0.22$).

Trait MSRS

In young adults, MSRS scores were not significantly correlated with either Baseline T3-Fz coherence ($r = 0.11$, $p = 0.26$) or Baseline total body sway ($r = -0.05$, $p = 0.38$). There were a similar lack of significant correlations observed in older adults between MSRS scores either Baseline T3-Fz coherence ($r = -0.09$, $p = 0.30$) or Baseline total body sway ($r = -0.25$, $p = 0.06$).

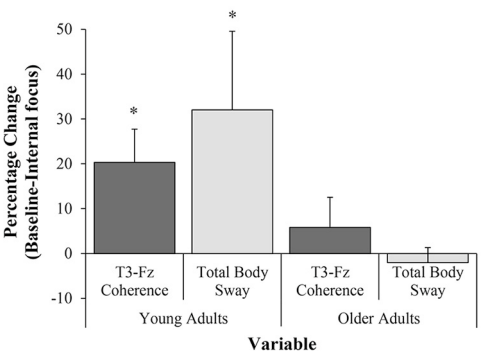


FIGURE 3 | Mean percentage change (mean change ± standard error of the mean change) between Baseline and Internal focus in T3-Fz coherence and total body sway for young and older adults, *percentage change significant to $p < 0.05$. Note: Positive values indicate an increase during Internal focus, compared to Baseline.

DISCUSSION

The current study provides strong support for the notion that adopting an internal focus of attention can disrupt performance of motor tasks that are typically governed by largely automatic processes—with young adults demonstrating greater postural sway during conditions of Internal focus. The current findings support the original notion proposed by Wulf and colleagues (5, 6, 10), in addition to numerous subsequent suggestions [e.g., (11, 12, 19)], that the adoption of an internal focus disrupts the ability to control motor performance in a task typically governed using largely automatic processes. While previous research has used EEG to infer alterations in attentional focus during a postural task (32), to our knowledge, this is the first instance where such associations have been demonstrated and compared between young and older adult groups.

We aimed to also evaluate whether this principle could be readily translated to clinical contexts by replicating the protocol in a cohort of older adults, while normalizing for task-difficulty. We had expected to observe comparable results in both our young and older adult cohorts, given both the older adults' relatively high-levels of physical functioning and the attempts to normalize task difficulty between-groups. However, any statistically significant effect of the internal focus manipulation (on both EEG T3-Fz coherence and postural sway) was restricted to young adults, as no significant changes in either measure were observed in older adults (see **Figure 3**).

Observations in Young Adults

Given the weight of evidence supporting an association between internal focus of attention and disrupted motor performance on tasks normally regulated through "automatic" processes, any contradictory results would have been highly unexpected. Nevertheless, given the scale of recent and ongoing efforts to apply this perspective to various clinical (i.e., complex) contexts [e.g., (17, 18, 33)], it was important to re-establish these fundamental associations using an objective corroboration of the attention manipulation used. We suggest that our current

observations in young adults fulfill this objective and, while further research is necessary to better-establish underlying mechanisms mediating this relationship, our findings help to establish a foundation from which we can evaluate the degree to which such associations translate to other contexts and populations.

It is important to note that, when calculating the percentage change in EEG T3-Fz coherence and postural sway between Baseline and Internal conditions, no significant correlation was found between these two variables. In light of previous validations of the EEG protocol (20, 21, 25) and the clear changes observed in EEG T3-Fz coherence between conditions in young adults indicating a greater reliance on cognitive verbal-analytical processes to regulate motor output, we suggest that the lack of any statistical association between metrics indicating percentage change cannot be primarily due to poor sensitivity in the EEG T3-Fz measurement. As such, despite our results highlighting an increase in both conscious movement processing and disrupted postural stability during conditions of internal focus in young adults (see **Figure 3**), the current data show no evidence for the concept that the degree of increased conscious control is associated with magnitude of behavioral change.

According to the basic principle that a propensity to consciously control movement will jeopardize movement automaticity and compromise motor performance, one would also expect to observe an association between MSRS scores—a trait measurement of an individual's propensity to consciously control and monitor their movement—and total body sway at Baseline. Our results, however, show no such association. In contrast to the clear support the current results (in young adults) show for the seminal findings of Wulf and colleagues (5, 6), the lack of any significant correlation observed concerning the MSRS raises important concerns about whether simple measures of dispositional traits can be expected to associate with complex attentional processes across a range of tasks. This proposal is further supported by a similar lack of association between MSRS scores and EEG T3-Fz coherence during Baseline—results in line with previous research which demonstrates a lack of between-group difference (based on MSRS scores) in EEG T3-Fz coherence (20, 21). While previous research has suggested a weak positive association between the MSRS and postural sway in young adults during a simple, quiet standing task whereby participants were instructed to stand as still as possible while standing in a comfortable, self-selected stance (34), no such associations were evident in older adults. This led the authors to suggest that scores on the trait measure of the MSRS may not necessary reflect the true amount of conscious involvement that individuals will "reinvest" into postural control—and instead propose that "…state measures of conscious movement processing (i.e., using MSRS as a context specific measure or assessing neural activity)" [(34), p. 448] may provide a more accurate indication of state processes.

Observations in Older Adults

We predicted that significant Baseline-Internal focus increases in both EEG T3-Fz and postural sway observed in younger adults (see **Figure 3**) would also be observed in older adult participants. Considering that attempts were made to normalize task difficulty between groups and the circumstance that the cohort of older adults were relatively highly functioning both in cognition and physical status, we saw no clear reason to expect findings to contradict those observed in young adults. The lack of significant results observed in our older adult cohort is therefore surprising, as previous research suggests that adopting an internal focus of attention may disrupt the "automatic" processes typically used to regulate posture, leading to superfluous muscle activity and constrained, less effective motor outputs in both young and older adults (10). However, it is worth noting that this previous research tends to contrast conditions of internal focus with an external focus of attention, rather than exploring how directing attention internally alters postural control when compared to a baseline no-instruction condition [e.g., (5–8)]. As such, it is possible that these previous results are a consequence of the positive impact of an external, rather than a negative effect of an internal focus of attention—an idea supported by findings presented by Richer et al. (9). The internal focus manipulation did, however, negatively impact young adults' regulation of postural stability. The lack of significant effect on either EEG T3-Fz coherence or postural sway was only observed in the older adult sample. We offer several speculations below in an attempt to rationalize these null results.

It is possible that our cohort of older adults adopted an internal focus of attention during Baseline trials, thus reducing the potential for change between conditions. For example, while the young adults may have been able to achieve the task of "standing as still as possible" with relatively "automatic" postural control processes, it is possible that such instructions may have induced a more conscious strategy of postural control in the older adult sample. This would support the notions presented previously by Boisgontier et al. (1), who suggest an age-related increase in the level of controlled conscious processing needed to regulate postural stability. However, we suggest this to be unlikely, due to the identical between-group values in Baseline EEG T3-Fz coherence (*young adult* $M = 0.33$, $SD = 0.12$; *older adult* $M = 0.33$, $SD = 0.13$). It is, however, possible that while EEG T3-Fz coherence is sensitive at detecting within-subject change in conscious movement processing during postural tasks [as indicated by the significant increase in coherence observed between Baseline and Internal focus in young adults in the present study, in addition to results presented previously by both Chu and Wong (21) and Ellmers et al. (20)], this method lacks sensitivity for detecting between-subject differences in internal focus. This could, potentially, account for the lack of association between MSRS scores and EEG T3-Fz coherence observed both in the present research and in previous studies (20, 21).

Another suggestion for the lack of comparable (to young adults) Baseline-Internal focus change in older adults relates to the potential between-group differences in how these instructions were interpreted and subsequently utilized to regulate posture. For example, Mak and colleagues (35, 36) have found evidence to suggest that the manner with which older adults alter their behavior following the adoption of an internal focus was dependent on previous experiences with falling—with these

experiences resulting in different interpretations of the internal focus instructions. For example, fallers might instinctively think about significant and problematic factors that jeopardize their balance on a daily basis, whereas their non-falling counterparts may be more inclined to focus attention on more generic movement rules. In other words, the manifestation of internal focus will likely be highly personalized and dependent on the unique interaction of traits and experiences present within each individual. While such individual differences will inevitably be present in young adults, we speculate that such differences are likely to be compounded by increased age and associated decline in automatic postural control mechanisms (1). Consequently, it is possible that while young adults relied on generic, explicit movement rules to control posture during Internal focus, their older adult counterparts instead adopted a more individualistic approach—which, for example, may have included ruminations unrelated to the conscious, cognitive control of posture and, thus, unlikely to have been registered through T3-Fz coherence. Regardless of the specific reasons, we must conclude that the basic notions proposed by Wulf and colleagues (5, 6, 10) cannot be assumed to readily translate to clinical contexts, even within a relatively simple "static" balance task.

In the complex attentional processes that have, hitherto, frequently been categorized as representing either an "external" or "internal" focus, the scope for between-subject differences are vast, especially when considering complexities associated with increased age and/or neurological impairment. To evaluate these complex processes we need to isolate and categorize the various multifaceted cognitive and attentional processes pertinent to different cohorts/conditions and associate changes in these measures with behavioral metrics indicative of both movement efficiency and efficacy. We anticipate that failure to acknowledge and evaluate these complex mechanisms will lead to the continued emergence of conflicting results, as identified by Kal et al. (18).

LIMITATIONS

This study is not without its limitations. Firstly, the study failed to measure self-reported changes in attentional focus. As such, it is possible that the lack of behavioral change observed in older adult participants was simply due to these participants simply failing to successfully engage in the manipulation and direct attention internally. We suggest that this is unlikely, as these internal focus instructions were derived from, and identical to, previous research demonstrating significant behavioral effects [e.g., (5, 6, 10)]. Another potential limitation of this research relates to the possibility that there were between-condition differences in the level of attention allocated toward the postural task. For example, as the task involved participants standing in a challenging stance whilst holding a 2-m pole, it is possible that the differences observed between how young and older adults responded to the internal instructions may have been a consequence of differences in Baseline levels of task prioritization: Whilst the older adults may have been focused entirely on maintaining postural stability, it is possible that the young adults were also directing attention toward minimizing the movement of the pole. However, given that the postural task was designed to be challenging, and participants were instructed to "stand as still as possible," we deem it unlikely that participants would have been directing explicit attention toward the pole at the expense of maintaining postural stability.

CONCLUSIONS

The current study provides further support for the concept that adopting an internal focus of attention disrupts motor performance in tasks typically considered to be largely automatic. To our knowledge this is the first instance where such associations have been demonstrated in conjunction with an objective corroboration of the Internal focus condition; in this instance this was represented as an increase in EEG T3-Fz coherence. We aimed to evaluate whether this principle could be readily translated to clinical contexts by replicating the protocol in a cohort of older adults, while normalizing for task-difficulty. When instructing older adults to adopt an internal focus of attention during the balance task, we observed a lack of significant change in both EEG T3-Fz coherence and balance performance. We identify several reasons for this discrepancy. However, we conclude that, regardless of the underlying mechanisms, the current results indicate that we cannot assume that basic concepts associated with internal focus and motor performance (10) are easily transferrable to different cohorts/populations, especially those influenced by age-related changes.

AUTHOR CONTRIBUTIONS

VC and TW conceived this study. TE and WY designed the study. VC collected the data. VC, TE, and TM analyzed the data. All authors interpreted the results and wrote the manuscript. All authors read and approved the final manuscript.

FUNDING

This work was partially supported by a grant (Undergraduate Research Fellowship Programme) from the URFP Working Group at the University of Hong Kong.

ACKNOWLEDGMENTS

The authors appreciate the assistance from the Hong Kong Sheng Kung Hui Western District Elderly Community Centre in participants' recruitment. We are also grateful to Miss Debbie Chan, Miss Connie Chen, Miss May Leung and Dr. Fan Mengjiao for their support to the study.

REFERENCES

1. Boisgontier MP, Beets IA, Duysens J, Nieuwboer A, Krampe RT, Swinnen SP. Age-related differences in attentional cost associated with postural dual tasks: increased recruitment of generic cognitive resources in older adults. *Neurosci Biobehav Rev.* (2013) 37:1824–37. doi: 10.1016/j.neubiorev.2013.07.014
2. Woollacott M, Shumway-Cook A. Attention and the control of posture and gait: a review of an emerging area of research. *Gait Posture* (2002) 16:1–14. doi: 10.1016/S0966-6362(01)00156-4
3. Huxhold O, Li SC, Schmiedek F, Lindenberger U. Dual-tasking postural control: aging and the effects of cognitive demand in conjunction with focus of attention. *Brain Res Bull.* (2006) 69:294–305. doi: 10.1016/j.brainresbull.2006.01.002
4. Simoneau EM, Billot M, Martin A, Perennou D, Van Hoecke J. Difficult memory task during postural tasks of various difficulties in young and older people: a pilot study. *Clin Neurophysiol.* (2008) 119:1158–65. doi: 10.1016/j.clinph.2008.01.020
5. McNevin MH, Shea CH, Wulf G. Increasing the distance of an external focus of attention enhances learning. *Psychol Res.* (2003) 67:22–9. doi: 10.1007/s00426-002-0093-6
6. Wulf G, Mercer J, McNevin N, Guadagnoli MA. Reciprocal influences of attentional focus on postural and suprapostural task performance. *J Motor Behav.* (2004) 36:189–99. doi: 10.3200/JMBR.36.2.189-199
7. Polskaia N, Richer N, Dionne E, Lajoie Y. Continuous cognitive task promotes greater postural stability than an internal or external focus of attention. *Gait Posture* (2015) 41:454–8. doi: 10.1016/j.gaitpost.2014.11.009
8. Richer N, Polskaia N, Lajoie Y. The effects of attentional focus and cognitive tasks on postural sway may be the result of automaticity. *Gait Posture* (2017) 54:45–9. doi: 10.1016/j.gaitpost.2017.02.022
9. Richer N, Saunders D, Polskaia N, Lajoie Y. Continuous cognitive task promotes greater postural stability than an internal or external focus of attention in older adults. *Exp Aging Res.* (2017) 43:21–33. doi: 10.1080/0361073X.2017.1258214
10. Wulf G. Attentional focus and motor learning: a review of 15 years. *Int Rev Sport Exerc Psychol.* (2013) 6:77–104. doi: 10.1080/1750984X.2012.723728
11. Jackson RC, Ashford KJ, Norsworthy G. Attentional focus, dispositional reinvestment and skilled motor performance under pressure. *J Sport Exerc Psychol.* (2006) 28:49–68. doi: 10.1123/jsep.28.1.49
12. Marchant DC, Greig M, Bullough J, Hitchen D. Instructions to adopt an external focus enhance muscular endurance. *Res Q Exerc Sport* (2011) 82:466–73. doi: 10.1080/02701367.2011.10599779
13. Beilock S, Carr T, MacMahon C, Starkes J. When paying attention becomescounterproductive: impact of divided versus skill-focused attention on novice and experienced performance of sensorimotor skills. *J Exp Psychol.* (2002) 8:6–16. doi: 10.1037/1076-898X.8.1.6
14. Castaneda B, Gray R. Effects of focus of attention on baseball batting performance in players of differing skill levels. *J Sport Exerc Psychol.* (2007) 29:60–77. doi: 10.1123/jsep.29.1.60
15. Emanuel M, Jarus T, Bart O. Effect of focus of attention and age on motor acquisition, retention, and transfer: a randomized trial. *Phys Ther.* (2008) 88:251–60. doi: 10.2522/ptj.20060174
16. Perkins-Ceccato N, Passmore SR, Lee TD. Effects of focus of attention depend on golfers' skill. *J Sports Sci.* (2003) 21:593–600. doi: 10.1080/0264041031000101980
17. Cirstea MC, Levin MF. Improvement of arm movement patterns and endpoint control depends on type of feedback during practice in stroke survivors. *NeuroRehabil Neural Repair* (2007) 21:398–411. doi: 10.1177/1545968306298414
18. Kal E, van der Kamp J, Houdijk H, Groet E, van Bennekomm CAM, Scherder EJA. Stay focused! The effects of internal and external focus of attention on movement automaticity in patients with stroke. *PLoS ONE* (2015) 10:e0136917. doi: 10.1371/journal.pone.0136917
19. Kal E, van der Kamp J, Houdijk H. External attentional focus enhances movement automatization: a comprehensive test of the constrained action hypothesis. *Hum Move Sci.* (2013) 32:527–39. doi: 10.1016/j.humov.2013.04.001
20. Ellmers TJ, Machado G, Wong TWL, Zhu F, Williams AM, Young WR. A validation of neural co-activation as a measure of attentional focus in a postural task. *Gait Posture* (2016) 50:229–31. doi: 10.1016/j.gaitpost.2016.09.001
21. Chu CKH, Wong TWL. Conscious postural control during standing on compliant surface by older adults. *J Motor Behav.* (2018). doi: 10.1080/00222895.2018.1481820. [Epub ahead of print].
22. Young WR, Olonilua M, Masters RSW, Dimitriadis S, Williams AM. Examining links between anxiety, reinvestment and walking when talking by older adults during adaptive gait. *Exp Brain Res.* (2015) 234:161–72. doi: 10.1007/s00221-015-4445-z
23. Masters R, Maxwell J. The theory of reinvestment. *Int Rev Sport Exerc Psychol.* (2008) 1:160–83. doi: 10.1080/17509840802287218
24. Haufler AJ, Spalding TW, Santa Maria DL, Hatfield BD. Neuro-cognitive activity during a self-paced visuospatial task: comparative EEG profiles in marksmen and novice shooters. *Biol Psychol.* (2000) 53:131–60. doi: 10.1016/S0301-0511(00)00047-8
25. Zhu FF, Poolton JM, Wilson MR, Maxwell JP, Masters RSW. Neural co-activation as a yardstick of implicit motor learning and the propensity for conscious control of movement. *Biol Psychol.* (2011) 87:66–73. doi: 10.1016/j.biopsycho.2011.02.004
26. Chiu HFK, Lee HC, Chung WS, Kwong PK. Reliability and validity of the cantonese version of mini-mental state examination: a preliminary study. *J Hong Kong Coll Psychiatr.* (1994) 4:25–8.
27. Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* (1975) 12:189–98. doi: 10.1016/0022-3956(75)90026-6
28. Berg K, Wood-Dauphinée S, Williams JI, Gayton D. Measuring balance in the elderly: preliminary development of an instrument. *Physiother Can.* (1989) 41:301–31. doi: 10.3138/ptc.41.6.304
29. Jasper HH. The ten-twenty electrode system of the international federation. *Electroencephalogr Clin Neurophysiol.* (1958) 10:371–5.
30. Masters RSW, Eves FF, Maxwell JP. Development of a movement specific reinvestment scale. In: Morris T, Terry P, Gordon S, Hanrahan S, Ievleva L, Kolt G, et al. editors. *Proceedings of the ISSP 11th World Congress of Sport Psychology,* Sydney, NSW (2005).
31. Fritz CO, Morris PE , Richler JJ . Effect size estimates: current use, calculations, and interpretation. *J Exp Psychol Gen.* (2012) 141:2–18. doi: 10.1037/a0024338
32. Huang CY, Zhao CG, Hwang S. Neural basis of postural focus effect on concurrent postural and motor tasks: phase-locked electroencephalogram responses. *Behav Brain Res.* (2014) 274:95–107. doi: 10.1016/j.bbr.2014.07.054
33. Kal E, Houdijk H, van der Kamp J, Houdijk H, Verhoef M, Prosee R, et al. Are the effects of internal focus instructions different from external focus instructions given during balance training in stroke patients? A double-blind randomized controlled trial. *Clin Rehabil.* (2018) 31:269215518795243. doi: 10.1177/0269215518795243
34. Uiga L, Capio CM, Ryu D, Wilson MR, Masters RSW. The role of conscious control in maintaining stable posture. *Hum Move Sci.* (2018) 57:442–50. doi: 10.1016/j.humov.2017.10.008
35. Mak TC, Young WR, Chan DC, Wong TW. Gait stability in older adults during level-ground walking: the attentional focus approach. *J Gerontol Series B* (2018). doi: 10.1093/geronb/gby115. [Epub ahead of print].
36. Mak CT, Young WR, Lam WK, Tse ACY, Wong TWL. The role of attentional focus on movement efficiency in older fallers and non-fallers during level-ground walking. (2018) *J Am Geriatr Soc.*

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 21 January 2019
doi: 10.3389/fneur.2018.01130

Tonic Neuromuscular Processing Affects Postural Adaptation Differently in Aging and Parkinson's Disease

*W. Geoffrey Wright**

Neuromotor Sciences Program, College of Public Health, Temple University, Philadelphia, PA, United States

The combination of phasic and tonic neuromuscular processes are involved in the maintenance of normal upright posture. The latter is of particular importance in some pathologies, such as Parkinson's Disease (PD), which is known by one of its cardinal symptoms—tonic dysfunction (i.e., rigidity). Changes in tonic function may also occur during healthy aging. In this investigation, somatosensory input was manipulated by changing the support surface orientation for prolonged periods of quiet stance (QS). The aim was to shed light on how long-term tonic responses called postural lean after-effects are affected by aging and age-related neuropathology. Forty one participants were tested: 19 healthy young (25±5 years), 13 healthy older (63±8 years), and 9 adults with PD (63±5 years). Baseline conditions were eyes-closed QS on a stable surface or standing on an unstable, sway-referenced (SR) surface. Four experimental conditions combined two types of toes-up ramp tilt adaptation (120 s of toes-up static 7° tilt or sinusoidal 7° ± 3° tilt) with two types of post-adaptation (120 s of QS or SR). Results revealed postural after-effects during post-adaptation QS showing significant anterior COP shift for both young and older adults ($p < 0.0001$), but not PD ($p > 0.06$, n.s.). Compared to young, postural after-effects in older adults showed longer decay constants and did not return to baseline COP within the 120 s post-adaptation period ($p < 0.05$). Postural after-effects during SR, which appeared as toes-up surface tilt were highly significant in healthy populations ($p = 0.001$), but took longer to develop in PD. Younger adults showed significantly larger dorsiflexion ($p < 0.01$) and faster decay constants than older adults ($p < 0.05$). In summary, (1) postural after-effects decayed to baseline when post-tilt surface was stable but were retained and even grew larger post-adaptation in the SR surface conditions in all groups, (2) postural after-effects differed between healthy age groups, (3) PD showed less adaptation to surface changes. Differences in size and decay of after-effects between healthy and PD groups suggest tonic neuromuscular processes play a role in how adaptable postural control is to changing surface conditions and this is affected by healthy aging and basal ganglia function.

Keywords: postural tone, rigidity, Parkinsion's disease, basal ganglia, pedunculopontine tegmental nucleus, dopamine

OPEN ACCESS

Edited by:
Joyce Fung,
McGill University, Canada

Reviewed by:
Caroline Paquette,
McGill University, Canada
Josep Valls-Sole,
Hospital Clínic de Barcelona, Spain

***Correspondence:**
W. Geoffrey Wright
wrightw@temple.edu

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *06 July 2018*
Accepted: *10 December 2018*
Published: *21 January 2019*

Citation:
Wright WG (2019) Tonic Neuromuscular Processing Affects Postural Adaptation Differently in Aging and Parkinson's Disease. Front. Neurol. 9:1130. doi: 10.3389/fneur.2018.01130

INTRODUCTION

Normal upright posture relies on accurately determining the orientation of the support surface with respect to gravity (1–3). While it is well-understood that phasic processes reliant on short latency automatic and reflexive pathways are important to posture and gait, background tonic neuromuscular activity also plays an important role in postural control and locomotion (4–7). Sustained fatigue-resistant muscle activity, referred to as tonus and more specifically postural tone, counteracts gravity and keeps the numerous body segments appropriately aligned in order to maintain upright, stable posture (8). The importance of tonic drive for healthy motor functioning has long been recognized in clinical practice, where tests of muscle tone are considered a highly sensitive sign for measuring central nervous system health. In many, neuropathologies, such as stroke, multiple sclerosis, and Parkinson's Disease (PD), muscle tone is used to assess health status and guide treatment (9–11). In fact, a cardinal symptom of PD is tonic dysfunction, which manifests as rigidity or hypertonicity (12, 13). This type of tonic dysfunction contributes to disabilities affecting balance, locomotion, and increased fall-risk (14–16). Changes in muscle tone and to the processes that control tonic level are present even in healthy aging, which can increase fall risk (17, 18). Falls in the elderly, whether healthy or neurologically impaired, are a leading cause of injury-related death and non-fatal hospitalization, with direct costs related to falls in older adults exceeding $30 billion per year in the US (19).

Postural control has been described as a sustained contraction produced by a descending tonic drive from tonigenic sub-cortical structures (20). A number of brainstem regions are thought to be involved in these tonic neuromuscular processes, which include mesopontine regions that have connectivity to the spinal cord, the basal ganglia, cerebellum, and cortical sensorimotor areas such as M1 and the supplementary motor area (7, 21). Basal ganglia-brainstem-spinal pathways have been identified in the regulation of postural tone and locomotion (6, 7, 22). Specifically, pathways from the substantia nigra pars reticulata (SNpr) to the pedunculopontine tegmental nucleus (PPTN) play an important role in regulating postural tone (7). The mesencephalic locomotor region (MLR) is also closely linked to SNpr and is important for preparing the postural system to begin locomotion (7). While much of this work was performed on animal models, there is also evidence from human case studies and surgical intervention. For example, a lesion in the posterolateral mesopontine tegmentum can also affect tone; the typical decrease in muscle tone (i.e., atonia) during REM sleep does not occur following damage to this region (23). A lesion to the more medial part of the pedunculopontine complex impairs the ability to stand and walk (24). The PPTN has also been used as a site for deep brain stimulation (DBS) surgery in PD patients (25, 26), which has shown positive impact on postural tone and gait (27). Identifying these tonogenic structures has shed some light on their involvement in postural control, but the importance of these subcortical processes is under-appreciated.

Systematically studying how tonic drive influences postural control in humans can be challenging because mechanical perturbations to the system must be long-lasting and behavioral measures must be sensitive enough to differentiate among short-term phasic responses (e.g., stretch reflexes), volitional interference due to conscious awareness of change, and the long-term tonic adaptations that one is interested in. One means of investigating this has been accomplished by examining the muscle set-points. A muscle set-point can be thought of as the postural tone of flexor and extensor muscle activity about a joint used to maintain a body part in a position, e.g., postural maintenance. While control of muscle set-points can show segmental autonomy, it is thought that in an intact system this is ultimately under the control of central command (8). Changes in set-point can be seen in lean after-effects, which have provided a useful behavioral technique for investigating tonic postural control. A lean after-effect is seen when normal upright stance, which typically aligns with gravity and is orthogonal to a horizontal surface, is altered (3, 28). Use of the support surface as a somatosensory reference for orientation is seen by alignment of the body to the surface when a surface is slowly tilted (2, 29, 30). However, this reference changes if it is altered for an extended period of time, for example, by standing on a stable, tilted surface or a dynamically tilted surface for a few minutes. The surface-to-body angular relation after a surface is tilted toes-up will be maintained in a dorsiflexed position when the surface is returned to horizontal, thus resulting in forward lean. This after-effect can also be observed on a sway-referenced (SR) surface, whereby the individual adopts a surface tilts toes up posture during the post-adaptation period (3). These lean after-effects and surface-tilt after-effects together fall under the umbrella term of postural after-effects. In both cases, they presumably represent a recalibration in postural reference frame with a new tonic set-point of muscle activity. Evidence that this after-effect is centrally driven is suggested by the fact that global postural variables, not simply local muscle group set-point, are altered (31). If centrally driven, this raises the question of how central disease or pathology might affect changes in set-point.

The goal of this study is to determine if tonic processes underlying postural control change across the lifespan or with disease by investigating postural after-effects in healthy young adults, healthy older adults, and adults with PD. The presence, magnitude, and time course of postural after-effects are assumed to be an indicator of some of the variables that drive tonic neuromuscular processing. Specifically, postural after-effects represent an ability to adapt to long-lasting sensory inputs, i.e., tonic input, which help define a set-point from which phasic activity originates. In other words, the starting point for a phasic movement is defined by an "initial condition" which is set by tonic control. The importance of investigating changes in postural adaptation is that dysfunction in tonic control likely plays a significant role in motor, postural, and gait deficits, which both healthy older (32) and to a greater degree PD populations must contend (15, 16, 33). As previous studies have shown, it may not simply be the presence of hypertonicity that causes postural instability and gait dyscoordination (34, 35), but rather how adaptable the motor system is when changing from one state to another (36). Greater understanding of these relationships could, in turn, lead to new and innovative treatment approaches

that improve the standard of living for our ever-growing aging population.

MATERIALS AND METHODS

Participants

Nineteen healthy, young participants (20–32 years old, 9 M), 13 healthy older adults (50–74 years old, 8 M), who were age and gender-matched to the PD participants, and 9 individuals with PD (53–70 years old, 6 M) participated in this study. All healthy participants had no known neuromuscular impairment, and no history of PD, neurological disease, or sensorimotor deficits. All PD participants were classified as Hoehn and Yahr 2–3 and were responsive to anti-Parkinson drug treatment as verified by the referring neurologists. Parkinson's Disease (PD) participants were tested ON medication. Participants were included only if able to stand unassisted for at least 10 min periods of time and had normal ankle range of motion (Dorsiflexion $= 12^{\circ}$, Plantarflexion $= 55^{\circ}$). The protocol was approved by the local IRB at Temple University, and all participants gave written, informed consent before participating in this study. Investigators adhered to the policies regarding protection of human participants as prescribed by the Helsinki Accords.

Protocols

All data was collected using a 3-degree of freedom (DOF) posture platform (Neurocom Inc.) with integrated dual triaxial AMTI (Watertown, MA) force plates. All conditions required participants to stand in a relaxed stable, upright posture with arms hanging comfortably to the sides with eyes-closed. In the traditional quiet standing (QS) conditions, the surface was fixed in place to provide a stable support surface during which center-of-pressure (COP) time series data was collected. During surface sway-referencing (SR) trials, the servo-driven surface has a pre-programmed capability to allow the surface to tilt with reference to changes in the COP. To ensure proper function of the surface SR, the participant's lateral malleoli were aligned with the rotation axis of the tiltable surface at the center of the force plate. Thus, the zero point for COP was aligned with the participant's ankle with positive COP values representing points anterior to the rotation/ankle axis.

The order of tests for participants first involved baseline testing in two 120 s conditions: Eyes-closed on a firm surface, and eyes-closed on a SR surface, i.e., forward sway causes the surface to tilt toes-down in an amount proportional to the forward COP shift, and vice versa. Participants were then tested in four conditions each lasting 240 s. The four counter-balanced conditions were as follows: (1) toes-up static-ramp for 120 s followed by standing on a SR surface for 120 s, (2) toes-up sine-ramp ($7^{\circ} \pm 3^{\circ} * \sin \frac{\pi t}{2}$ at 0.25 Hz) for 120 s followed by standing on a SR surface for 120 s, (3) toes-up sine-ramp ($7^{\circ} \pm 3^{\circ} * \sin \frac{\pi t}{2}$ at 0.25 Hz) for 120 s followed by quiet-stance on a static flat surface for 120 s, (4) toes-up static-ramp (7°) for 120 s followed by quiet-stance on a static flat surface for 120 s (**Figure 1**). All conditions were tested eyes-closed, shoes and socks removed, and a harness secured to the ceiling was used to prevent falls without restricting movement.

Data Collection and Analysis

Time series data was collected at 200 Hz sampling rate for all dependent variables (DV). In the static, flat surface conditions, only COP (cm) was collected since surface tilt equals zero at all times. In SR trials, COP and surface tilt (degrees) were collected. Only anterior-posterior (AP) COP was analyzed since all perturbations were along the AP axis. AP COP was measured relative to the axis of surface rotation. During SR trials, the surface is driven in response to the movement of the participant's COP with a gain of one by converting COP linear movement into a surface tilt angle normalized relative to the participant's height. Therefore, the COP data in the AP direction closely matches the surface orientation data in degrees, however, the zero-point of the surface orientation is able to change with a net shift in center of mass, while the phasic patterns of the COP and surface orientation remain similar with minimal low-pass filtering and negligible phase lag. Because data for all subjects in all four conditions were not available, either due to subject fatigue (in PD group), equipment failure, or data loss, the data from matching post-adaptation conditions (SR: Cond 1 pooled with Cond 2; Static flat surface: Cond 3 pooled with Cond 4) were pooled after it was determined that they did not differ significantly ($p > 0.34$, n.s.). All subsequent analyses were performed on pooled data.

Postural after-effects were compared using a 3 × 3 (time-by-group) mixed model repeated-measures analysis of variance (rmANOVA). The three time periods were baseline (an average of first and last quartile of the baseline time series), first quartile (Q1) of the 120 s period after the ramp adaptation, and last quartile (Q4) of the 120 s period after the ramp adaptation (3). When significant differences were found in the 3 × 3 rmANOVA, subsequent 2 × 3 and univariate rmANOVA and planned comparisons were tested to determine where these differences were. Specifically, following prolonged stance on a toes-up tilted surface during the adaptation phase (i.e., the first 120 s), the surface was returned to its flat position and the time series data was measured during the post-adaptation phase. This second 120 s was divided into four quartiles. The amplitude of lean after-effects was analyzed by comparing the average AP COP position between baseline and Q1 using a 2 × 3 rmANOVA. The decay of lean after-effects was analyzed by comparing the average AP COP position at Q1–Q4 using a 2 × 3 rmANOVA. To determine if the postural after-effect completely decayed after 120 s, Q4 was compared to baseline. In the SR conditions, the analysis of the amplitude and decay of surface-tilt after-effects was performed in a similar manner, the only difference being that average surface tilt angle at baseline, Q1, and Q4 was used. Significance was set at $p \leq 0.05$.

RESULTS

Baseline

Baseline AP COP was significantly different across groups [$F_{(2,37)} = 4.92$, $p = 0.013$, $\eta^2 = 0.21$]. PD participants showed a significantly greater anterior position of the AP COP (7.27 ± 0.59 cm), relative to healthy age-matched controls (5.79 ± 0.46 cm). The young adult group showed the smallest anterior distance between the center of the force plate and AP COP (5.06

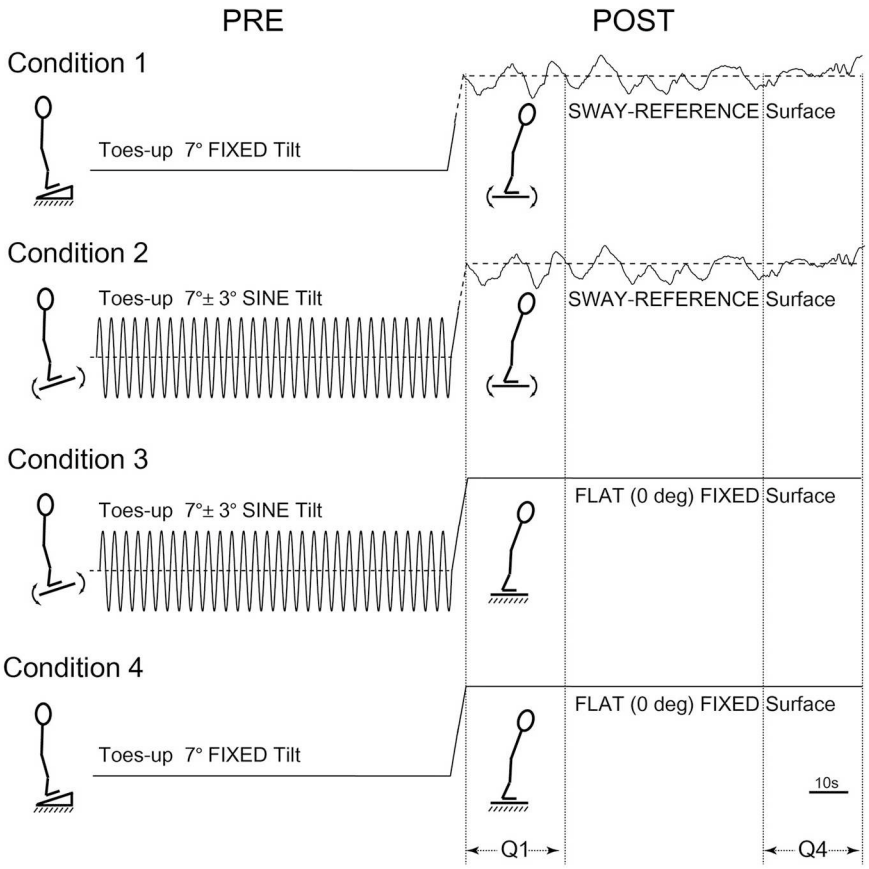


FIGURE 1 | Postural test conditions. Condition 1: toes-up static-ramp for 120 s followed by standing on a sway-referenced surface for 120 s. Condition 2: toes-up sine-ramp ($7^\circ \pm 3^\circ * \sin \frac{\pi t}{2}$ at 0.25 Hz) for 120 s followed by standing on a sway-referenced surface for 120 s. Condition 3: toes-up sine-ramp ($7^\circ \pm 3^\circ * \sin \frac{\pi t}{2}$ at 0.25 Hz) for 120 s followed by quiet-stance on a static flat surface for 120 s. Condition 4: toes-up static-ramp (7°) for 120 s followed by quiet-stance on a static flat surface (120 s).

± 0.38 cm), but was not different from the healthy older baseline COP ($p = 0.23$, n.s.). The average surface tilt during baseline SR measures showed no difference between groups [$F_{(2,37)} = 0.93$, $p = 0.40$, n.s.).

After-Effects on a Fixed Surface

The 3 × 3 rmANOVA showed significant main effects [$F_{(2,74)} = 24.4$, $p < 0.00001$, $\eta^2 = 0.40$] and a significant time-by-group interaction [$F_{(4,74)} = 3.35$, $p = 0.014$, $\eta^2 = 0.15$] (**Figure 2**). Looking specifically at the AP COP shift between baseline and Q1 (i.e., lean after-effect) while standing on a fixed surface after the 120 s of ramp tilt adaptation, a significant effect was found [$F_{(1,37)} = 47.4$, $p < 0.00001$, $\eta^2 = 0.56$]. A significant time-by-group interaction was found [$F_{(2,37)} = 4.19$, $p = 0.023$, $\eta^2 = 0.18$]. Planned comparisons revealed the young ($p < 0.00001$) and old ($p < 0.0003$) groups both had significant lean after-effects. While the PD group did not show a significant difference using an analysis of variance [$F_{(1,7)} = 5.02$, $p = 0.06$, n.s.], 7 out of the 8 PD participants (Exact binomial, $p = 0.031$) showed a forward shift in the AP COP, which is in the same direction as the healthy cohorts. The amplitude of lean after-effects of the older adult group were larger on average than the in PD group, but did not reach significance [$F_{(1,19)} = 4.02$, $p = 0.059$, $\eta^2 = 0.17$, n.s.]. However, the healthy young adult group showed a significantly larger lean after-effect than the PD group [$F_{(1,25)} = 7.38$, $p = 0.012$, $\eta^2 = 0.23$]. No difference was found between the younger and older healthy adult groups [$F_{(1,30)} = 1.64$, $p > 0.10$, n.s.].

The decay of the lean after-effect when standing on a fixed surface was analyzed by comparing AP COP at Q1 vs. Q4 (**Figure 2**). This revealed that the after-effects significantly decayed back toward the baseline over the course of 120 s post-adaptation period [$F_{(1,37)} = 33.8$, $p < 0.00001$, $\eta^2 = 0.48$]. Planned comparisons by group revealed the healthy younger ($p < 0.00001$) and older ($p = 0.0024$) adult groups both showed significant decay back toward baseline. However, the PD group did not decay during the post-adaptation period ($p = 0.50$, n.s.), despite having shown a small, albeit non-significant lean after-effect. These group differences were further substantiated by a significant time-by-group interaction [$F_{(2,37)} = 7.54$, $p < 0.002$, $\eta^2 = 0.29$]. When comparing the change from Q1 to Q4, the PD group did not change significantly, but the older healthy adult group did when compared to the PD group [$F_{(1,19)} = 4.77$, $p = 0.042$, $\eta^2 = 0.20$], and the younger group decayed even more than the older group [$F_{(1,30)} = 5.25$, $p = 0.029$, η^2

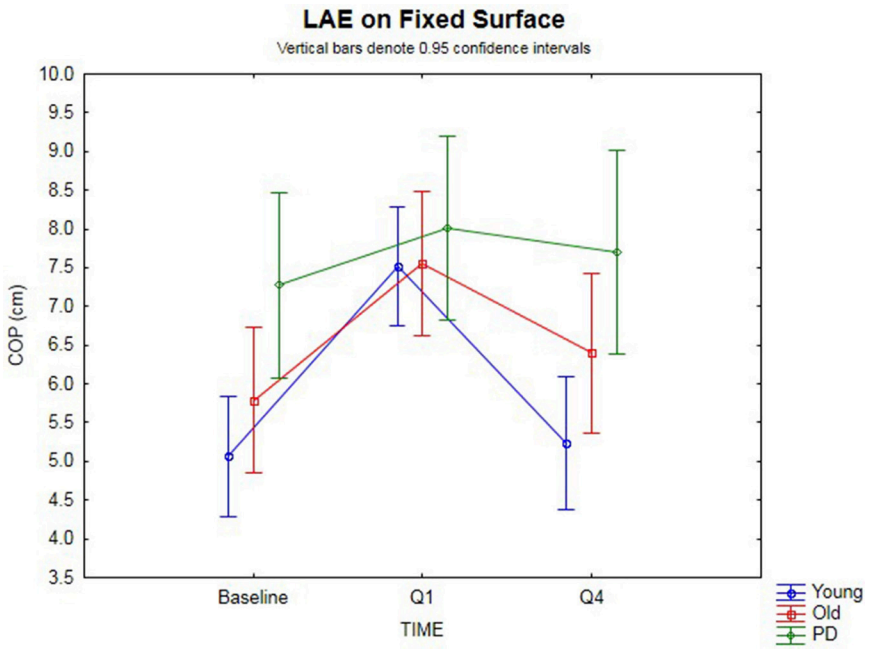


FIGURE 2 | Fixed surface COP during QS. Lean after-effects as measured by the AP COP position on a fixed surface at baseline, then following ramp tilt adaptation at Q1 and Q4. Q1 represents the first 30 s of post-tilt adaptation, which starts immediately after the 120 s of ramp tilt adaptation. Q4 is the last 30 s of the post-tilt adaptation period. The three lines represent each group (Young, Old, PD ON-meds). A positive value represents a forward shift in COP. The post-tilt adaptation values are the average of two trials—QS following fixed ramp tilt adaptation, QS following sine ramp tilt adaptation.

= 0.15], all suggesting differences in adaptation. There was no difference between baseline and Q4 for all groups [$F_{(1,37)}$ = 2.07, p= 0.15, n.s.] suggesting a return to baseline COP had occurred.

After-Effects on a Sway-Referenced Surface

The 3 × 3 rmANOVA showed significant main effects across time [$F_{(2,72)}$ = 37.4, p < 0.00001, η^2 = 0.51] and a significant time-by-group interaction [$F_{(4,72)}$ =4.27, p< 0.004, η^2 = 0.19] (**Figure 3**). Looking specifically at the initial surface-tilt after-effect in Q1, a significant toes-up change in surface-tilt between baseline and Q1 was observed while standing on a SR surface after the 120 s of ramp tilt adaptation [$F_{(1,36)}$ = 21.8, p = 0.00004, η^2 = 0.38]. Planned comparisons revealed that the healthy younger (p < 0.00001) and older (p = 0.008) adult groups both had significant postural after-effects in Q1 relative to baseline, but the PD group did not (p = 0.44, n.s.). The size of these after-effects were significantly different as revealed by a time-by-group interaction [$F_{(2,36)}$ = 3.37, p = 0.046, η^2 = 0.16]. Specifically, the tilt surface amplitude in the older adult group did not differ significantly from the younger adult [$F_{(1,30)}$ =2.62, p = 0.12, n.s.] or PD [$F_{(1,18)}$ = 1.58, p = 0.23, n.s.] groups at Q1 during the post-adaptation period, but the younger adult group showed a significantly larger toes-up surface tilt than the PD group [$F_{(1,24)}$ =4.98, p = 0.035, η^2 = 0.17].

The decay of the postural after-effects when standing on a SR surface was analyzed by comparing the angle of SR surface tilt at Q1 vs. Q4 (**Figure 3**). Unlike in the fixed surface post-adaptation conditions, the after-effects in the SR conditions grew significantly over the course of 120 s post-adaptation period [$F_{(1,36)}$ = 47.1, p < 0.00001, η^2 = 0.57]. In other words, the surface tilt after-effects did not decay during post-adaptation period, but instead showed a significant increase away from baseline, as has been shown before in healthy young adults (3). Planned comparisons revealed that all three groups, young (p < 0.00001), old (p < 0.0005), and PD (p < 0.01) showed a significant increase in toes-up surface tilt from Q1 to Q4 during 120 s post-adaptation period, however, the size of these after-effects were different across groups as revealed by the significant group-by-time interactions [$F_{(2,36)}$ = 3.27, p < 0.05, η^2 = 0.15]. Planned comparisons revealed that young adults showed a larger increase in toes-up surface tilt from Q1 to Q4 relative to the older adults [$F_{(1,30)}$ = 5.24, p = 0.029, η^2 = 0.15], but there was no difference between the older adult and PD groups for this variable [$F_{(1,18)}$ = 0.22, p = 0.64, n.s.].

DISCUSSION

Differences in postural adaptation were found between young and old age groups and between healthy and PD groups. These findings provide evidence that changes in postural adaptation exist not only when changes in tonic neuromuscular processing due to PD are present, but also due to healthy aging. The tonic differences were seen in both the initial adaptation resulting in lean after-effects, and in the decay pattern following the removal of the tonic tilt input. Significant postural after-effects were seen in all conditions for the healthy groups, regardless of the ramp

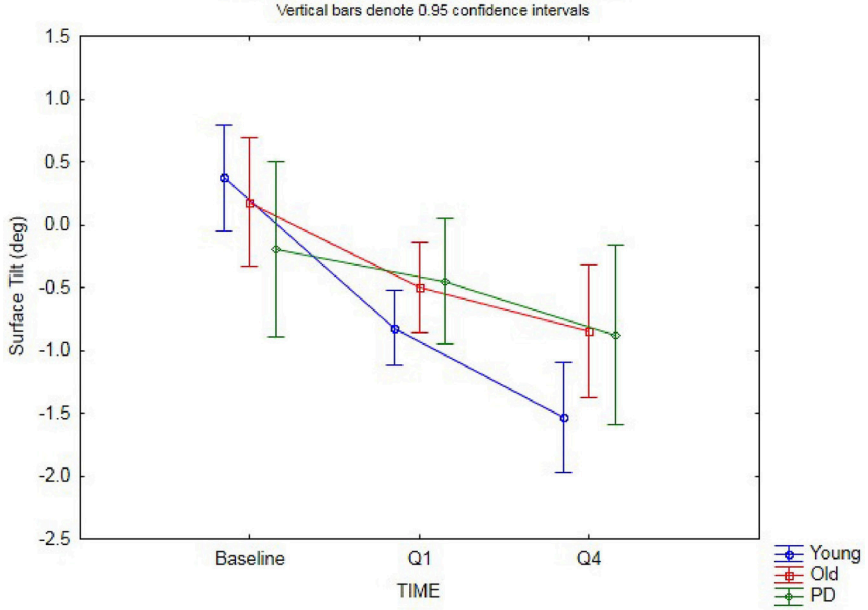


FIGURE 3 | Sway-reference surface tilt. Postural after-effects as measured by the degree of average surface tilt on a sway-referenced surface at baseline, then following ramp tilt adaptation at Q1 and Q4. Q1 represents the first 30 s of post-tilt adaptation, which starts immediately after the 120 s of ramp tilt adaptation. Q4 is the last 30 s of the post-tilt adaptation period. The three lines represent each group (Young, Old, PD ON-meds). A negative value represents a toes-up (dorsiflexed) surface tilt. The post-tilt adaptation values are the average of two trials—SR following fixed ramp tilt adaptation, SR following sine ramp tilt adaptation.

adaptation (fixed or sine ramp) or the post-adaptation condition (fixed or sway-referenced surface). However, when comparing the healthy older adults to the younger adults, the older adults showed a significantly different decay in their after-effects. When looking at the PD results, this group showed only a small, non-significant change in AP COP on average, and when tested on the SR surface, they also did not show a significant increase in surface tilt between the baseline and the 1st quartile, as was observed in the healthy groups. The only significant postural after-effect in the PD group was an increase in surface tilt between the 1st and 4th quartiles. Together these PD group results suggest that the tonic adaptability is not completely absent but it occurs to a much lesser degree in PD. These findings are discussed further in the following sections.

Postural After-Effects in Healthy Adults Affected by Age

Postural after-effects were present in all the healthy participants, which far exceeds the 50% prevalence reported when only a fixed ramp adaptation and fixed flat surface post-adaptation was employed in previous studies (28); their approach only allowed for lean after-effects, but did not investigate surface-tilt after-effects. By employing the techniques described in an earlier study (3), it was established that postural after-effects can be induced in most individuals. Using an experimental technique able to induce postural after-effects with such high prevalence was important when comparing between populations, since this reduced the need for extremely large sample sizes, and decreased the risk of being under-powered and missing effects (Type 2 errors). The use of a SR surface during the post-adaptation to measure postural after-effects addresses some of the limitations of the normal test of lean after-effects that had been performed on a fixed surface. For a lean after-effect to appear on a fixed surface, this requires that the test participant moves out of alignment with the gravitational vertical, e.g., forward lean. Maintenance of normal upright posture is accomplished using sensory input from vision, vestibular, and somatosensory inputs. In an eyes-closed paradigm, an individual might detect that they are leaning, rather than standing straight upright, using proprioceptive input from the feet soles and ankles and graviceptive inputs from the otoliths and specific internal organs (1, 37). Therefore, an individual may resist the lean after-effect because they are aware of being misaligned with vertical or even sense that they are approaching their limits of stability and are at risk of falling. Unconsciously, automatic postural processes may also be responsible for tonic changes in the postural set-point, causing the lean after-effect to dissipate quickly or not appear at all. When using a SR surface during the post-adaptation period, muscle set-points in the various body segments can be adopted without significantly moving the center-of-mass toward the limits of stability. This may account for the much higher prevalence of postural after-effects in the current populations.

Despite the fact that both the healthy older and younger adults all showed postural after-effects, when the amplitude and temporal dynamics of this adaptation process was analyzed, differences between age groups were found. At baseline, there were no significant differences in AP COP position or surface tilt

($p > 0.10$) that could account for a postural predisposition toward leaning. The younger adult group showed a faster return toward baseline COP in the fixed surface post-adaptation condition than the healthy older adults. This suggests that despite having a larger after-effect, they were able to efficiently use the reliable vestibular and somatosensory inputs to recalibrate their postural vertical relative to the fixed horizontal surface during the post-adaptation period. There was also a persistence of the surface-tilt after-effect on the sway-reference surface during post-adaptation period in younger adults that was greater than in the healthy older adults. This persistent and increasing postural after-effect can be seen as adaptive because the SR surface is not a reliable reference for maintaining upright posture and the vestibular vertical stays aligned with gravity throughout the postural after-effect in the SR condition. Therefore, the postural system maintains its last reliable set-point, i.e., dorsiflexed ankle. While the underlying physiological mechanism for this difference was not examined in the age-dissociated populations, one possible contribution to this difference in tonic behavior could be due to age-related loss of dopamine in healthy individuals. Even in older adults without PD, dopamine loss occurs at a rate of 7% per decade (38–40). This loss has been correlated with motor and postural control impairments (17, 41). Imaging studies suggest that this decrease in dopamine is related to the loss of dorsal SN cells in healthy older adults (42). The current evidence may provide further evidence of a behavioral link between the dopaminergic system, tonic neuromuscular processes, and changes in postural and motor control in a healthy aging population. Furthermore, when dopamine loss reaches pathological levels such as in PD, the effects of these tonic differences become even more pronounced, as discussed below.

Postural-After Effects in Parkinson's Disease

In addition to the evidence that aging alters postural adaptation, this study suggests basal ganglia disease does as well. The size and decay of postural after-effects in adults with PD were significantly different from healthy adults. Specifically, the size of after-effects was smaller than the healthy older and younger adults. And unlike in the healthy adults who showed decay of lean after-effects back to baseline when standing on the fixed surface, the small lean after-effects that the PD group showed did not decay back to baseline within the 120 s post-adaptation period. A similar finding on the SR surface occurred in that the PD's small toes-up surface-tilt after-effects did not change during the post-adaptation period. This suggests that PD's show less postural adaptation and it takes longer to change the posturally-relevant tonic muscle set-point than in healthy adults.

Difficulty in regulating appropriate levels of background postural tone has been shown before by using fast, external perturbations (36), but the current study shows that this difficulty extends far beyond phasic response time-scales. The conditions tested here were on the order of minutes and while healthy adults were able to adapt to new tonic neuromuscular inputs within tens of seconds, the PD group in some cases were unable to adapt for periods 10 times longer than that. Although, it is well-understood that phasic processes reliant on short latency, reflexive pathways and late occurring automatic postural responses affect posture and gait in PD (43, 44), the current study provides new evidence that tonic neuromuscular processing also plays an important role in postural adaptation. The background muscle tone present during postural maintenance is thought to provide a sustained muscle activity needed to counteract gravity and keep the numerous body segments appropriately aligned (1). The current study adds to the growing body of evidence that deficits in postural tonic control, especially in the axial musculature (15, 16) can play an important role in balance deficits in PD.

The dopamine system's role in postural tone and motor control in healthy and PD populations is known (7, 36, 44) and there is evidence that dopamine treatment can help posture and gait control in PD (45). However, there are numerous studies showing that these behaviors can be resistant to dopamine therapy even though other symptoms abate (44, 46). The origin of such prolonged tonic muscle contraction is thought to come from sub-cortical and brainstem structures (20), which are tightly connected to nigrostriatal regions. Among these structures are mesopontine tegmental regions with descending and ascending connectivity (21). The involvement of these neural regions in posture and gait has led researchers to use the PPTN as a site for implanting DBS electrodes in PD patients (25, 26). Although this has had mixed success [(47, 48)], at least a few studies have shown reduction in axial tone and improvement in the symptoms of Postural Instability and Gait Disturbance (PIGD) (27). While results from the current study provide some additional insight into how changes in function of the basal ganglia and associated nuclei can affect postural behavior, its likely that tonic dysfunction observed in PD is the result of a widely distributed cortical/subcortical network (49). Further evidence is needed to determine how effective targeted treatment of only the dopamine system may be, since standard dopaminergic pharmacological treatment of PD has in some cases been shown to have little effect on axial tone or symptoms related to posture and gait (15, 16, 44, 46). Studies are underway, which involve testing PD both ON and OFF medication in the current experimental procedure, which may provide additional insight into this question.

A number of alternative explanations were considered, all of which could not be completely ruled out. These findings presuppose that all participants had no limitation in their ankle joint, which was verified by screening all participants for normal ankle ROM. All participants were able to maintain dorsiflexion by standing un-aided on the toes-up tilted surface for the full 120 s adaptation period. In the sine-ramp tilted condition, this required at least 10° dorsiflexion, which is almost an order of magnitude greater than the size of the after-effect. Another explanation that can be ruled out is the forward lean that the PD showed at baseline. A symptom of PD is excessive kyphosis, marked by a forward stooped-posture, and there is some evidence (50), albeit mixed (51), that this inherent anterior flexion contributes to deficits in automatic postural stabilization. The presence of a significant anterior baseline shift in the PD group may have limited how large the lean after-effect could shift forward before reaching the limits of stability, however, the decay timeline still differed from the healthy group. Furthermore, during the post-adaptation period, the lean after-effect failed to return as quickly as the healthy adults. Additionally, in the baseline SR condition, there was

not a difference between groups. Another factor that could contribute to group differences in the after-effects is the presence of proprioceptive deficits in PD. These proprioceptive deficits may affect the ability to correctly orient stance relative to vertical and/or the surface (52–54). They may also be reflective of more general sensorimotor integration problem, which when treated can improve balance in PD (55). Finally, the role of bradykinesia must be considered since bradykinetic-rigidity dominant PD has been identified as one of the four subtypes of PD (56, 57). Bradykinesia is a slowness of movement often observable during phasic activity such as reaching, manipulation, or stepping. Bradykinesia during slow tonic activity is more difficult to measure. Because the underlying causes of bradykinesia and rigidity are not well-understood, one can speculate whether bradykinesia falls along a spectrum from akinesia to ballismus that is inversely related to hyper- and hypotonicity. Thus, while the current study did focus on very slow movements (>60 s), the role of bradykinesia could not be completely ruled out as a contributing factor.

CONCLUSION

In summary, (1) tonic postural after-effects were observed in all groups, however there were differences in amplitude and temporal properties between groups, (2) postural after-effects decayed to baseline when post-tilt surface was stable but were retained and even grew larger post-adaptation in the SR surface conditions in all groups, (3) PD participants showed less adaptation to surface changes than healthy age-matched and younger adults. Differences in size and decay of after-effects between young, old and PD groups suggest tonic neuromuscular processes play a role in how adaptable postural control is to changing surface conditions and this is affected by function of basal ganglia and associated nuclei as observed in healthy aging and neuropathology. Advancing our understanding of how posture and gait are coupled through phasic and tonic processes is a necessary step for improving rehabilitation of PD (58) and reducing fall risk in the aging population.

ETHICS STATEMENT

Temple University Institutional Review Board Informed written consent, Protocol #12358. All participants with Parkinson's Disease were informed that this research would involve no direct benefit to them, and they could choose to not participate or stop the experiment at any time, which would have no negative impact on them.

AUTHOR CONTRIBUTIONS

WW conceived and designed study, collected data, performed statistical analysis, and wrote the manuscript.

FUNDING

Publication of this article was funded in part by the Temple University Libraries Open Access Publishing Fund. This study was supported in part by pilot funding from the Veterans Administration Parkinson's Disease Research, Education and Clinical Center (PADRECC) in Philadelphia.

REFERENCES

1. Massion J. Postural control system. *Curr Opin Neurobiol*. (1994) 4:877–87. doi: 10.1016/0959-4388(94)90137-6
2. Wright WG, Horak FB. Interaction of posture and conscious perception of gravitational vertical and surface horizontal. *Exp Brain Res*. (2007) 182:321–32. doi: 10.1007/s00221-007-0990-4
3. Wright WG. Tonic postural lean after-effects influenced by support surface stability and dynamics. *Hum Mov Sci*. (2011) 30:238–48. doi: 10.1016/j.humov.2010.05.006
4. Gurfinkel V, Cacciatore TW, Cordo P, Horak F, Nutt J, Skoss R. Postural muscle tone in the body axis of healthy humans. *J Neurophysiol*. (2006) 96:2678–87. doi: 10.1152/jn.00406.2006
5. Magnus R. Cameron prize lectures on some results of studies in the physiology of posture. *Lancet* (1926) 208:531–6. doi: 10.1016/S0140-6736(01)27826-X
6. Sherrington CS. Postural activity of muscle and nerve. *Brain* (1915) 38:191–234. doi: 10.1093/brain/38.3.191
7. Takakusaki K, Tomita N, Yano M. Substrates for normal gait and pathophysiology of gait disturbances with respect to the basal ganglia dysfunction. *J Neurol*. (2008) 255 (Suppl. 4):19–29. doi: 10.1007/s00415-008-4004-7
8. Ivanenko Y, Gurfinkel VS. Human postural control. *Front Neurosci*. (2018) 12:171. doi: 10.3389/fnins.2018.00171
9. Fahn S, Elton RL. UPDRS Development Committee. Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Calne D, Goldstein M, eds. *Recent Developments in Parkinson's Disease*. Florham Park, NJ: Macmillan Healthcare Information (1987). p. 153–63.
10. Sheean G, McGuire JR. Spastic hypertonia and movement disorders: pathophysiology, clinical presentation, and quantification. *PM R* (2009) 1:827–33. doi: 10.1016/j.pmrj.2009.08.002
11. Marciniak C. Poststroke hypertonicity: upper limb assessment and treatment. *Top Stroke Rehabil*. (2011) 18:179–94. doi: 10.1310/tsr1803-179
12. Delwaide PJ. Parkinsonian rigidity. *Funct Neurol*. (2001) 16:147–56.
13. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology* (1967) 17:427–42. doi: 10.1212/WNL.17.5.427
14. Bartolić A, Pirtosek Z, Rozman J, Ribaric S. Postural stability of Parkinson's disease patients is improved by decreasing rigidity. *Eur J Neurol*. (2005) 12:156–9. doi: 10.1111/j.1468-1331.2004.00942.x
15. Wright WG, Gurfinkel VS, Nutt JG, Horak FB, Cordo PJ. Axial hypertonicity in Parkinson's disease: direct measurements of trunk and hip torque. *Exp Neurol*. (2007) 208:38–46. doi: 10.1016/j.expneurol.2007.07.002
16. Franzén E, Paquette C, Gurfinkel VS, Cordo PJ, Nutt JG, Horak FB. Reduced performance in balance, walking and turning tasks is associated with increased neck tone in Parkinson's disease. *Exp Neurol*. (2009) 219:430–8. doi: 10.1016/j.expneurol.2009.06.013
17. Cham R, Perera S, Studenski SA, Bohnen NI. Striatal dopamine denervation and sensory integration for balance in middle-aged and older adults. *Gait Posture* (2007) 26:516–25. doi: 10.1016/j.gaitpost.2006.11.204
18. Worapanwisit T, Prabpai S, Rosenberg E. Correlates of falls among community-dwelling elderly in Thailand. *J Aging Res*. (2018) 2018:8546085. doi: 10.1155/2018/8546085
19. Centers for Disease Control. (2018). Available online at: https://www.cdc.gov/homeandrecreationalsafety/falls/fallcost.html (Accessed May 10, 2018).
20. Gurfinkel VS, Levik Iu S, Lebedev MA. [Immediate and remote postactivation effects in the human motor system]. *Neirofiziologiia*. (1989) 21:343–51.

21. Aravamuthan BR, Stein JF, Aziz TZ. The anatomy and localization of the pedunculopontine nucleus determined using probabilistic diffusion tractography. *Br J Neurosurg*. (2008) 22 (Suppl. 1):S25–32. doi: 10.1080/02688690802448251
22. Mori S, Kawahara K, Sakamoto T, Aoki M, Tomiyama T. Setting and resetting of level of postural muscle tone in decerebrate cat by stimulation of brain stem. *J Neurophysiol*. (1982) 48:737–48. doi: 10.1152/jn.1982.48.3.737
23. Culebras A, Moore JT. Magnetic resonance findings in REM sleep behavior disorder. *Neurology* (1989) 39:1519–23. doi: 10.1212/WNL.39.11.1519
24. Masdeu JC, Alampur U, Cavaliere R, Tavoulareas G. Astasia and gait failure with damage of the pontomesencephalic locomotor region. *Ann Neurol*. (1994) 35:619–21. doi: 10.1002/ana.410350517
25. Caliandro P, Insola A, Scarnati E, Padua L, Russo G, Granieri E, et al. Effects of unilateral pedunculopontine stimulation on electromyographic activation patterns during gait in individual patients with Parkinson's disease. *J Neural Transm*. (2011) 118:1477–86. doi: 10.1007/s00702-011-0705-7
26. Thevathasan W, Coyne TJ, Hyam JA, Kerr G, Jenkinson N, Aziz TZ, et al. Pedunculopontine nucleus stimulation improves gait freezing in Parkinson disease. *Neurosurgery* (2011) 69:1248–53. doi: 10.1227/NEU.0b013e31822b6f71
27. Plaha P, Gill SS. Bilateral deep brain stimulation of the pedunculopontine nucleus for Parkinson's disease. *Neuroreport* (2005) 16:1883–7. doi: 10.1097/01.wnr.0000187637.20771.a0
28. Kluzik J, Horak FB, Peterka RJ. Differences in preferred reference frames for postural orientation shown by after-effects of stance on an inclined surface. *Exp Brain Res*. (2005) 162:474–89. doi: 10.1007/s00221-004-2124-6
29. Walsh EG. Standing man, slow rhythmic tilting, importance of vision. *Agressologie* (1973) 14:79–85.
30. Gurfinkel VS, Lipshits MI, Mori S, Popov KE. Postural reactions to the controlled sinusoidal displacement of the supporting platform. *Agressologie* (1975) 17:71–76.
31. Kluzik J, Peterka RJ, Horak FB. Adaptation of postural orientation to changes in surface inclination. *Exp Brain Res*. (2007) 178:1–17. doi: 10.1007/s00221-006-0715-0
32. Paquette C, Paquet N, Fung J. Aging affects coordination of rapid head motions with trunk and pelvis movements during standing and walking. *Gait Posture* (2006) 24:62–9. doi: 10.1016/j.gaitpost.2005.07.001
33. Schenkman M, Morey M, Kuchibhatla M. Spinal flexibility and balance control among community-dwelling adults with and without Parkinson's disease. *J Gerontol A Biol*. (2000) 55A:M441–5. doi: 10.1093/gerona/55.8.M441
34. Akram S, Frank JS, Jog M. Parkinson's disease and segmental coordination during turning: I. Standing turns. *Can J Neurol Sci*. (2013) 40:512–9. doi: 10.1017/S0317167100014591
35. Vaugoyeau M, Viallet F, Aurenty R, Assaiante C, Mesure S, Massion J. Axial rotation in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*. (2006) 77:815–21.
36. Horak FB, Frank J, Nutt J. Effects of dopamine on postural control in parkinsonian subjects: scaling, set, and tone. *J Neurophysiol*. (1996) 75:2380–96. doi: 10.1152/jn.1996.75.6.2380
37. Mittelstaedt H. A new solution to the problem of the subjective vertical. *Naturwissenschaften* (1983) 70:272–81. doi: 10.1007/BF00404833
38. Roth GS, Joseph JA. Cellular and molecular mechanisms of impaired dopaminergic function during aging. *Ann N Y Acad Sci*. (1994) 719:129–35. doi: 10.1111/j.1749-6632.1994.tb56824.x
39. Volkow ND, Ding YS, Fowler JS, Wang GJ, Logan J, Gatley SJ, et al. Dopamine transporters decrease with age. *J Nucl Med*. (1996) 7:554–9.
40. Kish SJ, Shannak K, Rajput A, Deck JH, Hornykiewicz O. Aging produces a specific pattern of striatal dopamine loss: implications for the etiology of idiopathic Parkinson's disease. *J Neurochem*. (1992) 58:642–8. doi: 10.1111/j.1471-4159.1992.tb09766.x
41. Volkow ND, Gur RC, Wang GJ, Fowler JS, Moberg PJ, Ding YS, et al. Association between decline in brain dopamine activity with age and cognitive and motor impairment in healthy individuals. *Am J Psychiatry* (1998) 155:344–9.
42. Vaillancourt DE, Spraker MB, Prodoehl J, Zhou XJ, Little DM. Effects of aging on the ventral and dorsal substantia nigra using diffusion tensor imaging. *Neurobiol Aging* (2012) 33:35–42. doi: 10.1016/j.neurobiolaging.2010.02.006
43. Rogers MW, Kennedy R, Palmer S, Pawar M, Reising M, Martinez KM, et al. Postural preparation prior to stepping in patients with Parkinson's disease. *J Neurophysiol*. (2011) 106:915–24. doi: 10.1152/jn.00005.2010
44. Bloem BR, Beckley DJ, van Dijk JG, Zwinderman AH, Remler MP, Roos RA. Influence of dopaminergic medication on automatic postural responses and balance impairment in Parkinson's disease. *Mov Disord*. (1996) 11:509–21. doi: 10.1002/mds.870110506
45. Bryant MS, Rintala DH, Hou JG, Charness AL, Fernandez AL, Collins RL, et al. Gait variability in Parkinson's disease: influence of walking speed and dopaminergic treatment. *Neurol Res*. (2011) 33:959–64. doi: 10.1179/1743132811Y.0000000044
46. Foreman KB, Wisted C, Addison O, Marcus RL, Lastayo PC, Dibble LE. Improved dynamic postural task performance without improvements in postural responses: the blessing and the curse of dopamine replacement. *Parkinsons Dis*. (2012) 2012:692150. doi: 10.1155/2012/692150
47. Ferraye MU, Debû B, Fraix V, Goetz L, Ardouin C, Yelnik J, et al. Effects of pedunculopontine nucleus area stimulation on gait disorders in Parkinson's disease. *Brain* (2010) 133(Pt 1):205–14. doi: 10.1093/brain/awp229
48. Ferraye MU, Debû B, Fraix V, Krack P, Charbardès S, Seigneuret E, et al. Subthalamic nucleus versus pedunculopontine nucleus stimulation in Parkinson disease: synergy or antagonism? *J Neural Transm*. (2011) 118, 1469–75. doi: 10.1007/s00702-011-0673-y
49. Baradaran N, Tan SN, Liu A, Ashoori A, Palmer SJ, Wang ZJ, et al. Parkinson's disease rigidity: relation to brain connectivity and motor performance. *Front Neurol*. 2013 4:67. doi: 10.3389/fneur.2013.00067
50. Bloem BR, Beckley DJ, van Dijk JG. Are automatic postural responses in patients with Parkinson's disease abnormal due to their stooped posture? *Exp Brain Res*. (1999) 124:481–8. doi: 10.1007/s002210050644
51. Jacobs JV, Dimitrova DM, Nutt JG, Horak FB. Can stooped posture explain multidirectional postural instability in patients with Parkinson's disease? *Exp Brain Res*. (2005) 166:78–88. doi: 10.1007/s00221-005-2346-2
52. Jacobs JV, Horak FB. Abnormal proprioceptive-motor integration contributes to hypometric postural responses of subjects with Parkinson's disease. *Neuroscience* (2006) 141:999–1009. doi: 10.1016/j.neuroscience.2006.04.014
53. Wright WG, Gurfinkel VS, King LA, Nutt JG, Cordo PJ, Horak FB. Axial kinesthesia is impaired in Parkinson's disease: effects of levodopa. *Exp Neurol*. (2010) 225:202–9. doi: 10.1016/j.expneurol.2010.06.016
54. Konczak J, Corcos DM, Horak F, Poizner H, Shapiro M, Tuite P, et al. Proprioception and motor control in Parkinson's disease. *J Mot Behav*. (2009) 41:543–52. doi: 10.3200/35-09-002
55. Fil-Balkan A, Salci Y, Keklicek H, Armutlu K, Aksoy S, Kayihan H, et al. Sensorimotor integration training in Parkinson's disease. *Neurosciences* (2018) 23:208–15. doi: 10.17712/nsj.2018.3.20180021
56. van Rooden SM, Visser M, Verbaan D, Marinus J, van Hilten JJ. Motor patterns in Parkinson's disease: a data-driven approach. *Mov Disord*. (2009) 24:1042–7. doi: 10.1002/mds.22512
57. Jankovic J, McDermott M, Carter J, Gauthier S, Goetz C, Golbe L, et al. Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. *Parkinson Study Group Neurol*. (1990) 40:1529–34. doi: 10.1212/WNL.40.10.1529
58. Mille ML, Creath RA, Prettyman MG, Johnson Hilliard M, Martinez KM, Mackinnon CD, et al. Posture and locomotion coupling: a target for rehabilitation interventions in persons with Parkinson's disease. *Parkinsons Dis*. (2012) 2012:754186. doi: 10.1155/2012/754186

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer CP and handling Editor declared their shared affiliation, at the time of the review.

frontiers in Neurology

ORIGINAL RESEARCH
published: 23 January 2019
doi: 10.3389/fneur.2018.01185

Balance Impairment in Radiation Induced Leukoencephalopathy Patients Is Coupled With Altered Visual Attention in Natural Tasks

Ioannis Bargiotas[1,2†], Albane Moreau[3†], Alienor Vienne[1], Flavie Bompaire[3,4], Marie Baruteau[3,4], Marie de Laage[3], Matéo Campos[3], Dimitri Psimaras[3,4], Nicolas Vayatis[2], Christophe Labourdette[2], Pierre-Paul Vidal[1,5], Damien Ricard[1,3,4,6] and Stéphane Buffat[1,4,7]*

[1] UMR 8257 Cognition and Action Group (CNRS, Service de Santé des Armées, Université Paris Descartes Paris Sorbonne Cité), Paris, France, [2] CMLA, ENS Cachan, CNRS, Université Paris-Saclay, Cachan, France, [3] Service de neurologie, Hôpital d'Instruction des Armées Percy, Service de Santé des Armées, Clamart, France, [4] OncoNeuroTox Center, Paris, France, [5] School of Automation, Hangzhou Dianzi University, Zhejiang, China, [6] Ecole du val de Grâce, Service de Santé des Armées, Paris, France, [7] Institut de Recherche Biomédicale des Armées, Brétigny-sur-Orge, France

OPEN ACCESS

Edited by:
Emily Keshner,
Temple University, United States

Reviewed by:
Anouk Lamontagne,
McGill University, Canada
Susan Lisa Morris,
Curtin University, Australia

***Correspondence:**
Stéphane Buffat
buffatstephane@gmail.com

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: 30 June 2018
Accepted: 21 December 2018
Published: 23 January 2019

Citation:
Bargiotas I, Moreau A, Vienne A, Bompaire F, Baruteau M, de Laage M, Campos M, Psimaras D, Vayatis N, Labourdette C, Vidal P-P, Ricard D and Buffat S (2019) Balance Impairment in Radiation Induced Leukoencephalopathy Patients Is Coupled With Altered Visual Attention in Natural Tasks. Front. Neurol. 9:1185. doi: 10.3389/fneur.2018.01185

Background: Recent studies have shown that alterations in executive function and attention lead to balance control disturbances. One way of exploring the allocation of attention is to record eye movements. Most experimental data come from a free viewing of static scenes but additional information can be leveraged by recording eye movements during natural tasks. Here, we aimed to provide evidence of a correlation between impaired visual alteration in natural tasks and postural control in patients suffering from Radiation-Induced Leukoencephalopathy (RIL).

Methods: The study subjects were nine healthy controls and 10 patients who were diagnosed with RIL at an early stage, with isolated dysexecutive syndrome without clinically detectable gait or posture impairment. We performed a balance evaluation and eye movement recording during an ecological task (reading a recipe while cooking). We calculated a postural score and oculomotor parameters already proposed in the literature. We performed a variable selection using an out-of-bag random permutation and a random forest regression algorithm to find: (i) if visual parameters can predict postural deficit and, (ii) which are the most important of them in this prediction. Results were validated using the leave-one-out cross-validation procedure.

Results: Postural scores indeed were found significantly lower in patients with RIL than in healthy controls. Visual parameters were found able to predict the postural score of RIL patients with normalized root mean square error (RMSE) of 0.16. The present analysis showed that horizontal and vertical eye movements, as well as the average duration of the saccades and fixations influenced significantly the prediction of the postural score in RIL patients. While two patients with very low MATTIS-Attention sub score showed the lowest postural scores, no statistically significant relationship was found between the two outcomes.

Conclusion: These results highlight the significant relationship between the severity of balance deficits and the visual characteristics in RIL patients. It seems that increased balance impairment is coupled with a reduced focusing capacity in ecological tasks. Balance and eye movement recordings during a natural task could be a useful aspect of multidimensional scoring of the dysexecutive syndrome.

Keywords: balance control, attention, ecological tasks, eye movements, machine learning, radiation-induced leukoencephalopathy, dysexecutive syndrome

INTRODUCTION

Radio-induced Leukoencephalopathy (RIL from now on) is a diffuse pathology of the white matter, consecutive to brain radiotherapy (RT) that was used to treat brain tumors. It is currently the most frequent and threatening delayed complication of cerebral RT. Symptoms may be manifested months or even decades after either cerebral RT alone or cerebral RT combined with chemotherapies (1). Cognitive impairment such as attention or memory deficits are the primary manifestations of the disease followed by balance and gait impairment and, at an advanced stage, urinary incontinence (1, 2). They have a significant impact on the patient's life, often permanently affecting his/her autonomy. Progressively, RIL patients may also suffer from severe dementia and total loss of autonomy (2–4). In the severe stage of RIL syndrome, patients may benefit from specific motor and cognitive re-education programs. Early diagnosis could be advantageous to prevent balance and gait disability.

Cognitive deficits are the earliest signs of RIL and affect mainly the attention and executive functions in a fronto-subcortical pattern with consequences on long-term memory and information processing (1, 3, 5–7). Anatomical white matter alterations after radiotherapy and/or chemotherapy have been recently correlated with cognitive impairment (8, 9). As dorsal periventricular tracts of the corona radiata -preferentially altered whatever the irradiation scheme- disrupt, patients progressively display balance and gait impairment resembling apraxia developing into dysexecutive syndrome (2). Chronic oculomotor dysfunction due to radiotherapy has been also previously reported. Clinical cases of patients with RIL reported deteriorated smooth pursuit eye movement with occasional saccadic intrusions as well as altered voluntary saccades. Still, the mechanisms remain unclear. Eye movement recordings have been reported as reflections of tenuous cognitive deficits before their clinical manifestation (10). Oculomotor and balance functions are also closely interwoven. Defective gaze behavior has been associated with impaired posture control in elderly (11) as well as in Parkinsonian patients (12) and it has been proposed as a biomarker of impaired posture (13). Several studies explored the interrelation between eye-movements and posture, since several brain regions (parietotemporal cortex, brainstem, superior colliculus, and cerebellum) are involved in both eye movements and postural control (14, 15).

Attention is necessary to both postural control (16) and eye movements (17, 18). The frontal cortex which is strongly connected to the parietal areas (19), may also play an important role in the interaction between visual and postural systems (20). Ecological tasks enable researchers to study the executive control of gaze and have been used in several contexts in recent years (14). In this context, it has been highlighted how prominent the role of attention and task demand toward explaining oculomotor behavior can be.

The newly proposed data mining techniques have been shown to have an added value to the exploitation of the available datasets, especially when multiple variables occur and the number of available individuals is limited. In this study, we explored posture and oculomotor control in patients recently diagnosed with RIL (using brain MRI), at the early stages of dysexecutive syndrome. At the process of the patients' neurological examination, no balance or gait impairment was detected. The present work, attempts to investigate (a) the level of association between early balance/gait and oculomotor deficits in RIL patients and (b) whether these balance/gait deficits reflect patients' cognition impairment. Early detection of balance, gait and oculomotor abnormalities in RIL patients could lead to new rehabilitation strategies and reassessment of current therapeutic interventions.

MATERIAL AND METHODS

Participants

Ten patients between 19 and 63 years old (average age 50.9 ± 15.9 years old; 4 women) and nine healthy participants between 27 and 54 years old (mean age 43.4 ± 10.2 years old; 3 women) participated in this study. The patients were enrolled in the Neurology department at Percy Hospital, Clamart (France), referred for RIL after a brain tumor treatment or metastatic prophylactic cerebral irradiation. Patients were examined by neurologists of our center, and inclusion criteria were: (i) Patients diagnosed with RIL according to MRI and clinical criteria as previously detailed (2). All patients had extensive FLAIR hyperintensities also in other lobes (at least one), different than this of the initial tumor location, as well as in corona radiata. (ii) with dysexecutive syndrome as defined by the GREFFEX criteria on the cognitive battery (2), (iii) with no complains of balance or gait impairment, (iv) normal visual acuity (corrected visual acuity with glasses was permitted) (v) having understood and agreed on the aim of the study and given informed consent. Exclusion criteria were (i) vestibular or proprioceptive dysfunctions according to the neurologist examination, (ii) balance impairment detected at the visual

TABLE 1 | Synthetic view of characteristics for the participants' sample.

Participant characteristics	Patients Mean (±*SD*)	Control subjects Mean (±*SD*)
Mean age (in years)	50.9 ±15.9	43.4 ±10.2
Women	4	3
Delay since brain irradiation (years)	13.6 ± 13	–
TYPE OF TUMOR		
Glioma	5	–
Medulloblastoma	2	–
Astrocytoma	1	–
Prophylactic brain irradiation	1	–
Primitive central nervous system lymphoma	1	–

Romberg test performed by the neurologist, (iii) ongoing psychiatric pathology, (iv) unable to understand and follow instructions.

The control subjects were all naïve regarding the aim of the study. They were recruited among the hospital personal. They had no complaint and no history of brain radiation, traumatic brain injury. **Table 1** presents a synthetic view of characteristics for the participants' sample.

Ethical Statement

This study was registered at ethical committee CPP Nord Ouest III with the number ID RCB: 2017-A01538-45. All participants (controls and patients) received written and oral information and gave written consent.

Ecological Tasks Assessment

The participants were instructed to follow a recipe to prepare a chocolate cake (See **Table A1**). During the entire task, a nurse accompanied both patients and control. The participants were equipped with a mobile eye tracking system (Tobii Pro Glasses 2, coupled with the Tobii pro lab analyzer edition software©, with a sampling frequency of 100 Hz). A calibration of the eye tracker was made at the beginning of the experiment. **Figure 1** provides a snapshot of the "reading recipe while cooking" task.

FIGURE 1 | Snapshot of a patient while reading the recipe. Note that the participant is wearing a Tobii glasses 2® eye tracking device and that there is a Clinical Research Nurse in the background. Written informed consent was obtained from the participant for the publication of this image.

Data Analysis

For the purpose of this study, we concentrated the oculomotor analysis on the time periods when the participants read the recipe. Algorithms and statistical analysis has been performed in Matlab platform R2018a.

Oculomotor Parameters

Most of the calculated parameters have been previously proposed as visual characteristic (21). The main idea of this feature engineering process is to base our analysis to already known parameters from the oculomotor scientific community to facilitate the reader's interpretation. However, in order to further exploit the richness of the eye movement in time, characteristics inspired by analytical studies with similar two-dimensional datasets (such as the center of mass coordinates changes in postural control research) (22, 23) were applied in the eye movement datasets. **Table 2** provides the names and the description/values (where needed) of the biomarkers that were initially included in the model.

Statistical Analysis

Postural differences between RIL patients and controls

All individuals completed the basic Romberg test (upright position, without shoes, feet placed in comfort for the patient but in the shoulders' projection area on the force platform, arms laying at the side, 25 s eyes open, 25 s closed eyes) on the Wii balance board® (WiiBB). WiiBB has non-constant frequency during the record and so the signal was resampled at 25 Hz using the SWARII algorithms previously described (24). For acclimatization purposes with WiiBB, a period of 35 s (minimum) has been kept before the open and closed-eyes recordings. Statokinesigrams were analyzed using the LAGMM (Local Analysis of Statokinesigrams using Gaussian Mixture Models) algorithm already proposed in (22) for statokinesigram datasets and it is available online (http://taureau.pppcmla.ens-cachan.fr/). Briefly, the proposed model creates a multidimensional profile for every individual using both open and closed eyes parameters and analyses their center of pressure (CoP) trajectories in "local parts" (time frames). The scores per individual are initially given by the value 1 minus the percentage of unquiet periods for both eyes closed and eyes open. The final score is given by the average of these two scores and it is scaled to the 0–100 scale. The given scores (0: Bad, 100: Excellent) for every individual were analyzed using the univariate non-parametric Wilcoxon test in order to see if there is a significant difference between controls and RIL patients.

Oculomotor and posture control correlation in RIL patients

Our objective was to propose a model that finds significant elements of ocular-postural coupling particularly for the RIL patients. Therefore, we checked the power of visual characteristic

TABLE 2 | Visual parameters that were initially calculated and included in the model.

Biomarkers	Description
DYNAMIC VISUAL PARAMETERS	
RangeX (degrees/s)	Range of horizontal eye movement per second during task
RangeY (degrees/s)	Range of vertical eye movement per second during task
RatioRange	RatioX/RatioY
VarianceX (degrees/s)	Variance of horizontal eye movement per second during task
VarianceY (degrees/s)	Variance of vertical eye movement per second during task
VelocityX (degrees/s)	Average instant velocity of horizontal eye movement during task
VelocityY (degrees/s)	Average instant velocity of vertical eye movement during task
Velocity (degrees/s)	Average instant velocity of eye movement during task
EllArea(degrees/s) Horizontal and vertical field of view	Confidence ellipse that covers the 95% of the trajectory points. The horizontal and vertical field of view per second are the axes of the ellipse.
STANDARD VISUAL PARAMETERS	
MeanFix (ms)	Average duration of fixations during task
VarianceFix (ms)	Variance of durations of fixations during task
SkewFix	Skewness of durations of fixations during task
KurtFix	Kurtosis of durations of fixations during task
MeanSac (ms)	Average duration of saccades during task
VarianceSac (ms)	Variance of durations of saccades during task
SkewSac	Skewness of durations of saccades during task
KurtSac	Kurtosis of durations of saccades during task
Fix2SacNratio	Number of Fixations/Number of Saccades

This table separates the parameters into dynamic [mostly inspired by the posture evaluation literature (22, 23) (upper part), and more standard visual parameters (Lower part)].

to predict the postural score only in RIL patients. We performed a regression prediction using the random forests algorithm (25) only for the RIL patients. Briefly, random forest uses multiple weak classifiers (such as decision trees) using random subsamples (randomly selected observations and biomarkers (i) for every tree) of the initial training sample and merges their results in order to get the final classification result. Due to the limited available dataset, results were validated using the well-known leave-one-out validation. Dataset was split N times where train-test was the N-1 and test set was every single individual one.

Moreover, in order to evaluate the influence of every variable in predicting the right label, we estimated the well-known out-of-bag predictor importance by random permutation (26). Briefly, the more critical is the predictor, the more important would be the affectation of the model error (d). The permutation of a non-influential predictor will have minimum or no effect on the model's error. So the final importance is given by

$$Imp_i = \bar{d}_i/\sigma_i \quad (1)$$

TABLE 3 | Patients' MATTIS-Attention sub-scores.

Patient	MATTIS attention sub-score
Patient 1	23/37
Patient 2	25/37
Patient 3	34/37
Patient 4	34/37
Patient 5	34/37
Patient 6	35/37
Patient 7	36/37
Patient 8	36/37
Patient 9	37/37
Patient10	37/37

Where Imp_i the importance of every biomarker i, $\bar{d}_i$ the average change of error after random permutation of biomarker i from trees that i was selected and σ_i is the standard deviation of the $d_i$for trees that i was selected. The out-of-bag predictor importance was run five times. Variables that the 25% quartile of Imp was >0.1 were marked as significant variables.

MATTIS-Attention Subscore and Correlation With Posture

As mentioned previously, all included patients had impaired scores on the tests from the GREFEX battery in a manner that dysexecutive syndrome could be diagnosed according to the GREFFEX criteria (27). However, it was difficult to give a general score of their cognitive impairment that takes into account all the scores of the battery. We assumed that the attention subscore of the MATTIS scale, included in the patients' GREFFEX battery (27), reflects their global cognitive impairment. **Table 3** summarizes the patients' MATTIS-Attention subscores. Below 31/37, the score is considered pathological (28).

Moreover, we used linear Pearson correlation for MATTIS-Attention and postural score in order to check the association of the posture dysfunction with the intensity of the cognitive impairment.

RESULTS

Postural Differences Between RIL Patients and Controls

Postural control was found significantly lower in patients [30 (17, 50)] [median, (whiskers)] than in controls individuals [62 (57, 69)] ($p < 0.01$). The boxplot in **Figure 2** below shows the clear separation between the two groups.

Visual Parameters: Differences Between RIL Patients and Controls

Table 4 below summarizes the values of the calculated parameters.

Visual Parameters and Posture in RIL Patients

Considering only the RIL population, we first checked the importance of the calculated parameters. **Figure 3** shows the

relative parameters' importance, which allows us to predict the final postural score of every participant.

The variables that have been finally selected are presented in **Table 5**.

Some of the selected parameters in **Table 5** (see also **Tables 3**, **4**) might have a certain overlap in terms of explanatory power (ex. RangeY, VarianceY, VelocityY). These variables should be seen more as unity (as a profile) rather than three independent and different parameters. Therefore, we generally observed that movement in horizontal (RangeX, VarianceX, VelocityX) and vertical axes (ex. RangeY, VarianceY, VelocityY) are both increased significantly with the degradation of postural control

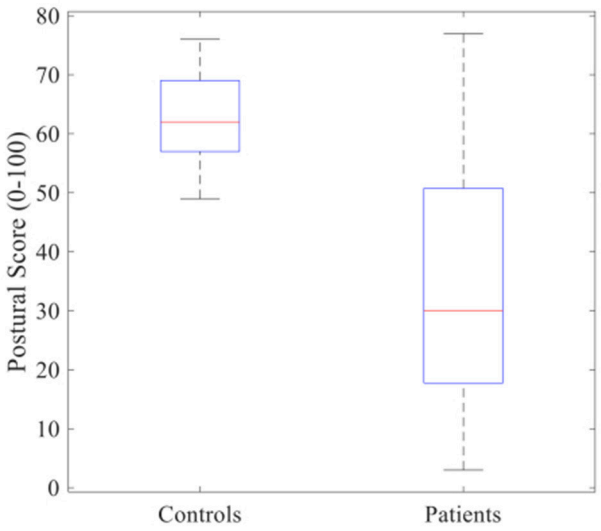


FIGURE 2 | Boxplot of postural score between controls and patients who suffer from radio-induced leukoencephalopathy (RIL). Red lines inside the boxes indicate median and end of boxes indicate the whiskers.
Non-parametric Wilcoxon test showed that RIL's score was found significantly lower compared to those of healthy controls ($p < 0.01$).

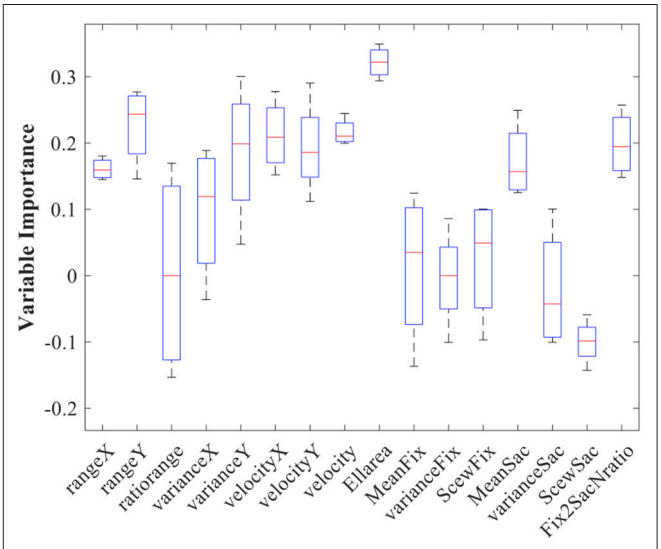


FIGURE 3 | Oculomotor Parameters' importance resulted by the prediction importance algorithm. Red lines indicate the median and the horizontal lines of boxes indicate the whiskers. The biomarkers with low whisker >0.1 were considered as predictors that have very high possibility to have a beneficial effect on the final predictions.

TABLE 4 | Average (±*SD*) of the included variables for RIL patients with relatively low and medium postural score.

Biomarkers	RIL Posture score<30 (*N* = 5)	RIL Posture score>30 (*N* = 5)	Controls (all have Posture score>30)
DYNAMIC VISUAL PARAMETERS			
RangeX (degrees/s)	14.6 ± 5.6	6.0 ± 1.6	10.7 ± 4.5
RangeY (degrees/s)	9.5 ± 3.7	3.4 ± 1.0	5.5 ± 2.1
RatioRange	1.6 ± 0.6	2.0 ± 0.8	2.1 ± 0.8
VarianceX (degrees/s)	4.8 ± 1.7	2.1 ± 0.5	3.6 ± 1.4
VarianceY (degrees/s)	3.1 ± 1.1	1.2 ± 0.4	1.8 ± 0.7
VelocityX (degrees/s)	65 ± 22	23 ± 12	67 ± 87
VelocityY (degrees/s)	52 ± 8	18 ± 8	38 ± 31
Velocity (degrees/s)	92 ± 91	33 ± 15	85 ± 97
EllArea(degrees/s), (field of view) (Horizontal/Vertical)	H:27.6 ± 9, V:10 ± 3.4	H:12 ± 2.5, V:3.7 ± 1.2	H:20.5 ± 7, V:6.4 ± 2.7
STANDARD VISUAL PARAMETERS			
MeanFix (ms)	153 ± 31	316 ± 141	226 ± 89
VarianceFix (ms)	169 ± 63	318 ± 149	134 ± 60
SkewFix	6.1 ± 4.2	3.1 ± 1.6	1.7 ± 0.8
MeanSac (ms)	52 ± 11	41 ± 5	44 ± 9
VarianceSac (ms)	39 ± 28	28 ± 11	36 ± 14
SkewSac	3.2 ± 1.8	1.8 ± 0.7	2.7 ± 1.6
Fix2SacNratio	0.37 ± 0.15	1.05 ± 0.36	0.74 ± 0.35

*RIL patients with relatively higher postural score had many ocular parameters significantly different (see **Table 5** below). Controls were presented in order to help the comparison between these populations. Worth to be noted that sometimes controls present values closer to the RIL with low postural control than those with relatively higher postural score.*

TABLE 5 | Biomarkers that were found valuable in the prediction process of the postural score for RIL patients.

Biomarkers	Median (whiskers) of Importance
DYNAMIC VISUAL PARAMETERS	
RangeX	0.16 (0.15, 0.18)
RangeY	0.24 (0.18, 0.27)
VarianceX	0.12 (0.02, 0.18)
VarianceY	0.19 (0.11, 0.26)
VelocityX	0.21 (0.17, 0.24)
VelocityY	0.18 (0.15, 0.23)
Velocity	0.21 (0.20, 0.22)
EllArea	0.32 (0.29, 0.34)
STANDARD VISUAL PARAMETERS	
MeanSac	0.15 (0.12, 0.21)
Fix2SacNratio	0.18 (0.15, 0.23)

*Horizontal and vertical eye movement increase significantly with the loss of postural control (see **Table 4** above) and also the saccades become numerous and more extensive (in duration).*

(**Table 4**). Considering the standard oculomotor parameters, the average duration of the saccades was also increased and the average fixation period has been dramatically dropped (see **Table 4**). Interestingly, not only durations but also the ratio between numbers of fixations and the number of saccades per second was decreased with the decrease in postural score.

Figure 4A below shows the scatter plot between the observed postural score and the predicted one (by oculomotor parameters). The prediction is fairly accurate with an RMSE = 0.2 (Normalized value–RMSE divided by 100–0). However, this value is increased by an individual (red STAR in the graph) that its prediction was not accurate. The RMSE without the outlier drops to 0.15. On the other hand, when we re-run the model after the inclusion of only the important parameters (**Table 5**), the prediction accuracy has been increased (RMSE = 0.16) (**Figure 4B**). However, the same patient as previously has been relatively mispredicted. The RMSE decreased at 0.11 after the exclusion of this case.

Posture and Attention

We correlated the measured postural score with the attention scale of the MATTIS-Attention subscore using the Pearson linear correlation coefficient. Despite the fact that the patients with lower MATTIS-Attention subscore also had a low postural score, (patients with 23/37 and 25/37 had a postural score of 5/100 and 26/100 respectively), all the other patients had score close to 37 and so we did not find any statistical significance in order to make safer conclusions ($r = 0.39$, $p = 0.28$).

DISCUSSION

One should bear in mind that the neurological examination of patients in question who suffered from RIL at the early stage of dysexecutive function, did not show any balance or gait impairment. The objective of the present work was: (1) to initially explore possible postural control degradation in the patients involved using a simple Romberg test and data mining techniques and consequently associate this degradation with cognitive impairment, (2) to investigate whether there is any relation between the aforementioned postural deficits and the oculomotor control. It was shown that the horizontal and the vertical eye movements as well as the average duration of the saccades are significantly increased in RIL patients with relatively low postural control compared to those with higher postural control. What's more, critical attentional deficits seemed to be coupled with postural impairment leading us to believe that further research into a larger population is required to validate these preliminary findings.

Postural and Visual Deficits in RIL Syndrome

This study is the first detailed report to our knowledge which connects the postural and visual deficits in a RIL patient's cohort. Despite the fact that initially the patients were not diagnosed either with balance or with gait dysfunction caused by the treated tumor or the RIL, these results present scores indicating postural impairments or at least lower scores compared to the healthy controls. Besides, RIL patients were found to suffer from various visual impairments, which, in result, may have contributed to imperfect information processing during complex tasks, such as the ecological reading task assigned. This is of significant importance because usual clinical tests appear less sensitive toward detecting such issues, despite relevant patient complaints.

Vision and Posture Association in RIL Patients

The proposed method offered the advantage of checking all parameters simultaneously and thus avoiding the consecutive univariate parametric or non-parametric tests (such as *T*-Tests or Wilcoxon with or without corrections) often criticized especially in exploratory studies (29). Although a predictive model has been used, this result should not be mistaken for a unidirectional causal relationship between oculomotor deficits and postural control. Our results should be seen mostly as a confirmation that vision deficits may reflect posture ones, and vice versa. The results seem promising in the sense that they strongly encourage further research in this direction, in order to gain a better insight into the neurological basis of the radiation-induced brain damage. Patients were characterized by an heterogeneity of the brain lesions caused by the tumor and a relative homogeneity of the delayed periventricular tracts disruption caused by brain irradiation. This taken into account, it is interesting to see that all patients showed both postural and visual impairments, even at various degrees. To our knowledge, such a phenomenon has never been reported in other conditions close to the radio induced leukoencephalopathy. However, recent studies have shown that there is a relation between saccades and posture in control populations. Saccadic eye movements affect posture by decreasing the magnitude of body sway both in children (30) and older adults (31). Three different mechanisms have been suggested, that work toward the visual stabilization of posture.

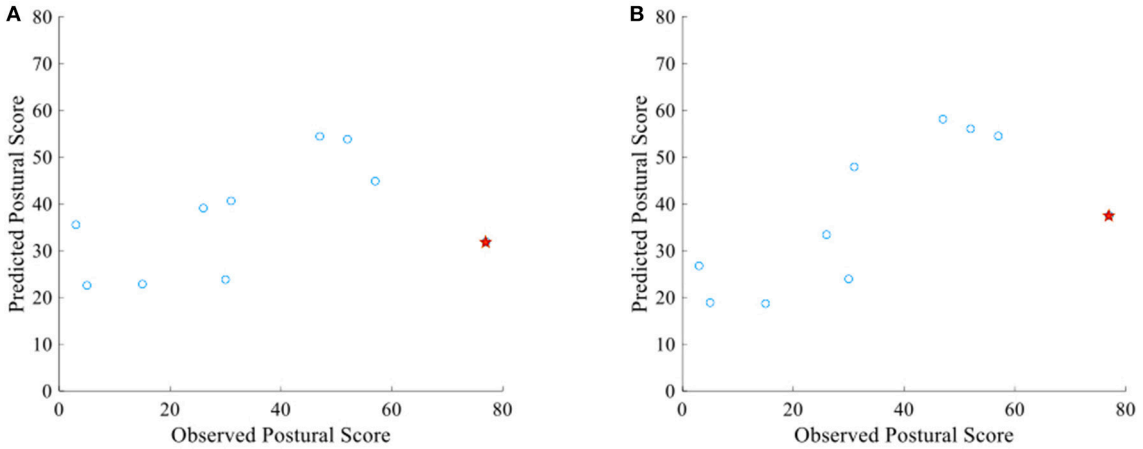


FIGURE 4 | (A) Scatter plot between observed and predicted postural score of RIL patients using all the oculomotor biomarkers mentioned in **Table 2** (RMSE = 0.2). **(B)** Scatter plot between observed and predicted postural score using only the selected oculomotor biomarkers mentioned in **Table 5** (RMSE = 0.16). Both graphs contain an outlier prediction which increases the RMSE significantly (Red star).

1. The afferent motion perception, which uses information contained in the optic flow to minimize retinal slip and stabilize the distance between the eye and visual scene.
2. The efferent motion perception, which is based on either the copy of motor command or extra visual muscle afferents that are consecutive to eye movements.
3. The attentional aspects that relate to the execution of the eye-movement task and possibly influence patients 'postural performance in the present study.

Specifically, attentional demands involved during the reading task, are consistent to an adaptive resource sharing model (32), which postulates that postural and supra-postural tasks compete for the same limited attentional resources. The increased body sway in RIL patients, despite increased saccadic movements, suggests at least a disruption in the normal relationship between saccades and posture. The fact that the patients in the present study suffered from a cognitive impairment, without clinical evidence for postural deficit, presents some interesting caveats to the cognitive penetrability of posture. We may suppose that altered visual strategy has a detrimental effect on posture (33). Also, ignoring irrelevant visual information is paramount to attend and interpret the essential parts of a visual event. We can assume that the modifications found in RIL patients have a detrimental effect on the quality of the visual input, but also partly upset the attentional system, as happens in Parkinsonians (34). This explains why, until recently, balance control was described as a predominantly automated motor process, requiring almost no cognitive input. However, recent studies have shown that alterations in executive function and attention lead to balance control disturbances (35). Our hypothesis and results are in line with these recent findings.

Limitations

There are several limitations we would like to address. In terms of chosen analysis, the current analysis (predictive model) highlighted the ability of oculomotor parameters to predict postural control, without excluding that posture parameters might also predict oculomotor deficits. Therefore, our results indicate a strong interrelation rather than a causal relationship between oculomotor deficits and postural control.

The limited number of available patients, especially in a single clinical center, restrains the evaluation. The fact that we could conduct such an experiment in the neurology department is a strong opportunity to better understand the RIL syndrome. Plans have been made to work toward a more multi-centric approach in the future. The fact that we did not find statistically significant correlation between postural score and MATTIS-Attention sub-score might be also due to the aforementioned lack of large cohort. However, it should be also mentioned that postural score derived by the basic Romberg test, which is not extremely demanding in terms of cognition, might be insufficient to reflect mild cognitive deficits. Richer Romberg protocols (such as dual task (36) which presumes that cognitive functions and postural control compete for limited attentional capacity (32, 37), might be more appropriate in order to acquire more sensitive postural scores.

Additionally, there is a delicate tradeoff between controllability and practical choices in an ecological setting. More precisely, it is necessary to use a cooking recipe and test the reading parameters for this task. The text has a procedural organization, and the corpus is related to a specific semantic field. A further point of contention is the age difference between patients and controls. Still, the primary visual issue between 40 and 50 years, namely presbyopia, cannot affect our results. To our knowledge, no difference has been reported in the statokinesigrams between 40 and 70 years old, either. Most changes in saccadic eye movement in healthy subjects occur after 60 years (38) and thus any age bias is expected to be minor.

Conclusion

The proposed method was based on multi-dimensional machine learning techniques. It offered the advantage of checking the importance of the ocular parameters to explain the postural impairment in RIL patients, while avoiding the consecutive Wilcoxon tests often criticized in exploration studies. The results of the present study are as follows. (1) Most RIL patients have significantly lower postural control scores when compared to the healthy controls. (2) The severity of these postural deficits is strongly associated with the increased vertical and horizontal eye movements as well as with longer saccades. (3) No statistically significant association was found between postural score and MATTIS-Attention sub-score in RIL patients. However, the fact that two RIL patients with very low MATTIS-Attention sub-score showed very low postural score too, is an element that needs further investigation. A larger sample of participants suffering from a wider range of postural stability and cognitive deficits as well as a richer Romberg protocol might be required to emphasize the reliability of the present result. Additional measures will enable researchers to clarify the underlying nature of the neurological lesions that cause cognitive impairment. Future works should focus on correlations of the above postural and visual deficits with brain imaging (MRI) as well as on the increase (as possible) of the sample.

A further establishment of the present results in the future, would render the ecological protocols and parameters we propose, as a complement of the cognitive tests, a major assistance in assessing the stage of the patients' conditions and facilitating the patients' follow-up examinations. Such approaches may also have a positive effect on the rehabilitation strategies at an early RIL stage.

AUTHOR CONTRIBUTIONS

SB and DR: Conceived and designed the experiment; AM, AV, and MC: Recordings of participants; IB, SB, DR, and AV: Analyzed the data; IB, AV, AM, FB, DP, MdL, MB, and CL: Contributed reagents, material, analysis tools; IB, SB, AV, and DR: Wrote the article; IB, SB, DR, NV, and P-PV: Review the article.

FUNDING

The project was funded by Institut pour la recherche sur la Moelle Epinière et l'Encéphale (IRME), the Centre national d'études spatiales (CNES), and the Direction Générale de l'Armement (DGA)-Grant PDH-1-SMO-2-0717.

ACKNOWLEDGMENTS

The authors wish to thank Mélanie Dandrieux for her invaluable contribution and dedications to the patients.

REFERENCES

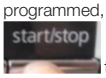
1. Soussain C, Ricard D, Fike JR, Mazeron J-J, Psimaras D, Delattre J-Y. CNS complications of radiotherapy and chemotherapy. *Lancet* (2009) 374:1639–51. doi: 10.1016/S0140-6736(09)61299-X
2. Bompaire F, Lahutte M, Buffat S, Soussain C, Ardisson AE, Terziev R, et al. New insights in radiation-induced leukoencephalopathy: a prospective cross-sectional study. *Support Care Cancer* (2018) 26:4217–26. doi: 10.1007/s00520-018-4296-9
3. Li J, Bentzen SM, Li J, Renschler M, Mehta MP. Relationship between neurocognitive function and quality of life after whole-brain radiotherapy in patients with brain metastasis. *Int J Radiat Oncol Biol Phys.* (2008) 71:64–70. doi: 10.1016/j.ijrobp.2007.09.059
4. Hahn CA, Dunn RH, Logue PE, King JH, Edwards CL, Halperin EC. Prospective study of neuropsychologic testing and quality-of-life assessment of adults with primary malignant brain tumors. *Int J Radiat Oncol Biol Phys.* (2003) 55:992–9. doi: 10.1016/S0360-3016(02)04205-0
5. Dirven L, Aaronson NK, Heimans JJ, Taphoorn MJB. Health-related quality of life in high-grade glioma patients. *Chin J Cancer* (2014) 33:40–5. doi: 10.5732/cjc.013.10214
6. Shprecher D, Schwalb J, Kurlan R. Normal pressure hydrocephalus: diagnosis and treatment. *Curr Neurol Neurosci Rep.* (2008) 8:371. doi: 10.1007/s11910-008-0058-2
7. Douw L, Klein M, Fagel SS, van den Heuvel J, Taphoorn MJ, Aaronson NK, et al. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. *Lancet Neurol.* (2009) 8:810–8. doi: 10.1016/S1474-4422(09)70204-2
8. Van Der Holst HM, van Uden IWM, Tuladhar AM, de Laat KF, van Norden AGW, Norris DG, et al. Cerebral small vessel disease and incident parkinsonism The RUN DMC study. *Neurology* (2015) 85:1569–77. doi: 10.1212/WNL.0000000000002082
9. Schuitema I, Deprez S, Van Hecke W, Daams M, Uyttebroeck A, Sunaert S, et al. Accelerated aging, decreased white matter integrity, and associated neuropsychological dysfunction 25 years after pediatric lymphoid malignancies. *J Clin Oncol.* (2013) 31:3378–88. doi: 10.1200/JCO.2012.46.7050
10. Hatcher-Martin JM, Factor SA. Freezing of gait: A rare delayed complication of whole brain radiation. *Parkinsonism Relat Disord.* (2016) 29:129–30. doi: 10.1016/j.parkreldis.2016.05.002
11. Chapman GJ, Hollands MA. Evidence for a link between changes to gaze behaviour and risk of falling in older adults during adaptive locomotion. *Gait Posture* (2006) 24:288–94. doi: 10.1016/j.gaitpost.2005.10.002
12. Vitório R, Gobbi LTB, Lirani-Silva E, Moraes R, Almeida QJ. Synchrony of gaze and stepping patterns in people with Parkinson's disease. *Behav Brain Res.* (2016) 307:159–64. doi: 10.1016/j.bbr.2016.04.010
13. Ewenczyk C, Mesmoudi S, Gallea C, Welter M-L, Gaymard B, Demain A, et al. Antisaccades in Parkinson disease a new marker of postural control? *Neurology* (2017) 88:853–61. doi: 10.1212/WNL.0000000000003658
14. Leigh RJ, Zee DS. *The Neurology of Eye Movements*. New York, NY: Oxford University Press (2015). doi: 10.1093/med/9780199969289.001.0001
15. Ouchi Y, Okada H, Yoshikawa E, Nobezawa S, Futatsubashi M. Brain activation during maintenance of standing postures in humans. *Brain* (1999) 122:329–38. doi: 10.1093/brain/122.2.329
16. Belenkii VE, Gurfinkel VS, Paltsev EI. *On the Control Elements of Voluntary Movements*. Biofizika (1967).
17. Deubel H, Schneider WX. Saccade target selection and object recognition: Evidence for a common attentional mechanism. *Vision Res.* (1996) 36:1827–37. doi: 10.1016/0042-6989(95)00294-4
18. Rizzolatti G, Riggio L, Dascola I, Umiltá C. Reorienting attention across the horizontal and vertical meridians: evidence in favor of a premotor theory of attention. *Neuropsychologia* (1987) 25:31–40. doi: 10.1016/0028-3932(87)90041-8
19. Gaymard B, Lynch J, Ploner CJ, Condy C, Rivaud-Péchoux S. The parieto-collicular pathway: anatomical location and contribution to saccade generation. *Eur J Neurosci.* (2003) 17:1518–26. doi: 10.1046/j.1460-9568.2003.02570.x

20. Bonnet CT, Szaffarczyk S, Baudry S. Functional synergy between postural and visual behaviors when performing a difficult precise visual task in upright stance. *Cogn Sci.* (2017) 41:1675–93. doi: 10.1111/cogs.12420
21. Holmqvist K, Nyström M, Andersson R, Dewhurst R, Jarodzka H, Van de Weijer J. *Eye Tracking: A Comprehensive Guide to Methods and Measures*. Oxford: OUP (2011).
22. Bargiotas I, Audiffren J, Vayatis N, Vidal P-P, Buffat S, Yelnik AP, et al. On the importance of local dynamics in statokinesigram: a multivariate approach for postural control evaluation in elderly. *PLoS ONE* (2018) 13:e0192868. doi: 10.1371/journal.pone.0192868
23. Audiffren J, Bargiotas I, Vayatis N, Vidal P-P, Ricard D. A non linear scoring approach for evaluating balance: classification of elderly as fallers and non-fallers. *PLoS ONE* (2016) 11:e0167456. doi: 10.1371/journal.pone.0167456
24. Audiffren J, Contal E. Preprocessing the Nintendo Wii board signal to derive more accurate descriptors of statokinesigrams. *Sensors* (2016) 16:1208. doi: 10.3390/s16081208
25. Breiman L. Random forests. *Mach Learn*. (2001) 45:5–32. doi: 10.1023/A:1010933404324
26. Breiman L. *Out-of-Bag Estimation*. Citeseer (1996).
27. Godefroy O. *Fonctions Exécutives et Pathologies Neurologiques et Psychiatriques: Évaluation en Pratique Clinique*. Groupe de Boeck (2008).
28. Schmidt R, Freidl W, Fazekas F, Reinhart B, Grieshofer P, Koch M, et al. The mattis dementia rating scale normative data from 1,001 healthy volunteers. *Neurology* (1994) 44:964. doi: 10.1212/WNL.44.5.964
29. Thiese MS, Arnold ZC, Walker SD. The misuse and abuse of statistics in biomedical research. *Biochem Medica* (2015) 25:5–11. doi: 10.11613/BM.2015.001
30. Ajrezo L, Wiener-Vacher S, Bucci MP. Saccades improve postural control: a developmental study in normal children. *PLoS ONE* (2013) 8:e81066. doi: 10.1371/journal.pone.0081066
31. Aguiar SA, Polastri PF, Godoi D, Moraes R, Barela JA, Rodrigues ST. Effects of saccadic eye movements on postural control in older adults. *Psychol Neurosci.* (2015) 8:19. doi: 10.1037/h0100352
32. Mitra S. Adaptive utilization of optical variables during postural and suprapostural dual-task performance: comment on Stoffregen,Smart, Bardy, and Pagulayan (1999). *J Exp Psychol Hum Percept Perform.* (2004) 30:28–38. doi: 10.1037/0096-1523.30.1.28
33. Teasdale N, Bard C, LaRue J, Fleury M. On the cognitive penetrability of posture control. *Exp Aging Res.* (1993) 19:1–13. doi: 10.1080/03610739308253919
34. Hill E, Stuart S, Lord S, Del Din S, Rochester L. Vision, visuo-cognition and postural control in Parkinson's disease: an associative pilot study. *Gait Posture* (2016) 48:74–6. doi: 10.1016/j.gaitpost.2016.04.024
35. Keshner EA, Slaboda JC, Day LL, Darvish K. Visual conflict and cognitive load modify postural responses to vibrotactile noise. *J Neuroeng Rehabil.* (2014) 11:6. doi: 10.1186/1743-0003-11-6
36. Huxhold O, Li SC, Schmiedek F, Lindenberger U. Dual-tasking postural control: aging and the effects of cognitive demand in conjunction with focus of attention. *Brain Res Bull.* (2006) 69:294–305. doi: 10.1016/j.brainresbull.2006.01.002
37. Woollacott MH. Systems contributing to balance disorders in older adults. *J Gerontol Ser A Biol Sci Med Sci.* (2000) 55:M424–8. doi: 10.1093/gerona/55.8.M424
38. Litvinova AS, Ratmanova PO, Evina EI, Bogdanov RR, Kunitsyna AN, Napalkov DA. Age-related changes in saccadic eye movements in healthy subjects and patients with Parkinson's disease. *Hum Physiol.* (2011) 37:161. doi: 10.1134/S0362119711010117

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

APPENDIX

Table A1| Recipe and associated elements per instruction.

Instruction	Elements/ actions
1. Melt the chocolate and the butter in the microwave. Mix well the two ingredients (The microwave is already programmed, just press  to start it).	• Chocolate bar Butter (opening and closing fridge) Container: choice Spoon: any choice Oven (opening + start + closing)
2. Mix the flour, the sugar and the egg yolks in a bowl.	• Flour Sugar Balance or measuring cup Eggs (opening and closing fridge) Containers (x2: white mixing and separation)
3. Stir the chocolate-butter mixture into the previous mixture.	• Optional: opening / closing oven if the mixture has not already been removed Spoon: choice Optional: dishwasher
4. Beat the egg whites with the electric mixer until stiff and fluffy.	• Electric mixer (plug, turn on) Whisks (to be installed on the mixer) Salad bowl where are the whites
5. Gently incorporate the egg whites in the mixture with a wooden spoon.	• Wooden spoon Salad bowl (egg whites, mix)
6. Pour the mixture into the mold.	• Bowl with mix Mold Spoon: choice

that actual recipe was presented in a more readable format, with a size font suitable for a distant reading.

frontiers in Neurology

ORIGINAL RESEARCH
published: 23 January 2019
doi: 10.3389/fneur.2018.01181

Examining Neural Plasticity for Slip-Perturbation Training: An fMRI Study

Prakruti J. Patel[1], *Tanvi Bhatt*[1]*, *Sophie R. DelDonno*[2], *Scott A. Langenecker*[2] and *Shamali Dusane*[1]

[1] Cognitive-Motor and Balance Rehabilitation Laboratory, Department of Physical Therapy, College of Applied Health Sciences, University of Illinois at Chicago, Chicago, IL, United States, [2] Department of Psychiatry, College of Medicine, University of Illinois at Chicago, Chicago, IL, United States

Perturbation-based balance training has shown to induce adaptation of reactive balance responses that can significantly reduce longer-term fall risk in older adults. While specific cortical and subcortical areas in control of posture and locomotion have been identified, little is known about the training-induced plasticity occurring in neural substrates for challenging tasks involving reactive balance control. The purpose of this study was to use functional neuroimaging to examine and determine the neural substrates, if any, involved in inducing adaptation to slip-like perturbations experienced during walking over 3 consecutive training days. We used a mental imagery task to examine the neural changes accompanied by treadmill-slip perturbation training. Ten healthy young adults were exposed to increasing magnitude of displacements during slip-like perturbations while walking, with an acceleration of 6 m/s^2 on a motorized treadmill for 3 consecutive days. Brain activity was recorded through MRI while performing imagined slipping and imagined walking tasks before and after the perturbation training. The number of compensatory steps and center of mass state stability at compensatory step touchdown were recorded. As compared with day 1 (first trial), on day 3 (last trial) there was a significant reduction in number of compensatory steps and increase in stability at compensatory step touchdown on the mid and highest perturbation intensities. Before perturbation training, imagined slipping showed increased activity in the SMA, parietal regions, parahippocampal gyrus, and cingulate gyrus compared with rest. After perturbation training, imagined slipping showed increased activation in DLPFC, superior parietal lobule, inferior occipital gyrus, and lingual gyrus. Perturbation training was not associated with decline in activity in any of the brain regions. This study provides evidence for learning-related changes in cortical structures while adapting to slip-like perturbations while walking. The findings reflect that higher-level processing is required for timing and sequencing of movements to execute an effective balance response to perturbations. Specifically, the CNS relies on DLPFC along with motor, parietal, and occipital cortices for adapting to postural tasks posing a significant threat to balance.

Keywords: fMRI, pertubation, balance, stability, cortex

OPEN ACCESS

Edited by:
Joyce Fung,
McGill University, Canada

Reviewed by:
Rachel Paes Guimarães,
Universidade Estadual de Campinas, Brazil
Caroline Paquette,
McGill University, Canada

***Correspondence:**
Tanvi Bhatt
tbhatt6@uic.edu

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *01 July 2018*
Accepted: *20 December 2018*
Published: *23 January 2019*

Citation:
Patel PJ, Bhatt T, DelDonno SR, Langenecker SA and Dusane S (2019) Examining Neural Plasticity for Slip-Perturbation Training: An fMRI Study. Front. Neurol. 9:1181. doi: 10.3389/fneur.2018.01181

INTRODUCTION

The central nervous system (CNS) possesses the ability to adapt to novel sensorimotor stimuli. With regards to controlling stability during dynamic balance tasks, the adaptive capacity of CNS has been studied by exposing healthy younger and older adults to repeated slip-like perturbations (1, 2). This is also known as perturbation training, a novel paradigm for preventing falls while walking. During subject-controlled perturbations, i.e., overground slip-like perturbations, the CNS utilizes error information from initial perturbations to shift from a feedback or reactive control to a feedforward or proactive control to produce protective responses (1, 3). Feedforward adaptations are observed in the form of reduced ankle dorsiflexion, increased knee flexion, and reduced heel contact velocity of the slipping leg which influence the ground reaction forces resulting in a reduced slip-perturbation intensity (4–7). On the other hand, during experimenter controlled perturbations, CNS relies predominantly on feedback system, for example, increasing compensatory step length to maintain a more forward center of mass state (position and velocity) at step completion, thus achieving a more stable position (8, 9). These studies provide a substantial understanding about the behavioral mechanisms involved in adaptation to perturbations however, the neural mechanisms underlying such adaptions remain unclear and largely speculative.

Extensive research has identified the widespread neural networks engaged in regular locomotion by examining both mental imagery of walking via functional magnetic resonance imagining (fMRI), and real walking through single-photon-emission-computed-tomography (SPECT) and positron-emission tomography (10, 11). While there is strong evidence for cortical and subcortical control of steady state walking (10–13), other studies show that a specific neural activation pattern is involved in challenging walking tasks. A recent study using high-density EEG identified cortical activity related to loss of balance while walking on a balance beam mounted on a treadmill. Interestingly, they found an increase in theta band spectral power in anterior cingulate, posterior cingulate, anterior parietal, sensorimotor and dorsolateral-prefrontal cortices exclusively during loss of balance from the balance beam (14). Another study using functional MRI reported modulation of brain activity, specifically in bilateral superior parietal lobule and middle occipital gyrus with mental imagery of walking on a narrow path compared with a wider path (15). The above studies suggest that maintaining balance in presence of task constraints is associated with different neural activation pattern than regular walking.

Neural adaptations to improvement in posture control has been examined predominantly during standing balance training through modulation of H-reflex responses (16). Many studies report down regulation of the spinal, H-reflex following single and multiple sessions of balance training (17, 18). For example, Trimble and Koceja reported a 26.2% reduction in the H-reflex amplitude post-training compared with pre-training (18). Similarly, Mynark and Koceja reported a reduction in H-reflex relative to background muscle activity after 2 days of balance training which related with reduced body sway while standing (19). It is suggested that adaptation to balance tasks through reduced modulation of H-reflex is accompanied by greater influence of the supraspinal mechanisms for balance control (20). While these studies provide evidence for a possible supraspinal modulation with improved balance control, the specific structures involved in adaptation to balance tasks are not known.

Balance recovery from external perturbations require rapid processing of sensorimotor information and execution of an accurate reactive or compensatory response (21). Walking involves constantly shifting balance between double and single-limb support phases while maintaining forward progression. Furthermore, external disturbance in balance can occur at any point in the gait cycle which increases the challenge for maintaining balance in case of an external disturbance. However, the neural changes involved in adaptation to external perturbations during walking are poorly understood. A few studies have examined corticomotor excitability before and after locomotor training using transcranial magnetic stimulation. Fisher et al. demonstrated an improvement in stride length and increased cortical silent period after high intensity locomotor training in people with Parkinson's disease, suggesting locomotor training alters the corticomotor activity (22). Furthermore, in stroke survivors, improvement in motor threshold (measured with TMS) following locomotor-balance training correlated with increased step length while walking (23). These studies support the view that locomotor training is related to modulation of cortical activity. It is therefore likely that perturbation based locomotor training could involve changes in neural activity.

Reactive balance responses are likely to engage brain areas related to evaluation of sensory information, development of a new motor plan or recalibration of an existing motor plan to carry out an appropriate action. Perturbation training studies (2, 24), neurophysiological studies (25, 26), and neuroimaging studies (27) support that reactive responses to large perturbations may be modulated through cortical regions particularly, motor cortex. For instance, Adkin et al. demonstrated a negative potential in the fronto-central cortical area occurring 100 ms after perturbation onset while standing (26). Such a response is linked with error detection (28), suggesting a role of cortical areas in modulating reactive balance responses. Although reactive responses involve long and short loop reflexes at spinal cord and brainstem levels (29–32), it is likely that initial adaptation to novel unexpected perturbations may involve cortical regions for error detection and feedback. Therefore, the purpose of this study was to identify the neural regions involved in adaptation to slip-like perturbations during walking. In particular, we were interested in identifying areas showing changes (increase or decrease) in activation during mental imagery of walking slip-perturbations after undergoing 3 consecutive days of treadmill-slip perturbation training among healthy young adults. Considering that slip perturbation was a novel stimulus during walking, we hypothesized that after training there would be increased activation in regions related to sensorimotor processing, balance control, sequence control, and memory.

METHODS

Participants

Ten young adults (27 ± 4 years; range 20–34 years) were enrolled into the study after obtaining a written informed consent approved by the Institutional Review Board. The participants were screened for magnetic resonance imaging (MRI) safety and any neurological, musculoskeletal or cardiovascular disorders. All participants underwent 3 days of treadmill-slip perturbation training while walking. They also performed mental imagery tasks in the MR scanner before and after perturbation training. **Figure 1** shows a schematic presentation of the study protocol.

Regular and Perturbed Walking Tasks

The regular and perturbed walking trials were performed before the first fMRI session (i.e., pre-training fMRI recording). In this session, all the participants were familiarized to regular walking on the treadmill and slipping while walking on the treadmill to facilitate mental imagery of these tasks in the MR scanner. A single regular walking and a single perturbed walking trial was performed. Participants stood at the center of the ActiveStep treadmill (Simbex, NH) with their feet shoulder width apart. All participants donned a safety harness which prevented their knees from touching the treadmill belt in case they experienced a fall.

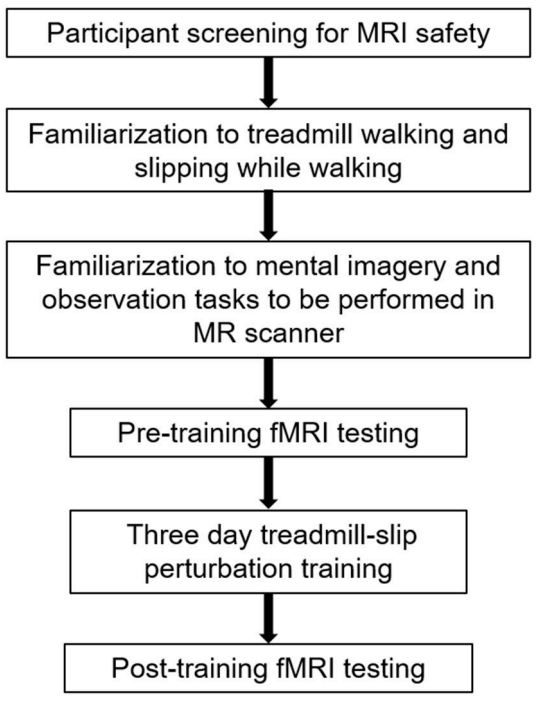


FIGURE 1 | A schematic representation of the experimental protocol. The initial session in the experimental protocol comprised participant screening for fMRI (functional magnetic resonance imaging) safety, familiarization to treadmill, and fMRI tasks, and the first, pre-training fMRI scan. The familiarization and pre-training scan were performed on the same day. This was followed by treadmill slip-perturbation training for 3 consecutive days. The next day after perturbation training, we performed the post-training fMRI scan.

While standing on the treadmill, participants faced a window covered with blinds to prevent any distraction in treadmill tasks. At the start of every treadmill trial, participants were reminded to look straight at the window in front of them. The treadmill walking tasks comprised of—(1) regular walking and (2) experiencing a single unexpected slip i.e., backward loss of balance while walking. During regular walking, participants were instructed to walk naturally and the treadmill speed was adjusted to their preferred walking speed (0.9–1.2 m/s). Participants walked at their preferred walking speed for 1 minute. Following this, participants were instructed that they may experience a sudden slip-like perturbation at an unpredictable instant on the following walking trial. Participants were asked to recover their balance to the best of their ability. Participants were exposed to a single slip-like perturbation with an acceleration of 12.00 m/s^2 (0.25 m displacement for 0.25 s). This perturbation intensity was chosen to provide a real-life like slipping and falling experience and to facilitate the mental imagery of slipping while walking in the MR scanner. During the walking tasks, participants were instructed to concentrate on the experience of walking on the treadmill with regards to movement of their body parts, differences in movement of the body segments and sensory stimuli experienced on the feet. The experimenter standing nearby provided verbal cues to assist the participants in noticing the body movements and sensations. The verbal cues included "focus on position of the different body segments" and "focus on the sensations on the feet." The same researcher provided these verbal cues to each participant. This procedure was performed only before the pre-training fMRI session and not before the post-training fMRI session.

Treadmill-Slip Perturbation Training

Participants were informed that they may or may not experience sudden slip-like perturbations while walking on a treadmill without any prior indication. First all participants walked naturally on the treadmill. The treadmill speed was adjusted to match their self-selected walking speed (0.9–1.2 m/s). After four natural walking trials, on the fifth walking trial, participants were exposed to a slip-like perturbation on the treadmill at an unexpected time. Participants were asked to perform a natural response to recover balance to the best of their ability and continue walking on the treadmill. The very first treadmill-slip perturbation was delivered at the lowest intensity (level I, distance 0.12 m for 0.2 s and acceleration 6 m/s^2). Further, participants were subjected to three more perturbation trials at the same intensity. If the participant successfully recovered from the treadmill-slips on three out of four perturbation trials (i.e., no falls) at a particular perturbation intensity, they were exposed to four additional treadmill-slip trials on the next higher perturbation intensity (level II, distance 0.18 m for 0.25 s and acceleration 6 m/s^2) wherein they were again exposed to four consecutive treadmill-slip perturbations. Following consecutive recoveries, participants were subjected to higher intensities of treadmill-slips up to the highest perturbation intensity (level VI) (**Figure 2A**). This comprised of the incremental treadmill-slip perturbation training block. After the incremental

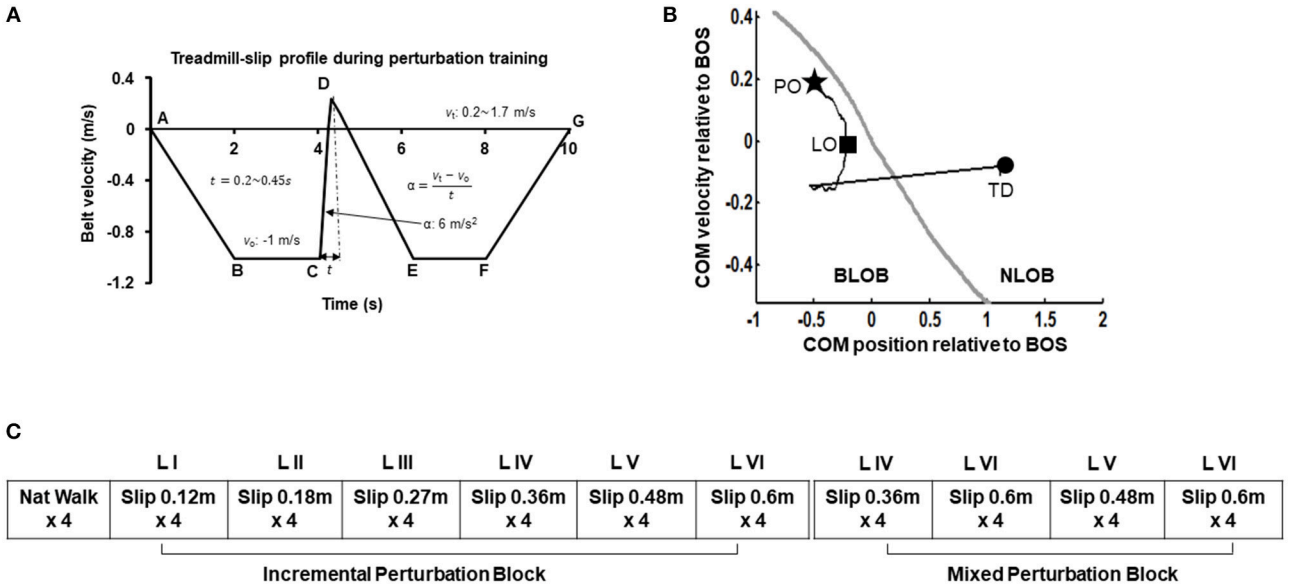


FIGURE 2 | (A) Treadmill-slip perturbation training profile of level III perturbation intensity with an acceleration of 6 m/s^2 at constant belt velocity of 1 m/s, and perturbation displacement and duration of 0.27 m and 0.3 s, respectively. Part A signifies the time instant at which the treadmill belt starts moving backwards and participant initiates walking. The treadmill belt backward velocity ramps up to −1 m/s (A to B), followed by a phase of constant velocity equal to the normal gait speed of healthy young adults (∼1 m/s) (B to C). Part C signifies the time instant at which treadmill belt movement reverses in the forward direction to initiate a slip-like perturbation. The treadmill belt suddenly accelerates at a rate of 6 m/s^2 (C to D), inducing a slip-like perturbation resulting in a backward loss of balance during walking. The treadmill belt then continues to move backward and accelerates (D to E) to reach the constant velocity allowing regular walking (E to F) followed by a gradual stop (F to G). v_O, initial belt velocity in m/s; v_t, terminal belt velocity in m/s; t, perturbation duration in seconds; α, belt acceleration in m/s^2. The six different perturbation intensities were generated by modulating time (t) taken to achieve the final velocity (v_t) at the constant acceleration of 6 m/s^2. **(B)** Treadmill-slip perturbation training protocol for 3 consecutive days demonstrating an initial incremental (increasing intensity) perturbation training block followed by a mixed perturbation block comprising of different perturbation intensities. *Nat walk*, Natural walking without experiencing any perturbations; *LI to LVI*: The difference levels of perturbation training intensities. **(C)** A typical trajectory of center of mass state (COM position and velocity) stability relative to the most posterior margin of base of support (BOS) (black line) from perturbation onset (PO, star) until the completion of the recovery response i.e., compensatory step touchdown (TD, circle). The gray like represents the theoretical threshold for backward loss of balance (BLOB) (37). After treadmill-slip onset, the COM state stability transitions to a more posterior (negative) state at compensatory step liftoff (LO) causing BLOB and then shifts to a more anterior (positive) state as the BOS is re-established with a compensatory step leading to no loss of balance (NLOB).

treadmill-slip perturbation training, participants were exposed to mixed treadmill-slip perturbation training block at levels IV–VI (**Figure 2B**). If the participant had a fall on any of the treadmill-slip trials in a given block, the perturbation intensity was not progressed to the higher level and the training continued at the same perturbation intensity followed by a mixed block of perturbations at the level where the participant fell and its consecutive next lower intensity. The same procedure was followed for 3 consecutive days of treadmill-slip perturbation training.

In each training session, all walking trials (perturbation and regular) lasted for 10 s. At the beginning of training session, participants were informed that they may or may not receive a perturbation on the following walking trials. In the perturbation trials, the perturbation onset was set to occur after initial 3–7 steps to reduce predictability of the perturbation. While the participants were aware that they would be exposed to several perturbed walking trials, they were unaware that they would be exposed to different perturbation intensities. The training perturbation intensity (acceleration and displacement) was selected such that it would sufficiently challenge participant's reactive balance as well as provide opportunity to improve reactive balance through training. Further, the training perturbation intensity was also chosen based on our previous study demonstrating that treadmill-based slip perturbation training at 5–6 m/s^2 with displacements 0.1 to 0.9 m improves reactive balance on novel overground slips (33).

fMRI Tasks

The fMRI sessions were conducted 3–4 days before the first treadmill-slip training session and immediately after the third training session on the same day. fMRI is a non-invasive functional neuroimaging technique wherein activation of brain areas is tracked by detecting the change in blood flow using the blood oxygen level dependent (BOLD) contrast. It is a widely used technique to map the brain regions linked with functions such as movement, speech, and cognition. Prior to each MR session, participants were trained on the mental imagery of the experimental tasks, instructing them to rely upon their experience of walking and slipping on the treadmill. Their ability to form a mental imagery was assessed with Vividness of Visual Imagery Questionnaire. During the observation tasks,

participants were instructed to observe a video of another person walking, or slipping while walking on the treadmill in a situation similar to what they had experienced during the familiarization trials. To facilitate participant's visualization of slipping while walking, the videos included the posterior (back) view of a person walking, or slipping while walking on the treadmill. All the imagined and observed tasks were performed before and after perturbation training. During the MRI session, subjects laid still in the MR scanner and were instructed to perform two different mental imagery tasks. While in the MR scanner, participants alternated between four tasks—(1) mental imagery of themselves slipping while walking on the treadmill (imagined slipping), (2) mental imagery of themselves walking on the treadmill (imagined walking), (3) observation of another person slipping while walking on the treadmill, and (4) observation of another person walking on the treadmill. These experimental tasks were interspersed with periods of rest. The duration of mental imagery, observation, and rest was 30 s. All tasks were presented in a randomized order. Each participant performed two blocks of two trials for each condition. We presented auditory cues to indicate the start and end of metal imagery tasks. At the beginning of mental imagery tasks, participants received the auditory cue "close your eyes and imagine yourself walking or slipping while walking on the treadmill." At the end of mental imagery tasks, participants received the auditory cue "open your eyes" to proceed to the next fMRI task. In the rest condition, participants were instructed to focus on "X" sign presented on the screen, trying not to think about anything else. After each MRI session, we surveyed the participants for the number of slips imagined in the imagined slipping condition.

Behavioral Data Acquisition and Analysis

Full body kinematics were recorded using an eight camera 3D motion capture system (Motion Analysis, Corp, Santa Rosa, California). The Helen Hayes marker set comprising of 29 passive markers placed on the bony landmarks of bilateral upper extremities and lower extremities, trunk and head was used to compute the joint centers and center of mass (COM) (34). The motion capture data was collected at a sampling rate of 120 Hz. The raw marker data were low-pass filtered through fourth-order Butterworth filter with a cut-off frequency of 6 Hz. A load cell connected in series with the harness measured the amount of body weight supported by the harness during each trial. The kinematic variables were computed using a custom-written algorithm in MATLAB (version 2014b, The Mathworks Inc, Natick, MA, USA).

Behavioral Outcomes

To examine adaptation to slip perturbation training we measured the following outcomes measures: (i) perturbation outcome, (ii) number of compensatory steps, and (iii) COM stability.

Perturbation outcome: For each perturbation trial, we determined whether the participant experienced a fall or showed a recovery response. The trial was identified as a fall if it was apparent that the participant was supported by the harness and the force exerted on the load cell exceeded 30% of the body weight for >1 s after perturbation onset (35), or when the subjects failed to initiate a stepping response resulting in a catch by the harness. The remaining trials were identified as recoveries.

Compensatory Step

The number of steps taken between perturbation onset (phase C–E in **Figure 2A**) to perturbation termination were counted. The first compensatory step was described as a step taken with the trailing limb and landing behind the slipping limb. The subsequent steps could be taken with the slipping or the trailing limb; however, always landing behind the contralateral limb. The compensatory stepping phase was also termed the loss of balance phase. If subjects were able to successfully take a forward step in presence of the perturbation it was considered a regular step with no balance loss. The Z-coordinate of the stepping limb heel marker was used to identify the unloading of the foot.

Stability

The center of mass (COM) position was calculated relative to the rear of the base of support (BOS) i.e., heel of the most posterior limb (slipping limb during single leg stance at liftoff of the trailing limb and trailing limb at step touchdown). The COM position was then normalized by the participant's foot length. The COM velocity was obtained by the first order differentiation of the COM position. The COM velocity was calculated relative to the heel velocity of the most posterior limb (similar to COM position) and normalized by a dimensionless fraction of $\sqrt{g^*h}$, where g denotes gravity and h denotes the individual's body height. The COM stability was computed as the shortest distance of the instantaneous COM state (position and velocity) with respect to the theoretical boundary for backward loss of balance (36, 37). A negative stability value indicated by a COM state below the threshold boundary signifies a greater predisposition for backward balance loss. If the stability value is 0 it indicates that the COM state lies on the computational boundary. While positive stability values signify recovery from loss of balance indicating the COM state lies within the boundary (**Figure 2C**). Stability values were obtained at touchdown of the first compensatory step.

fMRI Data Acquisition

Whole brain imaging was performed with a 3.0 T GE Discovery scanner (Milwaukee, WI) using a standard radio frequency coil and T2*-weighted pulse sequence. BOLD functional images were collected using a gradient-echo axial echo planar imaging sequence (38) at University of Illinois at Chicago. The following parameters were used: repetition time = 2,000 ms, echo time = 22.2 ms, flip angle = 90 degree, 64 by 64 parcellated matrix of 220 mm by 220 mm field of view, slice thickness = 3 mm, 44 slices, and voxel size of 3.4 mm by 3.4 mm. The repetition time is defined as the time between the beginning of two consecutive pulse sequences, the echo time is the time between the center of exciting *RF* pulse and the center of spin echo, and the field of view (FOV) is defined as the rectangular region over which the MRI image is acquired. The matrix size refers to the parcellations of the field of view. The matrix size determined the size of the voxels contained in the FOV. An axial T1 spoiled gradient structural image was obtained for each using 182 axial images and

1 mm in thickness for spatial normalization [minimum TR/TE (9.292 ms/3.77 ms) TI = 450 ms]. During scanning, participants completed the observed and imagined tasks. Prior to scanning, the importance of remaining motionless was conveyed to each participant. There were two runs of the experimental tasks, each lasting 5 min and 20 s, and acquiring 120 volumes. Overall, across the two runs, each of the mental imagery, observation and rest tasks were performed four times. Each condition was averaged across both runs, prior to the creation of subtraction contrast analyses.

fMRI Preprocessing

Images underwent slice-timing corrections with SPM8 (http://www.fil.ion.ucl.ac.uk/spm/doc/) and motion detection algorithms with FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). During pre-processing, images were visually inspected for motion >1.5 mm across more than three TRs. This motion check did not result in the exclusion of any participants from analyses. Structural and functional images were co-registered and then the co-registered T1-SPGR underwent spatial normalization (DARTEL to MNI template). The resulting normalization matrix was then applied to the slice-time-corrected, movement-adjusted time series data and smoothed with a 5 mm Gaussian kernel. Resulting T2* images were 2 mm on a side with isotropic voxels.

Statistical Analysis

The effect of perturbation training was analyzed by comparing the number of compensatory steps and COM state stability at touchdown between the first trial of first training session (day 1) and the last trial of last training session (day 3) for low, mid and highest perturbation levels (I, III, and VI). The change perturbation outcome and in number of compensatory steps between day 1 and day 3 was compared using the Wilcoxon Signed Rank test. The effect of perturbation intensity on perturbation outcome and number of steps was examined by Kruskal–Wallis test. A significant main effect was then followed up by Mann-Whitney U test for comparison between the perturbation intensities. The changes in COM state stability at touchdown was examined by 2 × 3 two-way analysis of variance (ANOVA) with stability at touchdown as dependent variable and perturbation intensity (I, III, and VI) and training sessions (day 1 and day 3) as independent variables. *Post hoc* paired and independent *t*-tests were performed to resolve any significant main effects and interactions. All 10 participants completed the three consecutive treadmill-slip perturbation training sessions. Therefore, all analyses were performed on 10 participants. The significance level was set at $p < 0.05$.

With regards to fMRI data analysis, we compared changes in neural activation before and after perturbation training only in the imagined conditions. Our recent study demonstrated that mental imagery of slipping induced greater engagement (corresponding with more areas of activation) of neural structures than the observation of slipping. There was no difference in neural activation between mental imagery and observation of regular walking (39). Based on these recent findings, in current study, we considered only the imagined conditions for comparing pre- to post-perturbation training fMRI changes. First, activation during rest in the pre-training scan was subtracted from activation during the experimental conditions in the pre-training scan to create two baseline contrasts of interest: baseline IS minus rest and baseline IW minus rest. Second, activation during rest in the post-training scan was subtracted from activation during the experimental conditions in the post-training scan to create two post-training contrasts of interest: post IS minus rest and post IW minus rest. Then, using a within-group ANOVA in SPM8, activation during the post-training scan was compared to pre-training activation by subtracting the respective contrasts of interest from each scan, e.g., baseline IS compared to post-training IS. We also examined the difference between post-training activations in the IS and IW conditions. A gray matter mask was applied and whole brain alpha of .01 was achieved for each contrast. The default familywise error option in SPM was not used. Instead, cluster extent was determined based upon 1000 Monte Carlo simulations in the bug-fixed 3dClustSim tool (40), resulting in a joint threshold of height and extent ($p < 0.01$, extent of 640 mm^3 or k = 80 voxels). The Monte Carlo approach was intended to balance Type I and Type II error.

RESULTS

Adaptation to Treadmill-Slip Perturbations

All participants upon perturbation onset (**Figure 2C**, star) experienced loss of balance observed by initiation of a backward compensatory step, with the COM state traveling below the computational backward balance loss threshold (**Figure 2C**, square) in response to treadmill-slip perturbation at all perturbation intensities. Participants demonstrated a compensatory step for recovery from balance loss resulting in a positive stability with the COM state lying above the threshold for backward balance loss (**Figure 2C**, circle). With regards to perturbation outcome, there was no difference in falls incidence on level I perturbations between day 1 (0%) and day 3 (0%) ($p > 0.05$). Similarly, there was no change in falls incidence on level III perturbations between day 1 (10%) and day 3 (0%) ($p > 0.05$). For level VI perturbation intensity, the incidence of falls significantly reduced from day 1 (60%, 6/10) to day 3 (0%) ($Z = -2.44$, $p < 0.05$).

On the lowest perturbation intensity (level I), there was no change in number of compensatory steps from day 1 to day 3 ($Z = -1.89$, $p > 0.05$, **Figure 3A**). The number of compensatory steps significantly reduced on the level III ($Z = -2.33$, $p < 0.05$) and level VI ($Z = -2.15$, $p < 0.05$) perturbations on day 3 compared with day 1. There was a significant main effect of perturbation level on number of steps. More number of steps were observed at higher perturbation intensities for day 1($\chi^2 = 14.32$, $p < 0.01$) and day 3 ($\chi^2 = 15.91$, $p < 0.01$). For COM state stability at compensatory step touchdown, comparison of the training session (day 1 and day 3) across the three perturbation intensities (levels I, III, and VI) showed no significant training session × level interaction $F_{(2,24)} = 0.06$, $p > 0.05$, **Figure 3B**. There was a significant main effect of training session $F_{(1,24)} = 10.67$, $p < 0.01$, partial $\eta^2 = 0.30$ and a significant main effect of

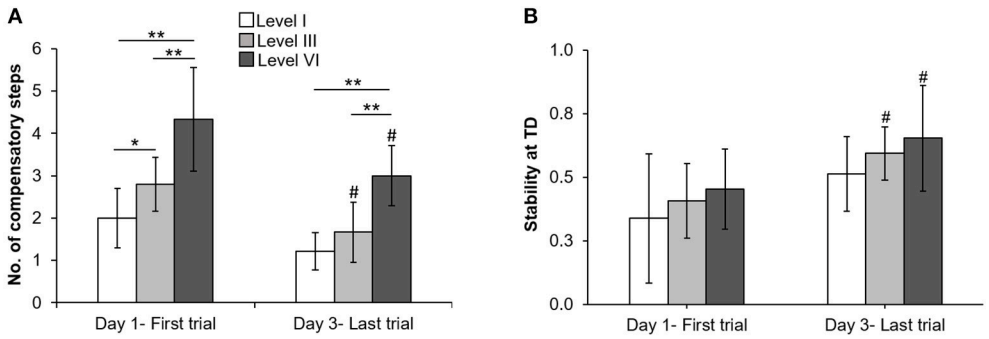


FIGURE 3 | Changes in mean (±SD) **(A)** number of compensatory steps after perturbation onset and **(B)** COM state stability at compensatory step touchdown (TD) at lowest (level I), mid (level III), and highest (VI) perturbation intensities between first training trial on day 1 and last training trial on day 3. $^{*}p < 0.05$ and $^{**}p < 0.01$ indicates significant differences between different perturbation intensities on the same day and $^{\#}p < 0.05$ indicates significant differences between same intensities on first (day 1) and last day (day 3).

perturbation intensity $F_{(2,24)} = 3.60$, $p < 0.05$, partial $\eta^2 = 0.23$. On lowest perturbation intensity (level I), there was no significant difference in stability at touchdown from day 1 and day 3 ($p > 0.05$). On level III & VI perturbation intensity, the stability at touchdown significantly increased from day 1 to day 3 ($t = -2.80$, $p = 0.01$ for level III, $t = -2.07$, $p = 0.03$ for level VI).

Changes in Neural Activation With Behavioral Adaptation

All participants reported the ability to form a mental image of a motor task prior to performing the fMRI tasks, with a median score of 4.5/5 on vividness of visual imagery of questionnaire. During both MRI sessions, the participants imagined 3–5 slips in the imagined slipping condition. At baseline, prior to treadmill-slip perturbation training imagined slipping and imagined walking demonstrated increased activation in several cortical and subcortical areas (**Table 1**). As compared with the rest condition, imagined slipping yielded activation in the frontal, parietal, and limbic regions including superior frontal gyrus (SMA, BA6), inferior frontal gyrus, inferior parietal lobule, parahippocampal gyrus, cingulate gyrus, and posterior cerebellum ($p < 0.01$, **Table 1**). Imagined walking demonstrated an increased activation in the left medial frontal gyrus (BA 32), left precentral gyrus, and right inferior frontal gyrus ($p < 0.01$, **Table 1**).

After treadmill-slip perturbation training, there was an increased activation in several cortical regions in the imagined slipping condition (**Table 2**). These include left middle frontal gyrus (dorsolateral prefrontal cortex, BA 9), right superior parietal lobule (BA 39), right inferior occipital gyrus (BA 18), and left lingual gyrus (BA 18) ($p < 0.01$). The heat map showing greater activation in cortical areas post-training compared with pre-training is shown in **Figure 4A**. None of the brain areas showed a decrease in activation post-training in the imagined slipping condition. Treadmill-slip perturbation training also influenced the brain activation in the imagined walking condition. There was an increased activation in the frontal, parietal, and occipital regions ($p < 0.01$), including left inferior frontal gyrus (BA 44), right inferior parietal lobule (BA 40), and right superior parietal lobule (BA 39) in the imagined walking condition (**Figure 4B**, **Table 2**). There was no significant decrease in activation in any of the brain regions post-training ($p > 0.01$). Further, a comparison of post-training imagined slipping and post-training imagined walking conditions revealed significant differences in cortical and subcortical activations between the two conditions ($p < 0.01$). Specifically, the bilateral anterior cerebellum, bilateral posterior cerebellum, superior and middle temporal gyrus, right middle frontal gyrus (BA 10), left supplementary motor area (BA 6), left precuneus (BA 31), anterior cingulate (BA 25), and posterior cingulate (BA 23), and left parahippocampal gyrus showed increased activation in post-training imagined slipping compared with post-training imagined walking condition (**Table 3**).

DISCUSSION

The current study provides evidence regarding the specific neural structures associated with mental imagery of slipping after adaptation to sudden slip-like perturbations while walking. Over a period of 3 consecutive days, the participants adapted to small and large magnitude treadmill-slip perturbations showing reduced incidence of falls and increased COM state stability at compensatory step touchdown on day 3 compared with day 1. Behavioral adaptation was accompanied by increased activation in several cortical and subcortical areas in the imagined slipping and imagined walking conditions. Finally, post-training imagined slipping showed greater engagement of motor, sensory, limbic, and cerebellar areas compared with post-training mental imagery of regular walking.

A general baseline activation was observed in SMA (superior frontal gyrus), inferior frontal gyrus, inferior parietal lobule, parahippocampal gyrus, and cingulate gyrus during imagined slipping (**Table 1**). But following 3 consecutive days of treadmill-slip perturbation training, we identified increased activity predominantly in the frontal and parietal cortical areas in the imagined slipping condition. These findings suggest a significant role of frontal and parietal cortical structures in learning a

TABLE 1 | Differences in brain activation between imagined slipping, imagined walking, and rest conditions in the pre-training fMRI session.

Contrast	Anatomical regions				Voxels	MNI coordinates			
	Lobe	Gyrus	BA	Side		x	y	z	*Z*-value
IS vs. Rest	Frontal	Superior frontal gyrus	6	L	130	−32	12	54	3.80
		Inferior frontal gyrus	45	R	475	56	10	22	3.92
	Parietal	Inferior parietal lobule	40	L	115	−46	−46	46	3.48
	Limbic	Parahippocampal	–	R	123	14	−10	−18	3.34
		Cingulate gyrus	24	L	3716	−4	−8	50	4.07
	Cerebellum	Posterior lobe-declive	–	R	210	28	−74	−28	3.77
				L	184	−38	−60	−30	3.54
IW vs. Rest	Frontal	Medial frontal gyrus	32	L	162	−6	6	50	3.49
		Precentral	–	L	100	−48	6	14	3.53
		Inferior frontal gyrus	44	R	95	54	10	20	3.11

IS, Imagined slipping; IW, Imagined walking; MNI, Montreal Neurological Institute; BA, Broadmann area; SMA, Supplementary motor area. All activations were observed at $p < 0.01$ and $k = 80$.

TABLE 2 | Differences in pre and post treadmill-slip perturbation training brain activation in imagined slipping and imagined walking conditions.

Contrast	Anatomical region				Voxels	MNI coordinates			
	Lobe	Gyrus	BA	Side		x	y	z	*Z*-value
IS	Frontal	Middle frontal gyrus	9	L	190	−48	26	30	3.44
	Parietal	Superior parietal lobule	39	R	87	30	−68	46	3.30
	Occipital	Inferior occipital gyrus	18	R	174	32	−92	−6	3.12
		Lingual gyrus	18	L	226	−22	−90	−10	3
IW	Frontal	Inferior frontal gyrus	44	L	140	−56	18	18	3.52
	Parietal	Inferior parietal lobule	40	R	201	38	−46	44	3.75
		Superior parietal lobule	39	R	268	28	−66	44	3.42

IS, Imagined slipping; IW, Imagined walking; MNI, Montreal Neurological Institute; BA, Broadmann area. All activations were observed at $p < 0.01$ and $k = 80$.

relatively novel, less practiced postural task related to perturbed locomotion. Behavioral adaptation to perturbations was evident on mid (level III) and highest (VI) perturbation intensities as the stability at compensatory step TD increased from day 1 to 3 reflecting that the participants acquired the ability to maintain a more anterior i.e., more stable COM state following perturbation. Thus, with repeated exposure to such perturbations, the reactive response was refined to achieve an improved dynamic stability control against slip-like perturbations.

We also found significant changes in neural activation evidenced by increased recruitment of dorsolateral prefrontal cortex (DLPFC, middle frontal gyrus, BA 9) after 3 consecutive days of perturbation training. Learning a new task requires attention which would be particularly higher in the early phase when the CNS is forming the association between the tasks details and the necessary responses (41). Thus, DLPFC which plays a key role in decision making and working memory (42), is likely recruited to temporarily store the sensorimotor and joint position information following each perturbation, to inhibit the unwanted response and carry out the perturbation specific response, as the CNS becomes progressively more aware of perturbation characteristics. Prefrontal cortex activation has been observed during tasks requiring greater balance demands rather than during static standing or regular walking e.g., walking on a narrow pathway (40) and heel-to-toe walking (14). Thus, increased activation in DLPFC during imagined slipping after training could suggest that significant attention is required to recover balance from sudden slip-like perturbations.

DLPFC is also implicated to play a role in learning novel tasks. It is particularly activated when performing tasks that involve learning new motor sequences (41, 43). It is postulated that with repeated perturbation exposure the CNS updates its internal representation of stability limits with the sensory feedback of previous trials and subsequently builds a motor repertoire. On subsequent exposure to a similar perturbation the CNS can trigger the motor repertoire with greater stability and resulting recovery strategies (36, 44, 45). Few studies have shown cortical modulation during reactive balance response preparation and execution even for the very first novel recovery response, primarily through involvement of prefrontal cortex, premotor and parietal areas (26, 27, 46). In our study, greater activation in DLPFC during imagined slipping after training indicates a potential role of the prefrontal lobe in developing the internal representation of the motor response for a relatively novel balance task. Although there is evidence that DLPFC activation reduces after the initial motor sequence learning phase (43),

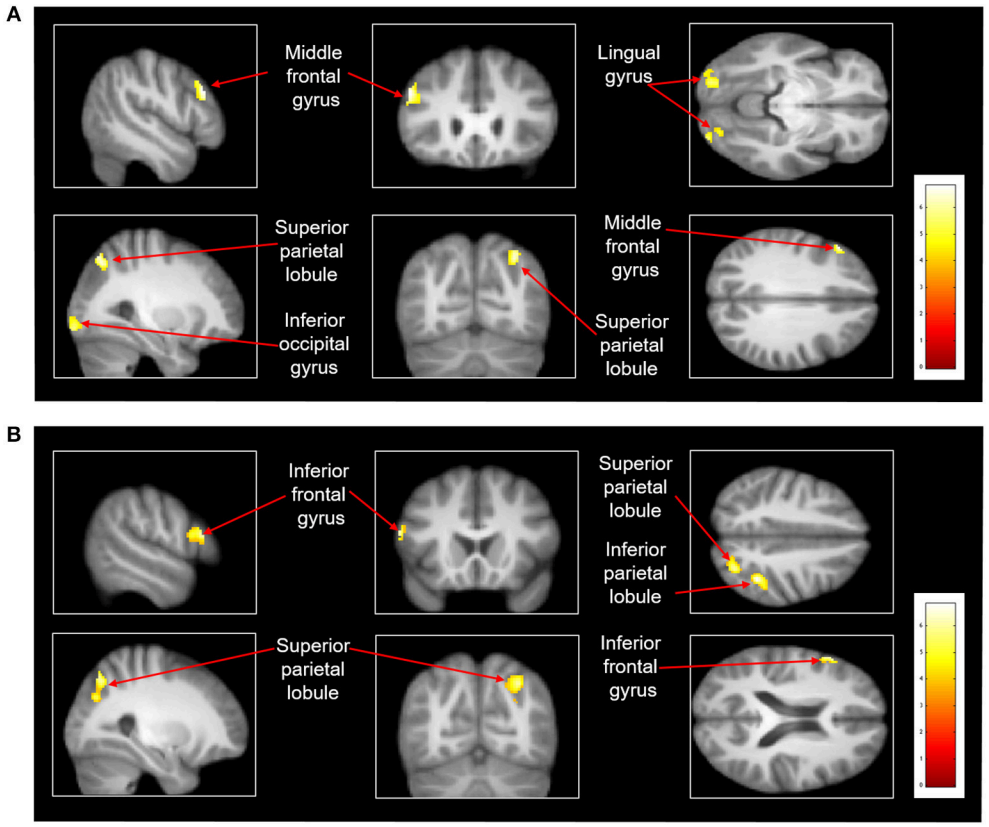


FIGURE 4 | Heat map demonstrating areas with greater activation in the **(A)** imagined slipping condition and **(B)** imagined walking condition after 3 consecutive days of treadmill-slip perturbation training. Increased activation was noted in different regions in the frontal, parietal, and occipital lobes ($p < 0.01$, k = 80).

we found increased activation in DLPFC in the post-training compared with pre-training imagined slipping. It is likely that such increase in prefrontal activation with a short training period may decline with further training or time lapse due to the process of consolidation as the behavioral learning response stabilizes.

Adaptation to treadmill-slip perturbations also showed increased activation in right superior parietal lobe (BA39) and BA 18 (right inferior occipital gyrus & left lingual gyrus) during imagined slipping. Activation in these areas suggests greater engagement of the association areas in the parietal and visual regions while learning complex postural tasks. Association areas seem to be involved in higher order processing of information rather than only identifying simple characteristics of the sensory input (47). With repeated exposure to varied intensities of slip-like perturbations, association areas perhaps combine the visual and kinesthetic feedback for faster processing of visuo-spatial information to aid decision making. Such involvement of visual and parietal association areas is consistent with adaptation to visuomotor tasks. Studies have shown activation of parieto-occipital sulcus while learning visuomotor tasks (48–50). Further, there is contribution of inferior occipital and lingual gyrus (BA 18) during adaptation and transfer of learned visuomotor tasks to the untrained hand (51). Considering that these areas did not show activation at baseline (before training) but showed increased activation post-training, suggests that the association areas could play a significant role in acquisition of movements requiring visuomotor coordination.

Limited studies have examined changes in brain activation pattern with adaptation of locomotor balance tasks. Ionta et al. examined cortical plasticity after a single session of treadmill-delivered locomotor-balance training via a mental imagery paradigm. They observed increased activation in SMA, thalamus, right basal ganglia, and right cerebellum during the imagined walking condition, after 20 min of walking practice (52). Our study extends findings to balancing during a locomotor task showing recruitment of specific brain regions after locomotor-balance training sessions. However, unlike Ionta et al. (52) our study showed increased activation post-training predominantly in the cortical regions. Such differences in current and previous findings could be related to the walking task. Ionta et al. (52) examined pre to post neural changes after regular walking, a task relatively more practiced task than perturbed walking. The authors suggest that increased recruitment of lower brain centers (subcortical regions) could be related to maintaining sequence, timing, and coordination of limb movements rather than recruiting higher centers to establish a new internal presentation of body schema. On the other hand, increased recruitment of higher brain centers (cortical areas) in our study

TABLE 3 | Differences in brain activation between post perturbation training imagined slipping and post perturbation training imagined walking conditions.

Contrast	Anatomical region				Voxels	MNI coordinates			
	Lobe	Gyrus	BA	Side		x	y	z	*Z*-value
IS vs. IW	Frontal	Medial frontal gyrus	10	R	1182	8	56	−4	4.56
		Superior frontal gyrus	6	L	125	−6	8	64	3.16
	Parietal	Precuneus	39	L	203	−40	−74	36	3.21
	Temporal	Superior temporal gyrus	38	L	225	−50	8	−12	3.16
		Middle temporal gyrus	39	R	107	54	−66	26	3.14
	Limbic	Posterior cingulate	31	L	1871	−8	−58	24	3.73
		Anterior cingulate	25	L	83	−6	20	−2	3.35
		Parahippocampal	–	R	105	24	−30	−20	3.30
	Cerebellum	Anterior lobe	–	R	182	14	−46	−30	3.62
			–	L	182	−8	−46	−28	3.21
		Posterior lobe	–	L	372	−8	−64	−24	3.33
			–	R	107	26	−76	−22	3.07

IS, Imagined slipping; IW, Imagined walking; MNI, Montreal Neurological Institute; BA, Broadmann area. All activations were observed at $p < 0.01$ and $k = 80$.

could be related to processing of novel somatosensory stimuli to learn and execute a different motor response than that involved in regular walking.

Before training, in the imagined slipping condition, activations were observed in SMA, parahippocampal gyrus, cingulate gyrus, and posterior cerebellum (see **Table 1**) which was not modulated (neither increased nor decreased) through adaptive perturbation training (see **Table 2**). These findings suggest that the above areas could be consistently activated pre- and post-training in balance recovery from treadmill-slip perturbations. Activation in these brain centers also represents recruitment of indirect neural pathways, predominantly responsible for planning and modulation of movements during locomotor tasks (11). This idea is also supported by another study showing increased activation of SMA and parahippocampal gyrus during imagined locomotor task which involved navigating around a series of obstacles (53). Similarly, in our study, repeated exposure to external perturbations would require extensive planning based on prior exposures, monitoring of ongoing movements at the time of perturbation, and executing a planned response.

Locomotor treadmill-slip perturbation training also resulted in an increased activation in the parietal regions during imagined walking. The 3-day training task although was targeted to improve reactive balance, it also provided substantial walking exercise and hence could have provided some locomotor training itself. Further, the subjects who participated in training were asked not to perform any form of locomotor exercise training (treadmill walking, running, bicycling etc.) during the perturbation training period. Secondly, considering that both imagined conditions involved walking, it is likely that both conditions could share similar neural pathways and therefore resulted in increased activation in some common cortical areas after perturbation training. Nevertheless, we found that after perturbation training, the brain activity differed between imagined slipping and walking conditions.

Post-training, imagined slipping compared with imagined walking yielded greater activity in medial and superior frontal, parietal, cingulate, parahippocampal, and cerebellar regions. Some of these regions also demonstrate increased activation in imagined-slipping post-perturbation training, suggesting that changes in neural activation pre- and post- imagined slipping could be related to slip-perturbation training. In contrast to regular walking, slipping introduces movement errors in walking that need corrective responses and therefore, possibly exerts higher cognitive load for balance control. Accordingly, we found stronger brain activity in post-training imagined slipping vs. post-training imagined walking. The slip-perturbation training resulted in improved reactive postural stability through feedback learning which involved mapping of movement errors and updating the resultant motor responses. Regions such as medial frontal region, anterior cingulate, and cerebellum are associated with motor error detection and error-processing within the feedback control (54–56). These regions were particularly more active in post-training imagined slipping than post-training imagined walking, explaining that potentially different brain regions are engaged in learning reactive balance strategies in walking than regular walking.

Previous studies using functional imaging through mental imagery, electroencephalography, and functional near-infrared spectroscopy report a predominance of activity in left pre-frontal, frontal, and parietal regions during a relatively complex locomotor tasks (e.g., increasing walking speed, walking while talking, walking on a balance beam, and external perturbations in standing), suggesting that the left sensorimotor areas play a role in executing complex and skilled movements in locomotion (13, 14, 57, 58). Our findings concur with previous studies to some extent such that post-training, we found increased activation in left frontal areas in both the metal imagery conditions and increased activation in left fronto-parietal regions in post-training imagined slipping verses imagined walking.

Given that the evidence regarding neural pathways related to reactive balance is still emerging, this study provides novel insights into the specific brain areas involved in learning a locomotor reactive balance task in healthy young adults. Our findings should however be interpreted in light of some limitations. An important limitation of the study includes use of mental imagery instead of real locomotion. While there is some evidence regarding overlapping brain activity between mental imagery and overt movements (11, 59) the mental imagery of slipping while walking may not emulate the sensorimotor experience of actual movements. Further, it is difficult to ensure consistency in mental imagery across participants. Although we screened for the ability to perform mental imagery prior to MR scans, adherence to mental imagery during the scan is difficult to assess. We however decided to incorporate the fMRI approach based on the extensive evidence supporting use of mental imagery for examining neural activity of locomotor tasks (13, 15, 60) and to achieve better spatial resolution compared with other more portable imaging techniques like fNIRS or EEG (61). Additionally, the study design did not allow for identification of changes in neural activity during the exact instant when the participants imagined slipping. Therefore, we included the imagined walking as a control condition to be able to compare the differences, if any, in neural activity related to perturbed walking practice vs. regular walking practice. Due to lack of research on neural changes involved in adaptation to locomotor balance tasks, this study was designed as a proof of concept study and is therefore limited by a small sample size. While our study provides proof of feasibility, future studies with a larger sample size are recommended. Future investigations should also compare neural activation between perturbation-training and regular walking training for further insight into neural mechanisms specific to reactive balance adaptation.

This fMRI study identified a specific brain areas involved in learning of a locomotor reactive balance task involving balance recovery during slip-like external perturbations. The findings support that learning challenging balance tasks requiring precise and coordinated movements is associated increased activity in DLPFC, parietal, and visual association areas. In addition, there is continued activation of the parahippocampal and cingulate regions which assists in the learning process.

ETHICS STATEMENT

The study procedures were carried out in accordance with the recommended guidelines of the University of Illinois at Chicago Institutional Review Board. All participants were enrolled into the study after obtaining an informed written consent. The protocol was approved by University of Illinois, Biomedical and Biological Sciences Board.

AUTHOR CONTRIBUTIONS

All authors contributed significantly toward study execution and manuscript preparation. TB contributed toward conceptual idea/research design. TB and PP contributed toward project management, data collection, data analysis, and manuscript preparation. SL and SRD provided consultation for research design and data analysis. SD assisted with data analysis, data processing, and reviewing manuscript. TB provided research funding, equipment, and facilities for perturbation training.

FUNDING

This project was funded by Department of Physical Therapy at University of Illinois at Chicago start-up funds allocated to TB.

ACKNOWLEDGMENTS

The authors would like to thank Jay Wang, Ph.D. for assistance with behavioral data processing and Mike Flannery for assistance with fMRI data collection.

REFERENCES

1. Pavol MJ, Runtz EF, Edwards BJ, Pai YC. Age influences the outcome of a slipping perturbation during initial but not repeated exposures. *J Gerontol A Biol Sci Med Sci*. (2002) 57:M496–503. doi: 10.1093/gerona/57.8.M496
2. Parijat P, Lockhart TE. Effects of moveable platform training in preventing slip-induced falls in older adults. *Ann Biomed Eng*. (2012) 40:1111–21. doi: 10.1007/s10439-011-0477-0
3. Bhatt T, Pai YC. Long-term retention of gait stability improvements. *J Neurophysiol*. (2005) 94:1971–9. doi: 10.1152/jn.00266.2005
4. Bhatt T, Wening JD, Pai YC. Adaptive control of gait stability in reducing slip-related backward loss of balance. *Exp Brain Res*. (2006) 170:61–73. doi: 10.1007/s00221-005-0189-5
5. Brady RA, Pavol MJ, Owings TM, Grabiner MD. Foot displacement but not velocity predicts the outcome of a slip induced in young subjects while walking. *J Biomech*. (2000) 33:803–8. doi: 10.1016/S0021-9290(00)00037-3
6. Marigold DS, Patla AE. Strategies for dynamic stability during locomotion on a slippery surface: effects of prior experience and knowledge. *J Neurophysiol*. (2002) 88:339–53. doi: 10.1152/jn.00691.2001
7. Yang F, Pai YC. Role of individual lower limb joints in reactive stability control following a novel slip in gait. *J Biomech*. (2010) 43:397–404. doi: 10.1016/j.jbiomech.2009.10.003
8. Patel P, Bhatt T. Modulation of reactive response to slip-like perturbations: effect of explicit cues on paretic versus non-paretic side stepping and fall-risk. *Exp Brain Res*. (2015) 233:3047–58. doi: 10.1007/s00221-015-4367-9
9. Jobges M, Heuschkel G, Pretzel C, Illhardt C, Renner C, Hummelsheim H. Repetitive training of compensatory steps: a therapeutic approach for postural instability in Parkinson's disease. *J Neurol Neurosurg Psychiatry* (2004) 75:1682–7. doi: 10.1136/jnnp.2003.016550
10. Fukuyama H, Ouchi Y, Matsuzaki S, Nagahama Y, Yamauchi H, Ogawa M, et al. Brain functional activity during gait in normal subjects: a SPECT study. *Neurosci Lett*. (1997) 228:183–6. doi: 10.1016/S0304-3940(97)00381-9
11. la Fougere C, Zwergal A, Rominger A, Forster S, Fesl G, Dieterich M, et al. Real versus imagined locomotion: a [18F]-FDG PET-fMRI comparison. *Neuroimage* (2010) 50:1589–98. doi: 10.1016/j.neuroimage.2009.12.060
12. Miyai I, Tanabe HC, Sase I, Eda H, Oda I, Konishi I, et al. Cortical mapping of gait in humans: a near-infrared spectroscopic topography study. *Neuroimage* (2001) 14:1186–92. doi: 10.1006/nimg.2001.0905

13. Iseki K, Hanakawa T, Shinozaki J, Nankaku M, Fukuyama H. Neural mechanisms involved in mental imagery and observation of gait. *Neuroimage* (2008) 41:1021–31. doi: 10.1016/j.neuroimage.2008.03.010
14. Sipp AR, Gwin JT, Makeig S, Ferris DP. Loss of balance during balance beam walking elicits a multifocal theta band electrocortical response. *J Neurophysiol*. (2013) 110:2050–60. doi: 10.1152/jn.00744.2012
15. Bakker M, De Lange FP, Helmich RC, Scheeringa R, Bloem BR, Toni I. Cerebral correlates of motor imagery of normal and precision gait. *Neuroimage* (2008) 41:998–1010. doi: 10.1016/j.neuroimage.2008.03.020
16. Taube W. Neurophysiological adaptations in response to balance training. *deuTScHe Z Sportmedizin*. (2012) 63:273–7. doi: 10.5960/dzsm.2012.030
17. Schubert M, Beck S, Taube W, Amtage F, Faist M, Gruber M. Balance training and ballistic strength training are associated with task-specific corticospinal adaptations. *Eur J Neurosci*. (2008) 27:2007–18. doi: 10.1111/j.1460-9568.2008.06186.x
18. Trimble MH, Koceja DM. Effect of a reduced base of support in standing and balance training on the soleus H-reflex. *Int J Neurosci*. (2001) 106:1–20. doi: 10.3109/00207450109149734
19. Mynark RG, Koceja DM. Down training of the elderly soleus H reflex with the use of a spinally induced balance perturbation. *J Appl Physiol. (1985)*. (2002) 93:127–33. doi: 10.1152/japplphysiol.00007.2001
20. Chen YS, Zhou S. Soleus H-reflex and its relation to static postural control. *Gait Posture* (2011) 33:169–78. doi: 10.1016/j.gaitpost.2010.12.008
21. Maki BE, McIlroy WE. Postural control in the older adult. *Clin Geriatr Med*. (1996) 12:635–58.
22. Fisher BE, Wu AD, Salem GJ, Song J, Lin CH, Yip J, et al. The effect of exercise training in improving motor performance and corticomotor excitability in people with early Parkinson's disease. *Arch Phys Med Rehabil*. (2008) 89:1221–9. doi: 10.1016/j.apmr.2008.01.013
23. Yen CL, Wang RY, Liao KK, Huang CC, Yang YR. Gait training induced change in corticomotor excitability in patients with chronic stroke. *Neurorehabil Neural Repair*. (2008) 22:22–30. doi: 10.1177/1545968307301875
24. Pai YC, Bhatt T, Yang F, Wang E. Perturbation training can reduce community-dwelling older adults' annual fall risk: a randomized controlled trial. *J Gerontol A Biol Sci Med Sci*. (2014) 69:1586–94. doi: 10.1093/gerona/glu087
25. Solopova IA, Kazennikov OV, Deniskina NB, Levik YS, Ivanenko YP. Postural instability enhances motor responses to transcranial magnetic stimulation in humans. *Neurosci Lett*. (2003) 337:25–8. doi: 10.1016/S0304-3940(02)01297-1
26. Adkin AL, Quant S, Maki BE, McIlroy WE. Cortical responses associated with predictable and unpredictable compensatory balance reactions. *Exp Brain Res*. (2006) 172:85–93. doi: 10.1007/s00221-005-0310-9
27. Mihara M, Miyai I, Hatakenaka M, Kubota K, Sakoda S. Role of the prefrontal cortex in human balance control. *Neuroimage* (2008) 43:329–36. doi: 10.1016/j.neuroimage.2008.07.029
28. Dietz V, Quintern J, Berger W. Cerebral evoked potentials associated with the compensatory reactions following stance and gait perturbation. *Neurosci Lett*. (1984) 50:181–6. doi: 10.1016/0304-3940(84)90483-X
29. Dietz V, Quintern J, Boos G, Berger W. Obstruction of the swing phase during gait: phase-dependent bilateral leg muscle coordination. *Brain Res*. (1986) 384:166–9. doi: 10.1016/0006-8993(86)91233-3
30. Diener HC, Horak FB, Nashner LM. Influence of stimulus parameters on human postural responses. *J Neurophysiol*. (1988) 59:1888–905. doi: 10.1152/jn.1988.59.6.1888
31. Allum JH, Honegger F. A postural model of balance-correcting movement strategies. *J Vestib Res*. (1992) 2:323–47.
32. Zehr EP, Komiyama T, Stein RB. Cutaneous reflexes during human gait: electromyographic and kinematic responses to electrical stimulation. *J Neurophysiol*. (1997) 77:3311–25. doi: 10.1152/jn.1997.77.6.3311
33. Lee A, Bhatt T, Liu X, Wang Y, Pai YC. Can higher training practice dosage with treadmill slip-perturbation necessarily reduce risk of falls following overground slip? *Gait Posture* (2018) 61:387–392. doi: 10.1016/j.gaitpost.2018.01.037
34. de Leva P. Adjustments to Zatsiorsky-Seluyanov's segment inertia parameters. *J Biomech*. (1996) 29:1223–30. doi: 10.1016/0021-9290(95)00178-6
35. Yang F, Bhatt T, Pai YC. Role of stability and limb support in recovery against a fall following a novel slip induced in different daily activities. *J Biomech*. (2009) 42:1903–8. doi: 10.1016/j.jbiomech.2009.05.009
36. Pai YC. Movement termination and stability in standing. *Exerc Sport Sci Rev*. (2003) 31:19–25. Available online at: https://journals.lww.com/acsm-essr/Fulltext/2003/01000/Movement_Termination_and_Stability_in_Standing.5.aspx
37. Yang F, Anderson FC, Pai YC. Predicted threshold against backward balance loss in gait. *J Biomech*. (2007) 40:804–11. doi: 10.1016/j.jbiomech.2006.03.015
38. Glover GH, Thomason ME. Improved combination of spiral-in/out images for BOLD fMRI. *Magn Reson Med*. (2004) 51:863–8. doi: 10.1002/mrm.20016
39. Bhatt T, Patel P, Dusane S, DelDonno SR, Langenecker SA. Neural mechanisms involved in mental imagery of slip-perturbation while walking: a preliminary fMRI study. *Front Behav Neurosci*. (2018) 12:203. doi: 10.3389/fnbeh.2018.00203
40. Cox RW, Chen G, Glen DR, Reynolds RC, Taylor PA. FMRI clustering in AFNI: false-positive rates redux. *Brain Connect*. (2017) 7:152–171. doi: 10.1089/brain.2016.0475
41. Sakai K, Hikosaka O, Miyauchi S, Takino R, Sasaki Y, Putz B. Transition of brain activation from frontal to parietal areas in visuomotor sequence learning. *J Neurosci*. (1998) 18:1827–40. doi: 10.1523/JNEUROSCI.18-05-01827.1998
42. Meyer T, Qi XL, Stanford TR, Constantinidis C. Stimulus selectivity in dorsal and ventral prefrontal cortex after training in working memory tasks. *J Neurosci*. (2011) 31:6266–76. doi: 10.1523/JNEUROSCI.6798-10.2011
43. Floyer-Lea A, Matthews PM. Changing brain networks for visuomotor control with increased movement automaticity. *J Neurophysiol*. (2004) 92:2405–12. doi: 10.1152/jn.01092.2003
44. Horak FB, Diener HC. Cerebellar control of postural scaling and central set in stance. *J Neurophysiol*. (1994) 72:479–93.
45. Imamizu H, Sugimoto N, Osu R, Tsutsui K, Sugiyama K, Wada Y, et al. Explicit contextual information selectively contributes to predictive switching of internal models. *Exp Brain Res*. (2007) 181:395–408. doi: 10.1007/s00221-007-0940-1
46. Smith BA, Jacobs JV, Horak FB. Effects of magnitude and magnitude predictability of postural perturbations on preparatory cortical activity in older adults with and without Parkinson's disease. *Exp Brain Res*. (2012) 222:455–70. doi: 10.1007/s00221-012-3232-3
47. Young MP, Yamane S. Sparse population coding of faces in the inferotemporal cortex. *Science* (1992) 256:1327–31. doi: 10.1126/science.1598577
48. de Jong BM, van der Graaf FH, Paans AM. Brain activation related to the representations of external space and body scheme in visuomotor control. *Neuroimage* (2001) 14:1128–35. doi: 10.1006/nimg.2001.0911
49. Graydon FX, Friston KJ, Thomas CG, Brooks VB, Menon RS. Learning-related fMRI activation associated with a rotational visuo-motor transformation. *Brain Res Cogn Brain Res*. (2005) 22:373–83. doi: 10.1016/j.cogbrainres.2004.09.007
50. Culham JC, Cavina-Pratesi C, Singhal A. The role of parietal cortex in visuomotor control: what have we learned from neuroimaging? *Neuropsychologia* (2006) 44:2668–84. doi: 10.1016/j.neuropsychologia.2005.11.003
51. Anguera JA, Russell CA, Noll DC, Seidler RD. Neural correlates associated with intermanual transfer of sensorimotor adaptation. *Brain Res*. (2007) 1185:136–51. doi: 10.1016/j.brainres.2007.09.088
52. Ionta S, Ferretti A, Merla A, Tartaro A, Romani GL. Step-by-step: the effects of physical practice on the neural correlates of locomotion imagery revealed by fMRI. *Hum Brain Mapp*. (2010) 31:694–702. doi: 10.1002/hbm.20898
53. Malouin F, Richards CL, Jackson PL, Dumas F, Doyon J. Brain activations during motor imagery of locomotor-related tasks: a PET study. *Hum Brain Mapp*. (2003) 19:47–62. doi: 10.1002/hbm.10103
54. Grafton ST, Schmitt P, Van Horn J, Diedrichsen J. Neural substrates of visuomotor learning based on improved feedback control and

prediction. *Neuroimage* (2008) 39:1383–95. doi: 10.1016/j.neuroimage.2007.09.062
55. Hester R, Barre N, Murphy K, Silk TJ, Mattingley JB. Human medial frontal cortex activity predicts learning from errors. *Cereb Cortex* (2008) 18:1933–40. doi: 10.1093/cercor/bhm219
56. Marchal-Crespo L, Hollnagel C, Brugger M, Kollias S, Riener R. An fMRI pilot study to evaluate brain activation associated with locomotion adaptation. *IEEE Int Conf Rehabil Robot*. (2011) 2011:5975371. doi: 10.1109/ICORR.2011.5975371
57. Harada T, Miyai I, Suzuki M, Kubota K. Gait capacity affects cortical activation patterns related to speed control in the elderly. *Exp Brain Res*. (2009) 193:445–54. doi: 10.1007/s00221-008-1643-y
58. Yuan J, Blumen HM, Verghese J, Holtzer R. Functional connectivity associated with gait velocity during walking and walking-while-talking in aging: a resting-state fMRI study. *Hum Brain Mapp*. (2015) 36:1484–93. doi: 10.1002/hbm.22717
59. Porro CA, Francescato MP, Cettolo V, Diamond ME, Baraldi P, Zuiani C, et al. Primary motor and sensory cortex activation during motor performance and motor imagery: a functional magnetic resonance imaging study. *J Neurosci*. (1996) 16:7688–98. doi: 10.1523/JNEUROSCI.16-23-07688.1996
60. Blumen HM, Holtzer R, Brown LL, Gazes Y, Verghese J. Behavioral and neural correlates of imagined walking and walking-while-talking in the elderly. *Hum Brain Mapp*. (2014) 35:4090–104. doi: 10.1002/hbm.22461
61. Wittenberg E, Thompson J, Nam CS, Franz JR. Neuroimaging of human balance control: a systematic review. *Front Hum Neurosci*. (2017) 11:170. doi: 10.3389/fnhum.2017.00170

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer CP and handling Editor declared their shared affiliation at the time of the review.

frontiers in Neurology

REVIEW
published: 07 February 2019
doi: 10.3389/fneur.2019.00062

Motor Learning Deficits in Parkinson's Disease (PD) and Their Effect on Training Response in Gait and Balance: A Narrative Review

Markey Olson[1,2], *Thurmon E. Lockhart*[1]* *and Abraham Lieberman*[2]

[1] Locomotion Research Laboratory, School of Biological and Health Systems Engineering, Arizona State University, Tempe, AZ, United States, [2] Muhammad Ali Movement Disorders Clinic, St. Joseph's Hospital and Medical Center, Barrow Neurological Institute, Phoenix, AZ, United States

OPEN ACCESS

Edited by:
Emily Keshner,
Temple University, United States

Reviewed by:
Davide Martino,
King's College London, United Kingdom
Fabio Augusto Barbieri,
State University Paulista Júlio de Mesquita Filho, Brazil
Rodrigo Vitório,
São Paulo State University, Brazil

***Correspondence:**
Thurmon E. Lockhart
thurmon.lockhart@asu.edu

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: 31 July 2018
Accepted: 17 January 2019
Published: 07 February 2019

Citation:
Olson M, Lockhart TE and Lieberman A (2019) Motor Learning Deficits in Parkinson's Disease (PD) and Their Effect on Training Response in Gait and Balance: A Narrative Review. Front. Neurol. 10:62. doi: 10.3389/fneur.2019.00062

Parkinson's disease (PD) is a neurological disorder traditionally associated with degeneration of the dopaminergic neurons within the substantia nigra, which results in bradykinesia, rigidity, tremor, and postural instability and gait disability (PIGD). The disorder has also been implicated in degradation of motor learning. While individuals with PD are able to learn, certain aspects of learning, especially automatic responses to feedback, are faulty, resulting in a reliance on feedforward systems of movement learning and control. Because of this, patients with PD may require more training to achieve and retain motor learning and may require additional sensory information or motor guidance in order to facilitate this learning. Furthermore, they may be unable to maintain these gains in environments and situations in which conscious effort is divided (such as dual-tasking). These shortcomings in motor learning could play a large part in degenerative gait and balance symptoms often seen in the disease, as patients are unable to adapt to gradual sensory and motor degradation. Research has shown that physical and exercise therapy can help patients with PD to adapt new feedforward strategies to partially counteract these symptoms. In particular, balance, treadmill, resistance, and repeated perturbation training therapies have been shown to improve motor patterns in PD. However, much research is still needed to determine which of these therapies best alleviates which symptoms of PIGD, the needed dose and intensity of these therapies, and long-term retention effects. The benefits of such technologies as augmented feedback, motorized perturbations, virtual reality, and weight-bearing assistance are also of interest. This narrative review will evaluate the effect of PD on motor learning and the effect of motor learning deficits on response to physical therapy and training programs, focusing specifically on features related to PIGD. Potential methods to strengthen therapeutic effects will be discussed.

Keywords: Parkinson's disease, motor learning, gait and balance, motor training, postural learning, physical therapy, repeated perturbation training

INTRODUCTION

Parkinson's disease (PD), a neurological disorder characterized by bradykinesia, rigidity, tremor and postural instability and gait disability (PIGD), is known mainly as a degeneration of the dopaminergic neurons of the substantia nigra pars compacta. Resulting inhibition of the direct pathway and excitation of the indirect pathway in turn excites the globus pallidus interna (GPi), which leads to inhibition of the thalamus and the pedunculopontine nucleus (PPN) (1). Up to 80% of dopaminergic neurons may be destroyed before a patient exhibits significant signs of PD. The loss of such a substantial portion of dopaminergic cells affects the cardinal motor symptoms of PD and contributes to non-motor symptoms, including autonomic dysfunction, cognitive and neurobehavioral abnormalities, and sleep disorders (1–3). While levodopa is extraordinarily helpful for some of the symptoms of PD, others, especially related to PIGD and non-motor features, are relatively unaffected by current pharmacological or surgical treatments (4–10), making physical therapy and motor training one of the most promising current options for improving these symptoms (11–16). However, research indicates that PD leads to degradation of motor learning, which could limit the benefits of therapy (17–24). To maximize the benefit that may be achieved, the mechanisms of learning affected by PD need to be understood and the strategies that best circumvent these difficulties be researched.

While the dopaminergic system is the one most frequently implicated in PD, other neurological systems are also affected, including the cholinergic, noradrenergic, glutaminergic, and GABAergic pathways (25–28). The cholinergic system in particular has been intensely researched recently, though motor learning literature specifically related to the PPN and other cholinergic centers is still sparse. Research supports the effect of cholinergic denervation on attention, fall history, levodopa resistance, more advanced symptoms, and non-tremor dominant subtypes of PD (24, 29–32). All of these factors have also been related to motor learning degradation, suggesting that the cholinergic system and possibly other affected systems may play a role in modulating learning behavior (33–40). Multifactorial influence helps to explain somewhat heterogenous results of studies of both baseline gait and balance and motor learning in PD (17–24). Understanding these interconnected pathways and their effects in PD can help to identify the aspects of gait, balance and motor learning that patients struggle with and help to proscribe therapies and treatments most likely to benefit.

This paper will discuss previous research into the effects of PD on motor learning, focusing on the types of learning affected, the severity of these deficits, and modifications that might negate some of these effects. Taking these factors into account, recent research regarding the ability of patients with PD to respond to physical, exercise, and repeated perturbation training (RPT) therapies will be reported, with specific focus given to those studies related to the training of gait and balance. Methods utilized for literature review and article selection are further detailed in the **Appendix**. Future directions for research into the mechanisms related to gait, balance, and motor learning in PD and potential training strategies to improve motor learning and retention will also be discussed.

MOTOR LEARNING IN PD

Studies have closely linked the striatal system to motor learning (22, 41, 42), suggesting that patients with PD would, in addition to the degradation of their movement patterns at baseline, have difficulty acquiring movement schema to learn tasks. However, studies examining the ability of patients with PD to learn and adapt to motor tasks have been somewhat inconsistent (11–24, 43–51). While studies indicate that individuals with PD are still able to learn motor tasks, there is disagreement about the amount and type of possible improvement. One explanation for this is that conflicting studies utilized different types of learning. Specific aspects of learning are more severely impacted by PD than others, especially in the early stages of the disease. It has been indicated that people with PD are able to learn specific tasks, though they may need more practice than healthy controls to do so, but that these skills are not easily generalizable to other tasks, even if those tasks are similar (22, 43–48). The slower rate of learning, lack of generalizability, and the difficulty individuals with PD exhibit in dual-tasking imply that people with PD are still able to learn in a feedforward manner, but that they are unable to easily adjust to changes requiring use of automatic or reactive mechanisms. Because of this inability, they have difficulty adapting to changing conditions or monitoring multiple tasks, both of which are often required for balance and gait. To better understand why this is this case, it is important to differentiate types of motor learning and how they are specifically affected by PD.

Explicit vs. Implicit Learning

Existing literature about the deficits of persons with PD in explicit and implicit learning has been somewhat conflicting, due in part to differing experimental definitions of the terms. Implicit, or procedural learning, is generally defined as motor skill learning acquired incidentally through practice and is often considered to be due to unconscious or reactive mechanisms. Explicit learning, on the other hand (or declarative learning), is more intentional learning often defined as consciously learned. It is based on past similar experience and has previously referred to cognitive tasks, such as remembering lists of words, while motor tasks would have been grouped with procedural learning. Because of this, motor learning researchers, in adapting implicit vs. explicit learning definitions to describe aspects of motor learning, have often differed in exact usage, which has led to confusion about what aspects are affected in PD. In order to better clarify the types of learning affected by PD, this paper will discuss the results of papers using differing definitions of explicit vs. implicit learning separately and then attempt to unite these findings in a cohesive, multifaceted whole.

The most commonly adopted definition of implicit learning is the ability of subjects to learn a repeating task without awareness of the pattern (in comparison with ability to learn a randomized task), while explicit learning may be measured as the ability to improve in the context of a known pattern. Studies have

indicated that implicit and explicit learning of this type utilize different neural pathways. Implicit learning is associated with basal ganglia structures while explicit learning is more closely associated with the medial temporal lobe, implying that patients with PD should have difficulty mainly with implicit learning (52–59). Most studies of motor learning in PD have found that this type of implicit learning is affected by PD, though whether this problem is an early symptom of the disease or a progressive complication is still unclear (20, 23, 24, 60–64). A recent study suggests that implicit learning involving the integration of multiple components is more affected by PD than single-component tasks (65), which might be related to attentional resources. There is some disagreement about whether explicit learning is spared in PD, with many studies finding that both implicit and explicit learning are affected to some extent (20, 61, 66). It is currently unknown to what degree potential explicit learning degradation is affected by factors, such as disease duration, degeneration of the cholinergic and other neurotransmitter systems, and comorbidities, such as dementia and cognitive decline. Studies appear to implicate PD in attenuation of both implicit and explicit learning processes defined in this matter. However, patients with PD still appear to be better able to operate in explicit than implicit conditions. While healthy controls completed a motor targeting task most accurately with minimal outside feedback, PD subjects were better able to complete the same task in the condition with the highest amount of feedback (67).

Other studies define implicit vs. explicit learning based on the amount of error present during learning trials. The generation of a large, sudden error is considered explicit learning while slow, gradual introduction of error, or restriction of error using guidance systems, is considered to induce implicit learning. This definition of learning found that patients were able to adapt to implicit changes but struggled with or were completely unable to adapt to explicit perturbations, especially in the context of other tasks. A visuomotor perturbation study utilizing reaching tasks found that individuals with PD adapted similarly to healthy controls during introduction of small, gradual visuomotor perturbations leading to minimal errors, but were slower to adapt and displayed lowered magnitudes of adaptation during larger perturbations (68). A study examining the ability of subjects to learn a hammering task either with or without a guidance system found that those that were constrained by the guidance system showed increased learning and learning automaticity, as evidenced by ability to translate the hammering motion to dual-taking conditions. However, it is uncertain whether the learning effects obtained through this method translate to non-guided motions upon the removal of the guidance system (69). This implies that slow, gradual initiation of perturbations may be more helpful for patients with PD, such as through the use of assisted or constrained training. However, these results may not be easily translated to conditions outside of training unless training conditions are slowly scaled to mirror them.

Together, these results indicate that people with PD, while able to learn, have difficulty creating and switching between motor sets. They may require explicit information and additional practice relative to healthy age-matched controls to do so. The use of augmented cues (19, 67) and gradual introduction of perturbation (68, 69) may help patients to create feedforward motor sets. Such cues may be especially helpful during conditions that require attention to be divided or require reaction to unexpected perturbations. The ability of individuals with PD to retain training effects is also contested (19), possibly due to inability to automate sets.

In addition to the above definitions of implicit vs. explicit learning, a related concept of feedforward vs. reactive control of movement patterns is often discussed. A distinction does need to be made. One need not be consciously aware of a feedforward adaptation, though feedforward movements may be less likely to be fully automatized, and reactive mechanisms, while more akin to implicit learning, can also be trained explicitly. For this reason, feedforward and reactive mechanisms will be discussed separately in the next section.

Feedforward vs. Reactive Mechanisms

Patients with PD are thought to have major difficulties in staging reactive responses to motor perturbations. Bradykinesia, akinesia, reduced proprioceptive inputs, and other factors likely play a role in this disability. Impaired feedback mechanisms, commonly noted in PD, also play a role. Individuals with PD are known to have proprioceptive and tactile sensory deficits (70), leading to decreased feedback and increased noise and ambiguity during motor tasks. These deficits are thought to cause increased reliance on visual feedback and attention-based control (71). People with PD also have difficulty updating task information based on discrete feedback in decision-making trials (72), suggesting an inability to properly use feedback that is received. Patients with PD appear to be unable to correctly determine the importance of feedback and events (73), which likely contributes not only to deficits in learning but also to problems with attention and motivation.

However, it appears that an independent difficulty in creating, automatizing, and switching between motor sets is also involved. This progressive loss of automatic motor control increases reliance on goal-directed control mechanisms, even for habitual actions (22, 74). Many studies have found defects in reactive responses and responses to novel scenarios in PD but improvement with practice and feedforward planning (44, 45, 75–77). Similarly, it was found that people with PD react differently to planned vs. unplanned stopping during gait, whereas healthy controls do not. Patients with PD are better able to stop during planned scenarios, suggesting that feedforward modulation plays an effect (78). Specific defects in shifting between sets are evidenced by reliance on greater cognitive control (79, 80) and reduced automaticity, which causes dual-tasking deficits during movement (81, 82). Difficulty in acquiring and expressing habitual motor patterns has been shown to lead to impairments expressing automatic components of behavior (83, 84), learning implicitly (60–66, 85), performing an unfamiliar task (86), and combining information from different reference frames in order to guide movement (77, 87). However, while feedforward learning seems fairly intact, if slow, these learned sets may not be retained, further indicating an impairment in switching between motor sets (18, 21). In summary, patients with

PD have difficulty rapidly and flexibly switching between motor plans in a reactive or unconscious fashion. Such impairment leads to difficulties in novel tasks, tasks in which external factors may change needed forces and trajectories, and dual-tasks, in which two sets must be held simultaneously and rapidly switched between.

Factors Affecting Motor Learning in PD

A number of factors related to PD might have a major impact on the severity of impact on motor learning: severity and duration of disease, disease subtype (tremor dominant, PIGD dominant, etc.), amount of degeneration in dopaminergic and non-dopaminergic neurotransmitter systems, and cognitive symptoms. Most of these factors have not yet been well-researched. Research suggests that motor learning worsens with disease severity, though these trends are still characterized as weak to moderate. Worsening cognitive and axial symptoms especially appear to predict a decrease in motor learning ability (24, 30, 32). Axial symptoms in particular have been directly linked to worsening motor learning performance, even independently of overall disease severity (88). Specifically, patients with freezing of gait (FOG) seem to exhibit worse learning, retention, and generalization in motor learning tasks (29, 89, 90), though confounds make it difficult to determine the exact influence of a generally longer disease course and worsened disease severity, fall risk, and cognitive profile associated with FOG (91–93). Subtype of PD, as characterized by symptom profile, may play a role in impact on motor learning (31). Laterality of symptoms of PD may also affect acquisition of motor skills in PD, with left-onset PD being correlated with more errors during task acquisition than right-onset PD (94). However, motor learning is affected early in PD and learning deficits appear to be present on both sides, even before traditional symptoms are evident on the less-affected side (95).

Cognitive features of the disease, such as impairments in memory, attention, and executive function (EF) also play a role in motor learning. Memory and other components of EF are notably affected in PD, even early in the disease and with no apparent cognitive impairment (96, 97). These deficits have been attached to deficits in both motor symptoms (97–100) and in learning (101, 102), demonstrating that more widespread frontostriatal system involvement might be related to defects of motor learning in PD. Many of the specific aspects of EF impacted in PD, including planning and attentional deficits, information organization and retrieval, task-switching and establishment of a motor set, feedback-based learning, and sensitivity to interference during learning, directly affect the ability of individuals with PD to learn and modulate motor patterns (97, 98, 103, 104). Dual-tasking may be especially affected by these problems (105). Studies have shown that procedural and spatial memory is especially affected in PD, while verbal and episodic memories remain largely intact (103, 104, 106, 107), suggesting that areas of cognition associated with motor planning and execution may be preferentially affected by the disease. Deficits within attentional networks, and specifically the connections between the putamen and the motor cortex, prevent the sustained switch from controlled to automatic behavior (108). The close interplay between the cortical and subcortical areas regulating motor, cognitive, and motivational aspects of habitual, automatic movement are dysfunctional in PD (109).

In addition to direct effects of PD on motor learning, it has been suggested that external changes, such as medication and environment can impact the ability of patients to learn, retain, and update motor information. One of the most-researched factors affecting learning in PD is levodopa. While levodopa is remarkably beneficial in treating many aspects of PD, including tremor, rigidity, and bradykinesia, it is thought not to improve, or possibly even to worsen, certain aspects of motor learning. Additional deficits in motor learning while in the "on"-state (that is, while the short-term effects of levodopa are active) have been noted in upper (110) but not lower (111–114) extremity learning. However, differences in study design suggest that this difference may be due to the stage and type of learning studies, with specific portions of the acquisition phase of learning most affected (30). Levodopa may attenuate some of the motor deficits in learning while worsening cognitive aspects (115–117). This suggests that while dopaminergic dysfunction plays a role in motor learning, other systems, such as the frontostriatal system, are also key. While not yet well-researched, early data suggests that deep brain stimulation (DBS) might have a positive effect on learning (118). Environmental and task characteristics may also significantly affect ability to learn in PD. One study found that task difficulty significantly affected the ability of people with PD to learn relative to healthy controls. Dual-task and reactive tasks significantly reduced or even eliminated the ability of PD subjects, but not controls, to learn and retain improvements (119).

Increasing the amount of external information provided to individuals with PD, such as through cueing, can significantly improve acquisition, automaticity, and retention of motor tasks, even once cues are removed (67, 120). The beneficial effects of cueing on gait and motor learning (121, 122) in PD are likely largely caused by addressing cognitive factors of the disease, such as attention (71). By directing attention to the motor action being practiced and giving feedback about its correctness, cueing can facilitate feedforward learning. Reward and motivational pathways are also likely affected. PD is known to cause apathy, blunting subjective value of reward (123). This leads to a reduced tendency to evaluate and monitor outcomes and negatively impacts feedback-learning. By providing an external, objective reward, cueing may allow PD patients to incorporate the benefits of positive movement patterns (51).

EFFECT OF TRAINING ON PIGD

Based on studies of motor learning in PD, it is expected that training or therapy specifically targeting gait and balance would lead to significant improvement in these areas. However, these improvements might be less drastic, require more repetition, and be less generalizable to other tasks when compared to healthy controls. Current research appears to support this, as will be discussed in the proceeding sections. Still, there is still need for additional research to discern the types, quantity and

intensity of training that is most helpful to people with PD, the generalizability of this training to other tasks, the effectiveness of this training during novel or complex tasks, and the effect of both disease and external factors on learning rate and ability. The following sections will discuss results showing the effects both of traditional therapies, such as PT and exercise (when specifically focused on gait and balance practice) and of repeated perturbation training (an experimental concept that attempts to train individuals how to respond to unexpected perturbation by repeatedly eliciting such events) on gait and posture in PD.

Physical Therapy and Exercise Therapy

Studies of motor learning indicate that repeated and continued physical training may be the best method to counteract the degradation in motor behavior seen in PD. Physical and exercise therapy have long been noted to be beneficial for patients with PD, improving cardinal symptoms activities of daily living and increasing subjective quality of life (124–134). Recently, technological advancements in therapy delivery (such as through the use of virtual reality and other gamification elements) and ability to calculate objective outcome measures (using IMUs and similar technology) has led to an increasing interest in the effects of such therapies on PIGD features of PD. Many studies have noted improvements in gait and balance following these therapies (11, 127, 135–138). Studies have focused on determining the best types, intensity, and duration of therapy, the effects of the incorporation of technology (both in increasing duration and intensity of exercise and in improving PIGD symptoms), and the duration of sustained effect or need for repeated doses of therapy.

While there is great interest in the types of exercises and techniques that might be best applied to improve specific features of PD, controlled research studies documenting the comparative successes of different options are still relatively few in number. They have mostly utilized small sample sizes and have had somewhat conflicting results. Direct comparisons between studies are made more difficult by the lack of homogeneity between treatments (an example of differing treatment parameters may be seen in **Table 1** and outcomes are compared in **Table 2**). Many studies have differing definitions of treatments even when using the same name, and the duration, intensity, and frequency of training differ between studies. This is made more difficult by the fact that most trials compare results only to control groups (usually similar subjects not given any therapy regiment, but sometimes patients provided with therapy not intended to specifically improve balance) instead of other balance interventions. In the future, it will be important to compare intensity-matched treatment options directly in a controlled manner.

Research from motor learning shows that training should ensure enough repetition to allow adequate time for feedforward learning. Introducing exercises using scaffolding in the form of physical assistance, cueing, or enhanced information that is initially given but progressively removed may prove useful. It is also important that exercises be individually relevant but collectively diverse enough to provide meaningful change in multiple aspects of PIGD (188). The use of technology in training of gait and balance for PD has been of interest. Several studies have utilized gamification of training, technology to assist, resist or create movements or perturbation, augmented feedback and VR (119, 121, 139, 144, 155, 169, 172, 173, 179, 180, 182, 183, 189). Cueing in particular shows promise and is an important area of research (120, 145, 155, 157–162, 171, 173, 190).

The main therapy options that have been researched related to improvement of PIGD symptoms of PD are balance training, treadmill training, and resistance or strength training. Generally, strength training, including that focusing on the lower-limbs, has been found to be less likely to improve features of PIGD and is sometimes used as a control group in studies focusing on gait and balance therapies. However, a study comparing the effects of 7 weeks (2 h-long sessions per week) of resistance vs. balance training found that resistance training but not balance training contributed to significant improvements in the Fullerton Advanced Balance (FAB) scale and Unified Parkinson's Disease Rating Scale (UPDRS) scores, though between-group statistical comparison did not differ between the therapies (142). Gait speed and TUG have also shown improvement (129, 191).

A large number of studies regarding the effects of therapy of gait and balance have been related to the use of treadmill therapy (192, 193). Improvements in gait speed, stride length, and symptomatic scales have been noted both immediately and in the long-term following treadmill therapy (126, 146–148, 167). Additionally, some studies have noted improvement in post-urography following treadmill training, suggesting some level of generalizability (146). Improvements appear to be obtained long-term (146). These changes were noted in some studies after only a single session of training. Adverse events were not observed within these studies, and patients were able to achieve a high-intensity of training (149, 192). Treadmill training utilizing virtual reality to simulate dual-tasks and obstacles has been found to improve gait measures under diverse conditions (144). Studies also showed that treadmill therapy compared favorably to other therapy techniques. Pohl et al. comparing speed-dependent treadmill training, limited progressive treadmill training, conventional gait training, and non-intervention controls, found that treadmill training significantly improved gait parameters compared to both controls and conventional gait training (149). However, Myers et al. found that, while treadmill therapy, tango dance, and guided stretching all improved walking velocity and stride length, there was no difference between the three groups (150). Sale et al. found that robot-assisted walking, but not traditional treadmill training, improved gait velocity and stride length, though this result conflicts with all other such studies (151).

The addition of body-weight support to allow for increased intensity of training may help to increase the effect of treadmill therapy (151, 192). Miyai et al. reported that body-weight supported treadmill training significantly improved UPDRS scores, ambulation speed, and number of steps needed to complete a 10-meter walk when compared to traditional physical therapy (163, 164). Another study analyzing the effect of high-intensity body-weight supported treadmill training vs. lower intensity exercise or education, found that, while all three groups improved UPDRS scores, only the high-intensity treadmill

TABLE 1 | Comparison of study design from studies regarding the effect of therapy and training on quantitative measures of gait and balance.

Therapy type	Sample size (per group)	Treatments	Control/Comparison groups	# of Weeks	# of Sessions/Week	Session duration
Strength/resistance training	10–15 (139, 140)	High-intensity quadriceps (129)	Exercise (129, 141)	4 (140)	1–2 (141–143)	40–60 min (12, 129, 139–142)
	20–25 (12, 129, 142, 143)	Lower limb (12, 139–142)	Multi-component (12, 139, 141, 142)	7 (142)	3 (129, 140)	60–90 min (143)
	65–70 (141)	PRE (143)	Balance (142)	12 (12, 129, 139)	3–5 (12, 139)	
			RPT (140)	24 (141)		
				104 (143)		
Gait training	<10 (126)	Treadmill walking (126, 144–154)	Overground walking (146, 155, 156)	1 (149)	1(149)	20–30 min (120, 126, 145, 149, 154, 155, 157–161)
	10–15 (145–147, 150, 152, 156, 157, 162–166)	Robot-assisted (151, 153, 167)	Exercise/Conventional therapy (147, 149, 164, 165, 167)	3 (120)	2 (154, 155)	40–60 min (144, 147, 148, 151, 153, 156, 163–165, 167)
	15–20 (149)	BWSTT (160, 161, 163–165)	Tango (150)	4 (151, 153, 157, 159–161, 163, 164, 167)	2–3 (152)	Progressive (146, 152, 166)
	20–25 (144, 148, 153, 159–161, 167, 168)	Backward gait (156)	Stretching (150)	5 (146, 152)	3 (120, 144–148, 156–158, 163–166)	Not given (150)
	150–160 (120)	Cued gait (120, 145, 152, 155, 157–162)	Education/Normal Treatment (160, 161, 165)	6 (126, 144, 145, 155, 166)	4 (126, 160, 161)	
		Cued treadmill walking (159)	RPT (154)	8 (154, 156, 158, 165)	5 (151, 153)	
			None (120, 126, 144, 148, 149, 153, 156–158, 166)	12 (148, 150)	6 (167)	
				24 (147)	7 (159)	
					Not given (150)	
Balance training	<10 (169, 170)	Cued (169, 171)	Exercise (172)	4 (171)	2 (142, 173, 174)	20–30 min (170, 171, 173)
	10–15 (171, 173, 174)	Weight-shift (142, 174)	Resistance (142)	6 (169, 173)	3 (13, 169–172, 175)	30–40 min (169)
	20–25 (142, 175)	Sensory perturbation (13, 170, 172, 173, 175)	Balance + resistance (170)	7 (13, 142, 172)		40–60 min (13, 142, 172, 174, 175)
	30–35 (13)	Virtual reality (173)	Home-based balance (13, 174, 175)	8 (174, 175)		
	35–40 (172)		No training (171, 173)	10 (170)		
			None (169)			
Multi-component training	<10 (170)	Balance + resistance (170)	Balance (170)	3 (176)	1–2 (141, 143, 177)	40–60 min (12, 139, 141, 170, 177, 178)
	10–15 (143, 177, 178)	Treadmill + obstacles + balance (178)	Resistance (12, 137, 139, 141)	4 (168, 178)	3 (170, 178)	60–120 min (143, 168)
	25–30 (12, 139)	Gait + balance (12, 139, 168, 176)	Stretching (141)	10 (170, 177)	3–5 (12, 139)	Not given (176)
	30–35 (168, 176)	mFC (177)	No training (168, 177, 178)	12 (12, 139)	3–14 (168)	
	65–70 (141)	Tai chi (141, 177)	None (176)	24 (141)	6 (176)	
				104 (143)		

(Continued)

TABLE 1 | Continued

Therapy type	Sample size (per group)	Treatments	Control/Comparison groups	# of Weeks	# of Sessions/Week	Session duration
Home-based gait training	10–15 (179)	Home-based cueing (179, 180)	Conventional gait and cognitive (in-home) (181)	2 (179)	3 (180)	20–30 min (179–181)
	20–25 (180)	Walking (180)	None (179)	6 (180, 181)	4 (181)	
	55–65 (181)	Dual-tasking (181)			7 (179)	
Home-based balance training	10–15 (162, 174, 182–184)	Sensory perturbation (175)	Therapist-guided balance (172, 174, 175)	6 (182–184)	2 (174, 182, 183, 185)	20–30 min (185)
	20–25 (175)	Tailored exercise (162)	Exercise (182, 183, 185)	7 (172)	3 (140, 172, 175, 184)	40–60 min (140, 172, 174, 175, 182–184)
	35–40 (172)	Wii Fit (172, 182–185)	Education (182, 183)	8 (174, 175)	Not given (162)	Not given (162)
		Kinect (174)	None (162, 184)	10 (162)		
				12 (185)		
Repeated perturbation training (RPT)	<10 (15, 186)	Postural perturbation (16, 187)	Treadmill walking (14, 154)	1 (14, 186, 187)	1 (14, 186, 187)	20–30 min (14, 16, 154)
	10–15 (16, 140, 187)	Treadmill perturbation (14, 15, 154)	Resistance (140)	2 (16)	2 (154)	40–60 min (15)
	20–25 (14, 154)	Step training (140, 186)	No training (15)	4 (140)	3 (15)	Not given (186, 187)
			None (16, 186, 187)	8 (15, 154)	14 (16)	

BWSTT, body-weight supported treadmill training; PRE, progressive resistance exercise; mFC, modified fitness counts.
This table documents the study characteristics of each therapeutic study reviewed for this paper. Papers were characterized by type of therapy provided, and approximate sample size of each group per study (many studies had slightly unequal group sizes), control or comparison groups utilized, number of weeks and sessions of therapy and the duration of each therapy session were noted. Both the therapeutic method used and the duration/intensity of therapy varied widely between studies, showing a need for more standardized protocols in the future.

training significantly improved gait measures (165). Cueing also appears to improve results of treadmill training (152).

Other types of gait therapy have also shown to be effective. Overground walking, both backward and forward, have been evaluated and found to improve gait characteristics (156). Cued gait training appears to increase stride length, walking speed, dynamic post-urography, and Berg Balance Scale scores (120, 145, 155, 157–159). Wearing a home-based cueing system for as little as 30 min per session has been found to increase gait velocity and stride length and improve FOG (179, 180). Home-based dual-tasking therapy has been shown to improve stride length and cadence (181). Robotic-assisted gait therapy, in which a wearable robot assists in locomotion during training has also been shown effective in improving mobility (153, 160, 167). Studies comparing robot-assisted gait training with other gait therapies found than robot-assisted training may actually be more effective than treadmill therapy (153) and overground gait training with verbal cueing (160, 161).

Balance therapies utilizing static and dynamic stance are common and appear to be effective in improving many gait and balance measures. Atterbury et al. found that both therapist-led and home-based balance training improved walking velocity, cadence and stride length and Berg Balance Scale scores, though therapist-led therapy was more effective (175). A study comparing balance training with augmented feedback to a control group of lower-limb strength training found that balance training more significantly improved measures of limits-of-stability, one-leg stance, and gait, and was the only group to improve balance confidence (139). Cued sit-to-stand training has also been shown to improve balance and stability (171). Cued training during practice on courses involving turns reduced FOG (166). A study comparing the training of compensatory stepping using a dancing game with visual cues to a control group receiving strength training found that the step training significantly improved reaction time, movement velocity, limits of stability and UPDRS gait sub-score relative to the control group, but both groups improved gait velocity and only strength training improved cadence during gait (140).

Home-based balance therapies have often been researched in recent years, often using virtual reality and video game technology, such as Wii Fit (194). This type of training has been found to be effective in improving multiple features of gait and static stance, suggesting that home-based therapies may be an effective supplement or alternative to in-person therapies (172, 182–185). Dynamic balance is also improved, as measured by the Sensory Organization Test (SOT) (162). A trial using the Xbox Kinect found comparable improvements in TUG and Berg balance scores and a significantly greater

TABLE 2 | Quantitative gait and balance outcomes from training studies.

Therapy type	Results demonstrating improvement	Results not showing improvement	Ambiguous/Conflicting results
Strength/resistance training	Walking velocity (12, 129, 139–141, 143)	Stride length (139, 140, 143)	
	Cadence (143)	Double-support time (143)	
	TUG (129, 141, 142)	Dynamic posturography (140, 142)	
	FAB (142)	CGI (142)	
		ABC (139)	
Gait training	Walking velocity (120, 126, 144, 146, 148, 150–152, 154–159, 161–165, 167)	ABC (145)	Gait symmetry (161, 165)
	Stride/step length (126, 144, 146–148, 150–152, 155–159, 161, 163–165)	Fall frequency (145)	Gait variability (126, 144, 148, 162)
	Kinematic analysis (149, 153, 155)	Mini-BESTest (154)	FOGQ (152, 153, 159)
	FOG Assessment (166)		Cadence (144, 146–148, 152, 156, 158)
	Walking distance (timed) (144, 154, 155, 159, 161, 162)		TUG (146, 152, 154)
	Static posturography (146)		
	Dynamic posturography (145, 160)		
	Sit-to-stand (165)		
	Double support time (148, 149, 162, 165)		
	POMA (155, 160, 167)		
	BBS (145, 155, 160)		
	DGI (155)		
	RST (145)		
Balance training	Cadence (175)	Double support time (175)	TUG (142, 169, 174)
	Stride length (175)	FAB (142)	Dynamic posturography (13, 142, 174)
	FGA (175)	CGI (142)	Fall frequency (13, 172)
	Static Posturography (171)		ABC (13, 169, 172, 175)
	Sit-to-stand (171)		
	BBS (13, 169, 172, 174)		
	Walking velocity (172, 175)		
	DGI (172)		
Multi-component training	Kinematic analysis (176)	Double-support time (143)	Dynamic posturography (170, 178)
	Cadence (143)	DGI (178)	Walking velocity (12, 139, 141, 143, 168, 178)
	Fall frequency (12)		Step/stride length (139, 141, 143, 168)
	Dynamic posturography (12, 141)		ABC (139, 178)
	PPT (168)		BBS (177, 178)
	Turning (168)		
	TUG (141, 177)		
	Walking distance (timed) (177)		
Home-based gait training	Walking velocity (179, 180)	Gait variability (181)	FOGQ (179, 180)
	Mini-BESTest (180)	Walking distance (timed) (180)	
	Stride length (179, 181)	Falls Efficacy Scale (180)	
	Cadence (181)		
Home-based balance training	Stride length (175, 183)	Double support time (175)	ABC (172, 175, 184)
	FGA (175, 183)	Stride velocity (175)	
	TUG (182, 184)	Cadence (175)	

(Continued)

TABLE 2 | Continued

Therapy type	Results demonstrating improvement	Results not showing improvement	Ambiguous/Conflicting results
	Falls efficacy scale (182)	Fall frequency (172)	
	Walking velocity (172, 183, 184)	Walking distance (timed) (185)	
	Sit-to-stand (184)		
	BBS (172, 185)		
	CBM (184)		
	Static Posturography (184)		
	Dynamic posturography (182, 184)		
	POMA (184)		
	DGI (172)		
	Obstancle clearance (182)		
	Dynamic balance (162, 182)		
Repeated perturbation training (RPT)	Step initiation (16, 186)	Static posturography (14)	Dynamic balance (15, 140, 187)
	Compensatory step length (16)	FOG (15)	
	Walking velocity (14–16, 140, 154)	Mini-BESTest (154)	
	Walking distance (154)		
	Gait variability (14)		
	Stride/step length (15, 16, 140)		
	Cadence (15, 16)		
	Double support time (16)		
	Fall frequency (15)		
	TUG (154)		

FGA, functional gait analysis; ABC, activities-specific balance confidence scale; TUG, timed-up-and-go; POMA, Tinetti performance oriented mobility assessment; CBM, community balance and mobility assessment; FOGQ, freezing of gait questionnaire; BBS, Berg balance scale; DGI, dynamic gait index; RST, rapid step-up test, FAB, Fullerton advanced balance scale; CGI, clinical global impression scale; PPT, physical performance test.

This table shows the aspects of gait and balance found to be helped or not to be helped by different types of therapy. The studies that researched each aspect of gait and balance are recorded.

improvement in dynamic stability compared with traditional balance training (174). Yen et al. randomized patients to receive either virtual-reality based balance training, traditional balance training, or no therapy (control group) found that both training groups displayed improvements dynamic post-urography (SOT) (173). A balance training program utilizing audio-biofeedback was also found to improve Berg balance scores and TUG (169).

Combination therapies have also been utilized, but experimental confounds have made it somewhat difficult to interpret these results. Hirsch et al. compared combination balance and resistance therapy vs. balance training. They found that, while computerized dynamic post-urography measured by the SOT and muscle strength improved in both experimental groups, combination therapy demonstrated larger improvements. However, patients in the combination group were given 15 min of resistance therapy three times a week in addition to the thrice-weekly 30 min balance training sessions experienced by both groups, so it is difficult to determine how much of this greater effect is due to combination therapy vs. greater duration of therapy in the combination group. In addition, no comparison was made to a group receiving resistance therapy alone (170). A study which assigned the experimental group to complete balance and gait training and the control group to complete an equal number of sessions of strength training found that the experimental group was less likely to fall, fell less often and demonstrated greater reduction in postural response length and increase in stride length compared to controls (12). Gait and balance therapy has also been found to improve gait kinematics (176), gait velocity, step length, turning, and Physical Performance Test scores (168). A study comparing resistance with a multi-modal training program found that both groups similarly increased velocity and cadence of off-medication gait and plantarflexion strength, though other measures of spatial gait parameters were unaffected (143). Smania et al. found that a balance training program with locomotor training, but not a control group exposed to full body active joint mobilization, muscle stretching, and muscle coordination exercises, showed improvements in several measures of balance and balance confidence (13). Tai chi, a martial art form that addresses many components of gait and balance, has also been used with some success (141, 177). However, not all multi-component therapies have been found to be successful. Hirsch et al. found that a 4 weeks therapy utilizing treadmill training, obstacle course training, and balance training did not significantly improve any

features of gait relative to a treatment-free control group (178). This could be due to short therapy duration, low intensity of therapy, lack of sensitive outcome measures, or small sample size.

Repeated Perturbation Training

Traditional physical and exercise therapies have successfully improved the gait and balance of patients with PD. Motor learning challenges in PD demonstrate that specific, feedforward practice of events related to PIGD and falls may be even more effective than generic practice or strength training. This evidence has elicited interest in the utilization of repeated perturbation training (RPT) for the improvement of PIGD in PD. Specifically, repeated training of reactions to the types of unexpected perturbations that may lead to falls is thought to show promise in improving balance and decreasing falls in daily life. Because such perturbations take place in a controlled system, with the provision of supports as needed, they can be practiced safely. As noted in the section above, several successful therapy programs have incorporated forms of perturbation training. However, repeated perturbation testing, especially that using technology-assisted protocols, has not yet been widely adopted and research is still needed to determine the types of perturbation that are most helpful. The duration, frequency, and intensity in which these therapy sessions must occur and the generalizability of reactions from practiced perturbation to another novel type also need to be further researched.

Most of the studies of RPT within the PD population have focused on the effects of training during static or dynamic stance. Several studies utilizing the sudden and unpredictable movement of a platform under subject's feet have noted that repeated perturbations of this type generate a training effect, improving subject response in later trials. Visser et al. found that, while patients with PD always differed from age-matched healthy controls in kinematic and surface EMG measures of their response to the sudden tilting of the platform they are standing on, individuals with PD do show significant improvement in these balance reactions following training (187). van Ooteghem et al. achieved similar results when patients attempted to maintain balance while the support platform oscillated at random amplitudes (which repeated in sequence unknown to the subjects). People with PD improved reactions to this perturbation, shifted from feedback to feedforward mechanisms as a strategy for improving performance, and generalized learning to a different pattern of oscillatory movements. More widespread generalizability to other types of perturbation (e.g., sudden translation or other movement) was not tested (195).

Several studies have tested improvement of compensatory steps as a reaction to external perturbation. A study utilizing mechanically applied perturbation using a weighted pulley system attached to the shoulders found that the length of compensatory steps increased and time to step initiation shortened with repetition. Interestingly cadence and step length during gait also improved, implying some level of generalizability to normal gait (16). Peterson et al. found that people with PD are capable of motor learning when repetitive forward and backward translations are applied to the support surface and that these improvements were retained a day later, but they did not generalize to lateral translations. Interestingly, the patients in this study were found to exhibit the most improvement in the first trial, while most studies found that individuals with PD need several trials before motor learning occurs (88). A study that utilized a combination of treadmill therapy and RPT in which perturbations found that this training resulted in a reduction in falls and improvements in gait and dynamic balance (15).

Only a few studies have previously reported on the ability of perturbations during dynamic gait to improve PIGD in PD. Roemmich et al. found that people with PD are able to adapt when split belts of a treadmill were rotated at differing speeds beneath them, and aftereffects and shorter re-adaptation indicated that these changes might be retained (17). Klamroth et al. showed that perturbation treadmill training utilizing tilt, in comparison to traditional treadmill walking, was able to induce adaptation and improve gait velocity and variability. A small effect was noted in static postural control, which could indicate possibility for generalized effect (14). Steib et al. found that treadmill perturbation therapy can induce changes in dynamic balance and gait, generating greater effects than a treadmill training control group (154). While these studies have been promising, much more research is needed to determine the clinical efficacy of RPT for gait, including the number, duration, and intensity of sessions needed, the duration in which effects of treatment may last, the types of changes induced by various types of perturbations, and the effect these changes have on decreasing both real-life fall incidents and simulated falls under different conditions. Perturbation during step initiation could also be an area of interest, possibly for reducing start hesitation, a form of FOG. Rogers et al. found that perturbation, either through a drop or an elevation of the support surface under the initiating foot, timed directly at the point of step initiation, elicited adaptation of stepping response to preserve stability and that this augmentation could improve postural and locomotor coupling (186).

CONCLUSIONS AND FUTURE DIRECTIONS

Research related to motor learning in PD and effects of therapy programs in PD populations indicate that patients with PD are capable of motor learning. However, this learning may be slower, of smaller magnitude, and less generalizable relative to healthy individuals. A combination of sensory degradation and neurological degeneration (affecting physical, attentional, and learning capabilities) may make adaptation to feedback difficult, forcing patients with PD to rely on feedforward methods of learning. Gait and balance are inherently subject to constantly changing environmental and other conditions, making feedforward control difficult; however, training may improve this ability. In order to more effectively train individuals with PD in forming feedforward strategies, it is important that therapies are targeted at the symptoms they intend to improve, that patients be given ample feedback about their current movement patterns and needed improvement, and that duration, intensity, and timing of therapy sessions be set to maximize motor learning. In this case, frequent and intense workouts,

with duration long enough to achieve learning effect without resulting in fatigue, would be ideal. Therapies should also attempt to incorporate additional feedback (possibly in the form of verbal prompts, cues, or augmented reality systems).

Current research has shown that therapy programs specifically targeted to improve factors related to gait and balance can significantly improve these features. Resistance training, balance training, treadmill training, and repeated perturbation training have all been shown to exhibit these effects. However, more research is still needed to determine what therapies are more effective for specific aspects of PIGD (e.g., resistance training may help to increase voluntary muscle activation and movement amplitude and improve bradykinesia while RPT may reduce falls or FOG) and what aspects or exercises of these therapy modalities are most helpful for these improvements. Efforts should be made to standardize treatments and outcome measures from all treatment groups so that direct comparisons can be made. Studies in which duration and intensity of different types of therapies are as well-matched as possible are urgently needed. The study of combination therapies, the use of varying types of exercises in order to increase different aspects of gait and balance, and the use of enhanced feedback, assistance and body support, and cueing systems will be instrumental features of study. The generalizability of therapeutic effect is also a concern; for example, eliciting perturbations during stance may not help to improve reactions to perturbations during gait. It is important to research the generalizability of each type of training in order to better target training to treat those specific aspects of PIGD most bothersome to the patient. This would maximize the benefit derived from therapy while minimizing duration, avoid patient fatigue and more reasonably adhering to insurance coverage as the research moves into the clinical sphere.

Patients with PD seem to rely largely on feedforward learning, even in cases, such as response to external perturbation or changing conditions. The effects of situations that might interfere with learning feedforward movement patterns, such as dual-tasking or operating under reduced sensory feedback, need to be studied. It has been seen that individuals with PD have special difficulty with certain tasks, including gait and balance under these conditions. Further research could reveal interesting information about motor learning and maintaining and updating motor loops in PD. The use of augmented feedback to induce learning of proper patterns could help to facilitate the transfer of feedforward methods learned to situations that are likely to induce falls and is also of interest for research. Because gait and balance both involve constantly changing conditions and some degree of dual tasking is quite common, assisting the improvement of these skills could be vital to reducing falls. As of yet, little research has focused upon this training or upon the limits of feedforward control in managing PIGD.

Research into motor learning and control can directly facilitate improvements in therapy. While preliminary, current research suggests that as much exercise as possible, both through therapy and through continued home and gym exercise, should be recommended. Therapy should address as closely as possible the active concerns patients with PD are experiencing (such as balance, treadmill, or lower-limb focused resistance training for patients known to be experiencing severe PIGD). At present, the exact exercises prescribed are largely variable, but the addition of more evidence-based research in the field will help to determine the best potential options based on patient profile. A high level of feedback is recommended, possibly through the use of VR, cueing or other augmented feedback technologies.

AUTHOR CONTRIBUTIONS

MO was responsible for compiling the sources used within this review and writing the drafted manuscript. TL and AL provided additional articles, discussed possible implications, and revised the manuscript.

ACKNOWLEDGMENTS

We would like to thank the Bob and Renee Parsons Foundation for sponsoring the Falls Research Program at the Muhammed Ali Movement Disorders Clinic. We would also like to thank the members of the Locomotion Research Laboratory and the Muhammad Ali Movement Disorders Clinic.

REFERENCES

1. Shulman JM, Jager PLD, Feany MB. Parkinsons disease: genetics and pathogenesis. *Annu Rev Pathol.* (2011) 6:193–222. doi: 10.1146/annurev-pathol-011110-130242
2. Jankovic J. Parkinsons disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry* (2008) 79:368–76. doi: 10.1136/jnnp.2007.131045
3. Sveinbjornsdottir S. The clinical symptoms of Parkinsons disease. *J Neurochem.* (2016) 139:318–24. doi: 10.1111/jnc.13691
4. Curtze C, Nutt JG, Carlson-Kuhta P, Mancini M, Horak FB. Levodopa is a double-edged sword for balance and gait in people with Parkinsons disease. *Mov Disord.* (2015) 30:1361–70. doi: 10.1002/mds.26269
5. Maurer C, Mergner T, Xie J, Faist M, Pollak P, Lucking CH. Effect of chronic bilateral subthalamic nucleus (STN) stimulation on postural control in Parkinson's disease. *Brain* (2003) 126:1146–63. doi: 10.1093/brain/awg100
6. Ferraye MU, Debû B, Pollak P. Deep brain stimulation effect on freezing of gait. *Mov Disord.* (2008) 23:S489–94. doi: 10.1002/mds.21975
7. Visser JE, Allum JHJ, Carpenter MG, Esselink RA, Speelman JD, Borm GF, et al. Subthalamic nucleus stimulation and levodopa-resistant postural instability in Parkinsons disease. *J Neurol.* (2008) 255:205–10. doi: 10.1007/s00415-008-0636-x
8. Hausdorff JM, Gruendlinger L, Scollins L, Oherron S, Tarsy D. Deep brain stimulation effects on gait variability in Parkinsons disease. *Mov Disord.* (2009) 24:1688–92. doi: 10.1002/mds.22554
9. Nantel J, Mcdonald JC, Bronte-Stewart H. Effect of medication and STN-DBS on postural control in subjects with Parkinson's disease. *Parkinsonism Relat Disord.* (2012) 18:285–9. doi: 10.1016/j.parkreldis.2011.11.005
10. Pötter-Nerger M, Volkmann J. Deep brain stimulation for gait and postural symptoms in Parkinsons disease. *Mov Disord.* (2013) 28:1609–15. doi: 10.1002/mds.25677
11. Yitayeh A, Teshome A. The effectiveness of physiotherapy treatment on balance dysfunction and postural instability in persons with Parkinson's disease: a systematic review and meta-analysis. *BMC Sports Sci Med Rehab.* (2016) 8:17. doi: 10.1186/s13102-016-0042-0

12. Shen X, Mak MKY. Technology-assisted balance and gait training reduces falls in patients with Parkinson's disease. *Neurorehab Neural Repair* (2014) 29:103–11. doi: 10.1177/1545968314537559
13. Smania N, Corato E, Tinazzi M, Stanzani C, Fiaschi A, Girardi P, et al. Effect of balance training on postural instability in patients with idiopathic Parkinson's disease. *Neurorehab Neural Repair* (2010) 24:826–34. doi: 10.1177/1545968310376057
14. Klamroth S, Steib S, Gaßner H, Goßler J, Winkler J, Eskofier B, et al. Immediate effects of perturbation treadmill training on gait and postural control in patients with Parkinson's disease. *Gait Posture* (2016) 50:102–8. doi: 10.1016/j.gaitpost.2016.08.020
15. Protas EJ, Mitchell K, Williams A, Qureshy H, Caroline K, Lai EC. Gait and step training to reduce falls in Parkinson's disease. *NeuroRehabilitation* (2005) 20:183–90.
16. Jobges M. Repetitive training of compensatory steps: a therapeutic approach for postural instability in Parkinsons disease. *J Neurol Neurosurg Psychiatry* (2004) 75:1682–7. doi: 10.1136/jnnp.2003.016550
17. Roemmich RT, Nocera JR, Stegemöller EL, Hassan A, Okun MS, Hass CJ. Locomotor adaptation and locomotor adaptive learning in Parkinson's disease and normal aging. *Clin Neurophysiol.* (2014) 125:313–9. doi: 10.1016/j.clinph.2013.07.003
18. Pendt LK, Reuter I, Müller H. Motor skill learning, retention, and control deficits in Parkinsons disease. *PLoS ONE* (2011) 6:e21669. doi: 10.1371/journal.pone.0021669
19. Nieuwboer A, Rochester L, Müncks L, Swinnen SP. Motor learning in Parkinsons disease: limitations and potential for rehabilitation. *Parkinsonism Relat Disord.* (2009) 15:S53–8. doi: 10.1016/S1353-8020(09)70781-3
20. Wilkinson L, Khan Z, Jahanshahi M. The role of the basal ganglia and its cortical connections in sequence learning: evidence from implicit and explicit sequence learning in Parkinsons disease. *Neuropsychologia* (2009) 47:2564–73. doi: 10.1016/j.neuropsychologia.2009.05.003
21. Frith CD, Bloxham CA, Carpenter KN. Impairments in the learning and performance of a new manual skill in patients with Parkinsons disease. *J Neurol Neurosurg Psychiatry* (1986) 49:661–8. doi: 10.1136/jnnp.49.6.661
22. Redgrave P, Rodriguez M, Smith Y, Rodriguez-Oroz MC, Lehericy S, Bergman H, et al. Goal-directed and habitual control in the basal ganglia: implications for Parkinsons disease. *Nat Rev Neurosci.* (2010) 11:760–72. doi: 10.1038/nrn2915
23. Pascual-Leone A, Grafman J, Clark K, Stewart M, Massaquoi S, Lou J-S, et al. Procedural learning in Parkinsons disease and cerebellar degeneration. *Ann Neurol.* (1993) 34:594–602. doi: 10.1002/ana.410340414
24. Muslimovic D, Post B, Speelman JD, Schmand B. Motor procedural learning in Parkinsons disease. *Brain* (2007) 130:2887–97. doi: 10.1093/brain/awm211
25. Brichta L, Greengard P, Flajolet M. Advances in the pharmacological treatment of Parkinsons disease: targeting neurotransmitter systems. *Trends Neurosci.* (2013) 36:543–54. doi: 10.1016/j.tins.2013.06.003
26. Calabresi P, Picconi B, Parnetti L, Filippo MD. A convergent model for cognitive dysfunctions in Parkinsons disease: the critical dopamine–acetylcholine synaptic balance. *Lancet Neurol.* (2006) 5:974–83. doi: 10.1016/S1474-4422(06)70600-7
27. Francis PT, Perry EK. Cholinergic and other neurotransmitter mechanisms in Parkinsons disease, Parkinsons disease dementia, and dementia with Lewy bodies. *Mov Disord.* (2007) 22:S351–7. doi: 10.1002/mds.21683
28. Perez-Lloret S, Barrantes FJ. Deficits in cholinergic neurotransmission and their clinical correlates in Parkinson's disease. *NPJ Parkinsons Dis.* (2016) 2:16001. doi: 10.1038/npjparkd.2016.1
29. Peterson D, Horak F. Effects of freezing of gait on postural motor learning in people with Parkinson's disease. *Neuroscience* (2016) 334:283–9. doi: 10.1016/j.neuroscience.2016.08.017
30. Paul SS, Dibble LE, Peterson DS. Motor learning in people with Parkinson's disease: implications for fall prevention across the disease spectrum. *Gait Posture* (2018) 61:311–9. doi: 10.1016/j.gaitpost.2018.01.026
31. Vakil E, Herishanu-Naaman S. Declarative and procedural learning in Parkinsons disease patients having tremor or Bradykinesia as the predominant symptom. *Cortex* (1998) 34:611–20. doi: 10.1016/S0010-9452(08)70518-5
32. Stephan MA, Meier B, Zaugg SW, Kaelin-Lang A. Motor sequence learning performance in Parkinson's disease patients depends on the stage of disease. *Brain Cogn.* (2011) 75:135–40. doi: 10.1016/j.bandc.2010.10.015
33. Bohnen NI, Albin RL. The cholinergic system and Parkinson disease. *Behav Brain Res.* (2011) 221:564–73. doi: 10.1016/j.bbr.2009.12.048
34. Müller MLTM, Bohnen NI. Cholinergic dysfunction in Parkinson's disease. *Curr Neurol Neurosci Rep.* (2013) 13:377. doi: 10.1007/s11910-013-0377-9
35. Müller ML, Albin RL, Kotagal V, Koeppe RA, Scott PJ, Frey KA, et al. Thalamic cholinergic innervation and postural sensory integration function in Parkinson's disease. *Brain* (2013) 136:3282–9. doi: 10.1093/brain/awt247
36. Bohnen NI, Frey KA, Studenski S, Kotagal V, Koeppe RA, Scott PJH, et al. Gait speed in Parkinson disease correlates with cholinergic degeneration. *Neurology* (2013) 81:1611–6. doi: 10.1212/WNL.0b013e3182a9f558
37. Fling BW, Cohen RG, Mancini M, Nutt JG, Fair DA, Horak FB. Asymmetric pedunculopontine network connectivity in Parkinsonian patients with freezing of gait. *Brain* (2013) 136:2405–18. doi: 10.1093/brain/awt172
38. Gallea C, Ewenczyk C, Degos B, Welter M-L, Grabli D, Leu-Semenescu S, et al. Pedunculopontine network dysfunction in Parkinsons disease with postural control and sleep disorders. *Mov Disord.* (2017) 32:693–704. doi: 10.1002/mds.26923
39. Bohnen NI, Muller ML, Koeppe RA, Studenski SA, Kilbourn MA, Frey KA, et al. History of falls in Parkinson disease is associated with reduced cholinergic activity. *Neurology* (2009) 73:1670–6. doi: 10.1212/WNL.0b013e3181c1ded6
40. Lau B, Welter M-L, Belaid H, Vidal SF, Bardinet E, Grabli D, et al. The integrative role of the pedunculopontine nucleus in human gait. *Brain* (2015) 138:1284–96. doi: 10.1093/brain/awv047
41. Hikosaka O. Basal Ganglia—possible role in motor coordination and learning. *Curr Opin Neurobiol.* (1991) 1: 638–43. doi: 10.1016/s0959-4388(05)80042-x
42. Hikosaka O. Role of Basal Ganglia in control of innate movements, learned behavior and cognition—a hypothesis. *Adv Behav Biol.* (1994) 41:589–96. doi: 10.1007/978-1-4613-0485-2_61
43. Agostino R. Motor skill learning in Parkinsons disease. *J Neurol Sci.* (1996) 139:218–26. doi: 10.1016/s0022-510x(96)00060-3
44. Soliveri P, Brown RG, Jahanshahi M, Marsden CD. Effect of practice on performance of a skilled motor task in patients with Parkinsons disease. *J Neurol Neurosurg Psychiatry* (1992) 55:454–60. doi: 10.1136/jnnp.55.6.454
45. Worringham CJ, Stelmach GE. Practice effects on the preprogramming of discrete movements in Parkinsons disease. *J Neurol Neurosurg Psychiatry* (1990) 53:702–4. doi: 10.1136/jnnp.53.8.702
46. Behrman AL, Cauraugh JH, Light KE. Practice as an Intervention to improve speeded motor performance and motor learning in Parkinson's disease. *J Neurol Sci.* (2000) 174:127–36. doi: 10.1016/s0022-510x(00)00267-7
47. Jessop RT, Horowicz C, Dibble LE. Motor learning and Parkinson disease: refinement of movement velocity and endpoint excursion in a limits of stability balance task. *Neurorehab Neural Repair* (2006) 20:459–67. doi: 10.1177/1545968306287107
48. Swinnen SP, Steyvers M, Van Den Bergh L, Stelmach GE. Motor learning and Parkinson's disease: refinement of within-limb and between-limb coordination as a result of practice. *Behav Brain Res.* (2000) 111: 45–59. doi: 10.1016/s0166-4328(00)00144-3
49. Smiley-Oyen AL, Lowry KA, Emerson QR. Learning and retention of movement sequences in Parkinsons disease. *Mov Disord.* (2006) 21:1078–87. doi: 10.1002/mds.20906
50. Fernandes HA, Park NW, Almeida QJ. Effects of practice and delays on learning and retention of skilled tool use in Parkinsons disease. *Neuropsychologia* (2017) 96:230–9. doi: 10.1016/j.neuropsychologia.2017.01.020
51. Marinelli L, Quartarone A, Hallett M, Frazzitta G, Ghilardi MF. The many facets of motor learning and their relevance for Parkinsons disease. *Clin Neurophysiol.* (2017) 128:1127–41. doi: 10.1016/j.clinph.2017.03.042
52. Nissen, MJ, Bullemer P. Attentional requirements of learning: evidence from performance measures. *Cogn Psychol.* (1987) 19:1–32. doi: 10.1016/0010-0285(87)90002-8
53. Reber PJ, Squire LR. Parallel brain systems for learning with and without awareness. *Learn Mem.* (1994) 1:217–29. doi: 10.1101/lm.1.4.217

54. Reber PJ, Squire LR. Encapsulation of implicit and explicit memory in sequence learning. *J Cogn Neurosci.* (1998) 10:248–63. doi: 10.1162/089892998562681
55. Brown RG, Jahanshahi M, Limousin-Dowsey P, Thomas D, Quinn NP, Rothwell JC. Pallidotomy and incidental sequence learning in Parkinson's disease. *NeuroReport* (2003) 14:21–4. doi: 10.1097/00001756-200301200-00004
56. Doyon J, Gaudreau D, Laforce R Jr., Castonguay M, Bédard PJ, Bédard F, et al. Role of the striatum, cerebellum, and frontal lobes in the learning of a visuomotor sequence. *Brain Cogn.* (1997) 34:218–45. doi: 10.1006/brcg.1997.0899
57. Ferraro FR, Balota DA, Connor LT. Implicit memory and the formation of new associations in nondemented Parkinson's disease individuals and individuals with Senile dementia of the Alzheimer type: a serial reaction time (SRT) investigation. *Brain Cogn.* (1993) 21:163–80. doi: 10.1006/brcg.1993.1013
58. Sarazin M, Deweer B, Merkl A, Von Poser N, Pillon B, Dubois B. Procedural learning and striatofrontal dysfunction in Parkinsons disease. *Mov Disord.* (2002) 17:265–73. doi: 10.1002/mds.10018
59. Vakil E, Kahan S, Huberman M, Osimani A. Motor and non-motor sequence learning in patients with Basal Ganglia lesions: the case of serial reaction time (SRT). *Neuropsychologia* (2000) 38:1–10. doi: 10.1016/s0028-3932(99)00058-5
60. Hayes HA, Hunsaker N, Dibble LE. Implicit motor sequence learning in individuals with Parkinson disease: a meta-analysis. *J Parkinsons Dis.* (2015) 5:549–60. doi: 10.3233/jpd-140441
61. Abbruzzese G, Trompetto C, Marinelli L. The rationale for motor learning in Parkinson's disease. *Eur J Phys Rehabil Med.* (2009) 45:209–14.
62. Westwater H, McDowall J, Siegert R, Mossman S, Abernethy D. Implicit learning in Parkinsons disease: evidence from a verbal version of the serial reaction time task. *J Clin Exp Neuropsychol.* (1998) 20:413–8. doi: 10.1076/jcen.20.3.413.826
63. Smith JG, Mcdowall J. Impaired higher order implicit sequence learning on the verbal version of the serial reaction time task in patients with Parkinsons disease. *Neuropsychology* (2004) 18:679–91. doi: 10.1037/0894-4105.18.4.679
64. Gobel EW, et al. Implicit perceptual-motor skill learning in mild cognitive impairment and Parkinson's disease. *Neuropsychology* (2013) 27:314–21. doi: 10.1037/a0032305
65. Smith JG, Mcdowall J. The implicit sequence learning deficit in patients with Parkinsons disease: a matter of impaired sequence integration? *Neuropsychologia* (2006) 44:275–88. doi: 10.1016/j.neuropsychologia.2005.05.001
66. Ghilardi M-F, Eidelberg D, Silvestri G, Ghez C. The differential effect of PD and normal aging on early explicit sequence learning. *Neurology* (2003) 60:1313–9. doi: 10.1212/01.wnl.0000059545.69089.ee
67. Guadagnoli MA, Leis B, Van Gemmert AW, Stelmach GE. The relationship between knowledge of results and motor learning in Parkinsonian patients. *Parkinsonism Relat Disord.* (2002) 9:89–95. doi: 10.1016/s1353-8020(02)00007-x
68. Mongeon D, Blanchet P, Messier J. Impact of Parkinson's disease and dopaminergic medication on adaptation to explicit and implicit visuomotor perturbations. *Brain Cogn.* (2013) 81:271–82. doi: 10.1016/j.bandc.2012.12.001
69. Masters RSW, MacMahon KMA, Pall HS. Implicit motor learning in Parkinsons disease. *Rehab Psychol.* (2004) 49:79–82. doi: 10.1037/0090-5550.49.1.79
70. Avanzino L, Fiorio M, Conte A. Actual and illusory perception in Parkinsons disease and dystonia: a narrative review. *Front Neurol.* (2018) 9:584. doi: 10.3389/fneur.2018.00584
71. Azulay J, Mesure S, Blin O. Influence of visual cues on gait in Parkinsons disease: contribution to attention or sensory dependence? *J Neurol Sci.* (2006) 248:192–5. doi: 10.1016/j.jns.2006.05.008
72. Ryterska A, Bogacz R, Brown P. What are people with Parkinsons disease really impaired on when it comes to making decisions? A meta-analysis of the evidence. *Neurosci Biobehav Rev.* (2013) 37:2836–46. doi: 10.1016/j.neubiorev.2013.10.005
73. Zalla T, Sirigu A, Pillon B, Dubois B, Agid Y, Grafman J. How patients with Parkinsons disease retrieve and manage cognitive event knowledge. *Cortex* (2000) 36:163–79. doi: 10.1016/s0010-9452(08)70522-7
74. Hikosaka O, Isoda M. Switching from automatic to controlled behavior: cortico-basal ganglia mechanisms. *Trends Cogn Sci.* (2010) 14:154–61. doi: 10.1016/j.tics.2010.01.006
75. Day BL, Dick JP, Marsden CD. Patients with Parkinsons disease can employ a predictive motor strategy. *J Neurol Neurosurg Psychiatry* (1984) 47:1299–306. doi: 10.1136/jnnp.47.12.1299
76. Catalá MM, Woitalla D, Arampatzis A. Reactive but not predictive locomotor adaptability is impaired in young Parkinsons disease patients. *Gait Posture* (2016) 48:177–82. doi: 10.1016/j.gaitpost.2016.05.008
77. Krebs H, Hogan N, Hening W, Adamovich SV, Poizner H. Procedural motor learning in Parkinsons disease. *Exp Brain Res.* (2001) 141:425–37. doi: 10.1007/s002210100871
78. Bishop M, Brunt D, Marjama-Lyons J. Do people with Parkinsons disease change strategy during unplanned gait termination? *Neurosci Lett.* (2006) 397:240–4. doi: 10.1016/j.neulet.2005.12.031
79. Morris ME, Iansek R, Matyas TA, Summers JJ. The pathogenesis of gait hypokinesia in Parkinsons disease. *Brain* (1994) 117:1169–81. doi: 10.1093/brain/117.5.1169
80. Jones D, Rochester L, Birleson A, Hetherington V, Nieuwboer A, Willems AM, et al. Everyday walking with Parkinsons disease: understanding personal challenges and strategies. *Disabil Rehab.* (2008) 30:1213–21. doi: 10.1080/09638280701828955
81. Wu T, Hallett M. Neural correlates of dual task performance in patients with Parkinsons disease. *J Neurol Neurosurg Psychiatry* (2008) 79:760–6. doi: 10.1136/jnnp.2007.126599
82. Plotnik M, Dagan Y, Gurevich T, Giladi N, Hausdorff JM. Effects of cognitive function on gait and dual tasking abilities in patients with Parkinson's disease suffering from motor response fluctuations. *Exp Brain Res.* (2010) 208:169–79. doi: 10.1007/s00221-010-2469-y
83. Schwab, Robert S. Control of two simultaneous voluntary motor acts in normals and in Parkinsonism. *Arch Neurol Psychiatry* (1954) 72:591. doi: 10.1001/archneurpsyc.1954.02330050061010
84. Hoshiyama M, et al. Hypokinesia of associated movement in Parkinsons disease: a symptom in early stages of the disease. *J Neurol.* (1994) 241:517–21. doi: 10.1007/bf00873512
85. Knowlton BJ, Mangels JA, Squire LR. A neostriatal habit learning system in humans. *Science* (1996) 273:1399–402. doi: 10.1126/science.273.5280.1399
86. Adamovich S, Berkinblit M, Hening W, Sage J, Poizner H. The interaction of visual and proprioceptive inputs in pointing to actual and remembered targets in Parkinson's disease. *Neuroscience* (2001) 104:1027–41. doi: 10.1016/S0306-4522(01)00099-9
87. Schneider JS, Lidsky TI. *Basal Ganglia and Behavior: Sensory Aspects of Motor Functioning*. Toronto, ON: Huber (1987).
88. Peterson DS, Dijkstra BW, Horak FB. Postural motor learning in people with Parkinson's disease. *J Neurol.* (2016) 263:1518–29. doi: 10.1007/s00415-016-8158-4
89. Vandenbossche J, Deroost N, Soetens E, Coomans D, Spildooren J, Vercruysse S, et al. Impaired implicit sequence learning in Parkinsons disease patients with freezing of gait. *Neuropsychology* (2013) 27:28–36. doi: 10.1037/a0031278
90. Heremans E, Nackaerts E, Vervoort G, Broeder S, Swinnen SP, Nieuwboer A. Impaired retention of motor learning of writing skills in patients with Parkinson's disease with freezing of gait. *PLoS ONE* (2016) 11:e0148933. doi: 10.1371/journal.pone.0148933
91. Lamont RM, Morris ME, Menz HB, Mcginley JL, Brauer SG. Falls in people with Parkinson's disease: a prospective comparison of community and home-based falls. *Gait Posture* (2017) 55:62–7. doi: 10.1016/j.gaitpost.2017.04.005
92. Peterson DS, King LA, Cohen RG, Horak FB. Cognitive contributions to freezing of gait in Parkinson disease: implications for physical rehabilitation. *Phys Ther.* (2015) 96:659–70. doi: 10.2522/ptj.20140603
93. Paul SS, Sherrington C, Canning CG, Fung VSC, Close JCT, Lord SR. The relative contribution of physical and cognitive fall risk factors in people with Parkinson's disease. *Neurorehab Neural Repair* (2013) 28:282–90. doi: 10.1177/1545968313508470
94. Huang P, Tan Y, Liu D, Herzallah MM, Lapidow E, Wang Y, et al. Motor-symptom laterality affects acquisition in Parkinsons disease: a cognitive and functional magnetic resonance imaging study. *Mov Disord.* (2017) 32:1047–55. doi: 10.1002/mds.27000

95. Dan X, King BR, Doyon J, Chan P. Motor sequence learning and consolidation in unilateral de novo patients with Parkinson's disease. *PLoS ONE* (2015) 10:e0134291. doi: 10.1371/journal.pone.0134291
96. Cameron IG, Pari G, Alahyane N, Brien DC, Coe BC, Stroman PW, et al. Impaired executive function signals in motor brain regions in Parkinsons disease. *NeuroImage* (2012) 60:1156–70. doi: 10.1016/j.neuroimage.2012.01.057
97. Cooper JA, Sagar HJ, Jordan N, Harvey NS, Sullivan EV. Cognitive impairment in early, untreated Parkinsons disease and its relationship to motor disability. *Brain* (1991) 114:2095–122. doi: 10.1093/brain/114.5.2095
98. Wang Y, Zhao J, Li D, Peng F, Wang Y, Yang K, et al. Associations between cognitive impairment and motor dysfunction in Parkinson's disease. *Brain Behav.* (2017) 7:e00719. doi: 10.1002/brb3.719
99. Schönberger AR, Barbe MT, Hagelweide K, Kühn AB, Fink GR, Schubotz RI. Joint principles of motor and cognitive dysfunction in Parkinson's disease. *Neuropsychologia* (2013) 51:1417–25. doi: 10.1016/j.neuropsychologia.2013.04.011
100. Moustafa AA, Chakravarthy S, Phillips JR, Crouse JJ, Gupta A, Frank MJ, et al. Interrelations between cognitive dysfunction and motor symptoms of Parkinson's disease: behavioral and neural studies. *Rev Neurosci.* (2016) 27:535–48. doi: 10.1515/revneuro-2015-0070
101. Taylor AE, Saint-Cyr J, Lang A. Memory and learning in early Parkinsons disease: evidence for a frontal lobe syndrome. *Brain Cogn.* (1990) 13:211–32. doi: 10.1016/0278-2626(90)90051-o
102. Packard MG, Knowlton BJ. Learning and memory functions of the basal ganglia. *Annu Rev Neurosci.* (2002) 25:563–93. doi: 10.1146/annurev.neuro.25.112701.142937
103. Foerde K, Braun EK, Shohamy D. A trade-off between feedback-based learning and episodic memory for feedback events: evidence from Parkinson's disease. *Neurodegen Dis.* (2013) 11:93–101. doi: 10.1159/000342000
104. Thomas V, Reymann J, Lieury A, Allain H. Assessment of procedural memory in parkinsons disease. *Prog NeuroPsychopharmacol Biol Psychiatry* (1996) 20:641–50. doi: 10.1016/0278-5846(96)00037-1
105. Yogev G, Giladi N, Peretz C, Springer S, Simon ES, Hausdorff JM. Dual tasking, gait rhythmicity, and Parkinsons disease: which aspects of gait are attention demanding? *Eur J Neurosci.* (2005) 22:1248–56. doi: 10.1111/j.1460-9568.2005.04298.x
106. Pillon B, Ertle S, Deweer B, Sarazin M, Agid Y, Dubois B. Memory for spatial location is affected in Parkinsons disease. *Neuropsychologia* (1996) 34:77–85. doi: 10.1016/0028-3932(95)00086-0
107. Roy S, Park NW, Roy EA, Almeida QJ. Interaction of memory systems during acquisition of tool knowledge and skills in Parkinsons disease. *Neuropsychologia* (2015) 66:55–66. doi: 10.1016/j.neuropsychologia.2014.11.005
108. Wu T, Liu J, Zhang H, Hallett M, Zheng Z, Chan P. Attention to automatic movements in Parkinsons disease: modified automatic mode in the striatum. *Cereb Cortex* (2014) 25:3330–42. doi: 10.1093/cercor/bhu135
109. Ferrazzoli D, Ortelli P, Madeo G, Giladi N, Petzinger GM, Frazzitta G. Basal ganglia and beyond: the interplay between motor and cognitive aspects in Parkinson's disease rehabilitation. *Neurosci Biobehav Rev.* (2018) 90:294–308. doi: 10.1016/j.neubiorev.2018.05.007
110. Vaillancourt DE, Schonfeld D, Kwak Y, Bohnen NI, Seidler R. Dopamine overdose hypothesis: evidence and clinical implications. *Mov Disord.* (2013) 28:1920–9. doi: 10.1002/mds.25687
111. Roemmich RT, Hack N, Akbar U, Hass CJ. Effects of dopaminergic therapy on locomotor adaptation and adaptive learning in persons with Parkinsons disease. *Behav Brain Res.* (2014) 268:31–9. doi: 10.1016/j.bbr.2014.03.041
112. Anderson ED, Horak FB, Lasarev MR, Nutt JG. Performance of a motor task learned on levodopa deteriorates when subsequently practiced off. *Mov Disord.* (2013) 29:54–60. doi: 10.1002/mds.25702
113. Hayes HA, Hunsaker N, Schaefer SY, Shultz B, Schenkenberg T, Boyd LA, et al. Does dopamine replacement medication affect postural sequence learning in Parkinson's disease? *Motor Control* (2015) 19:325–40. doi: 10.1123/mc.2014-0039
114. Peterson DS, Horak FB. The effect of levodopa on improvements in protective stepping in people with Parkinson's disease. *Neurorehab Neural Repair* (2016) 30:931–40. doi: 10.1177/1545968316648669
115. Ruitenberg MF, Duthoo W, Santens P, Notebaert W, Abrahamse EL. Sequential movement skill in Parkinsons disease: a state-of-the-art. *Cortex* (2015) 65:102–12. doi: 10.1016/j.cortex.2015.01.005
116. Ruitenberg MF, Duthoo W, Santens P, Seidler RD, Notebaert W, Abrahamse EL. Sequence learning in Parkinsons disease: Focusing on action dynamics and the role of dopaminergic medication. *Neuropsychologia* (2016) 93:30–9. doi: 10.1016/j.neuropsychologia.2016.09.027
117. Beigi M, Wilkinson L, Gobet F, Parton A, Jahanshahi M. Levodopa medication improves incidental sequence learning in Parkinsons disease. *Neuropsychologia* (2016) 93:53–60. doi: 10.1016/j.neuropsychologia.2016.09.019
118. Meissner SN, Südmeyer M, Keitel A, Pollok B, Bellebaum C. Facilitating effects of deep brain stimulation on feedback learning in Parkinson's disease. *Behav Brain Res.* (2016) 313:88–96. doi: 10.1016/j.bbr.2016.06.062
119. Mendes FADS, Pompeu JE, Lobo AM, Silva KGD, Oliveira TDP, Zomignani AP, et al. Motor learning, retention and transfer after virtual-reality-based training in Parkinsons disease – effect of motor and cognitive demands of games: a longitudinal, controlled clinical study. *Physiotherapy* (2012) 98:217–23. doi: 10.1016/j.physio.2012.06.001
120. Rochester L, Baker K, Hetherington V, Jones D, Willems A, Kwakkel G, et al. Evidence for motor learning in Parkinsons disease: acquisition, automaticity and retention of cued gait performance after training with external rhythmical cues. *Brain Res.* (2010) 1319:103–11. doi: 10.1016/j.brainres.2010.01.001
121. Gómez-Jordana LI, Stafford J, Peper C, Craig CM. Virtual footprints can improve walking performance in people with Parkinsons disease. *Front Neurol.* (2018) 9:681. doi: 10.3389/fneur.2018.00681
122. Rubinstein TC, Giladi N, Hausdorff JM. The power of cueing to circumvent dopamine deficits: a review of physical therapy treatment of gait disturbances in Parkinsons disease. *Mov Disord.* (2002) 17:1148–60. doi: 10.1002/mds.10259
123. Zénon A, Duclos Y, Carron R, Witjas T, Baunez C, Régis J, et al. The human subthalamic nucleus encodes the subjective value of reward and the cost of effort during decision-making. *Brain* (2016) 139:1830–43. doi: 10.1093/brain/aww075
124. Pompeu JE, Mendes FADS, Silva KGD, Lobo AM, Oliveira TDP, Zomignani AP, et al. Effect of Nintendo Wii^{TM}-based motor and cognitive training on activities of daily living in patients with Parkinsons disease: a randomised clinical trial. *Physiotherapy* (2012) 98:196–204. doi: 10.1016/j.physio.2012.06.004
125. Keus SH, Bloem BR, Hendriks EJ, Bredero-Cohen AB, Munneke M. Evidence-based analysis of physical therapy in Parkinsons disease with recommendations for practice and research. *Mov Disord.* (2007) 22:451–60. doi: 10.1002/mds.21244
126. Herman T, Giladi N, Erlich S, Gruendlinger L, Hausdorff J. Six weeks of intensive treadmill training improves gait and quality of life in patients with Parkinson's disease: a pilot study. *Gait Posture* (2005) 21, 1154–8. doi: 10.1016/S0966-6362(05)80311-X
127. Goodwin VA, Richards SH, Taylor RS, Taylor AH, Campbell JL. The effectiveness of exercise interventions for people with Parkinsons disease: a systematic review and meta-analysis. *Mov Disord.* (2008) 23:631–40. doi: 10.1002/mds.21922
128. Baatile J, Langbein WE, Weaver F, Maloney C, Jost MB. Effect of exercise on perceived quality of life of individuals with Parkinson's disease. *J Rehab Res Dev.* (2000) 37:529–34.
129. Dibble LE, Hale TF, Marcus RL, Gerber JP, Lastayo PC. High intensity eccentric resistance training decreases bradykinesia and improves quality of life in persons with Parkinsons disease: a preliminary study. *Parkinsonism Relat Disord.* (2009) 15:752–7. doi: 10.1016/j.parkreldis.2009.04.009
130. Crizzle AM, Newhouse IJ. Is physical exercise beneficial for persons with Parkinson's disease? *Clin J Sport Med.* (2006) 16:422–5. doi: 10.1097/01.jsm.0000244612.55550.7d
131. Comelia CL, Stebbins GT, Brown-Toms N, Goetz CG. Physical therapy and Parkinsons disease: a controlled clinical trial. *Neurology* (1994) 44(3, Part 1):376–8. doi: 10.1212/WNL.44.3_Part_1.376

132. Yousefi B, Tadibi V, Khoei AF, Montazeri A. Exercise therapy, quality of life, and activities of daily living in patients with Parkinson disease: a small scale quasi-randomised trial. *Trials* (2009) 10:67. doi: 10.1186/1745-6215-10-67
133. Comelia CL, Stebbins GT, Brown-Toms N, Goetz CG. Physical therapy and Parkinsons disease: a controlled clinical trial. *Neurology* (1994) 44(3, Part 1):376. doi: 10.1212/wnl.44.3_part_1.376
134. Mak MK, Wong-Yu IS, Shen X, Chung CL. Long-term effects of exercise and physical therapy in people with Parkinson disease. *Nat Rev Neurol.* (2017) 13:689–703. doi: 10.1038/nrneurol.2017.128
135. Klamroth S, Steib S, Devan S, Pfeifer K. Effects of exercise therapy on postural instability in Parkinson disease. *J Neurol Phys Ther.* (2016) 40:3–14. doi: 10.1097/NPT.0000000000000117
136. Kolk NM, King LA. Effects of exercise on mobility in people with Parkinsons disease. *Mov Disord.* (2013) 28:1587–96. doi: 10.1002/mds.25658
137. Shen X, Wong-Yu IS, Mak MK. Effects of exercise on falls, balance, and gait ability in Parkinson's disease. *Neurorehab Neural Repair* (2015) 30:512–27. doi: 10.1177/1545968315613447
138. Morris ME, Martin CL, Schenkman ML. Striding out with Parkinson disease: evidence-based physical therapy for gait disorders. *Phys Ther.* (2009) 90:280–8. doi: 10.2522/ptj.20090091
139. Shen X, Mak MKY. Balance and gait training with augmented feedback improves balance confidence in people with Parkinson's disease. *Neurorehab Neural Repair* (2014) 28:524–35. doi: 10.1177/1545968313517752
140. Shen X, Mak M. Repetitive step training with preparatory signals improves stability limits in patients with Parkinson's disease. *J Rehab Med.* (2012) 44:944–9. doi: 10.2340/16501977-1056
141. Li F, Harmer P, Fitzgerald K, Eckstrom E, Stock R, Galver J, et al. Tai Chi and postural stability in patients with Parkinsons disease. *N Engl J Med.* (2012) 366:511–9. doi: 10.1056/nejmoa1107911
142. Schlenstedt C, Paschen S, Kruse A, Raethjen J, Weisser B, Deuschl G. Resistance versus balance training to improve postural control in Parkinsons disease: a randomized rater blinded controlled study. *PLoS ONE* (2015) 10:e0140584. doi: 10.1371/journal.pone.0140584
143. Rafferty MR, Prodoehl J, Robichaud JA, David FJ, Poon C, Goelz LC, et al. Effects of 2 years of exercise on gait impairment in people with Parkinson disease. *J Neurol Phys Ther.* (2017) 41:21–30. doi: 10.1097/NPT.0000000000000163
144. Mirelman A, Maidan I, Herman T, Deutsch JE, Giladi N, Hausdorff JM. Virtual reality for gait training: can it induce motor learning to enhance complex walking and reduce fall risk in patients with Parkinsons disease? *J Gerontol Ser A Biol Sci Med Sci.* (2010) 66A:234–40. doi: 10.1093/gerona/glq201
145. Harro CC, Shoemaker MJ, Frey O, Gamble AC, Harring KB, Karl KL, et al. The effects of speed-dependent treadmill training and rhythmic auditory-cued overground walking on balance function, fall incidence, and quality of life in individuals with idiopathic Parkinson's disease: a randomized controlled trial. *NeuroRehabilitation* (2014) 34:541–56. doi: 10.3233/NRE-141048
146. Bello O, Sanchez J, Lopez-Alonso V, Márquez G, Morenilla L, Castro X, et al. The effects of treadmill or overground walking training program on gait in Parkinsons disease. *Gait Posture* (2013) 38:590–5. doi: 10.1016/j.gaitpost.2013.02.005
147. Nadeau A, Pourcher E, Corbeil P. Effects of 24 wk of treadmill training on gait performance in Parkinson's disease. *Med Sci Sports Exerc.* (2014) 46:645–55. doi: 10.1249/mss.0000000000000144
148. Tseng I, Yuan R, Jeng C. Treadmill training improves forward and backward gait in early Parkinson disease. *Am J Phys Med Rehab.* (2015) 94:811–9. doi: 10.1097/phm.0000000000000273
149. Pohl M, Rockstroh G, Rückriem S, Mrass G, Mehrholz J. Immediate effects of speed-dependent treadmill training on gait parameters in early Parkinson's disease. *Arch Phys Med Rehab.* (2003) 84:1760–6. doi: 10.1016/S0003-9993(03)00433-7
150. Myers PS, Mcneely ME, Pickett KA, Duncan RP, Earhart GM. Effects of exercise on gait and motor imagery in people with Parkinson disease and freezing of gait. *Parkinsonism Relat Disord.* (2018) 53:89–95. doi: 10.1016/j.parkreldis.2018.05.006
151. Sale P, Pandis MF, Pera DL, Sova I, Cimolin V, Ancillao A, et al. Robot-assisted walking training for individuals with Parkinson's disease: a pilot randomized controlled trial. *BMC Neurol.* (2013) 13:50. doi: 10.1186/1471-2377-13-50
152. Schlick C, Ernst A, Bötzel K, Plate A, Pelykh O, Ilmberger J. Visual cues combined with treadmill training to improve gait performance in Parkinson's disease: a pilot randomized controlled trial. *Clin Rehab.* (2015) 30:463–71. doi: 10.1177/0269215515588836
153. Galli M, Cimolin V, De Pandis MF, Le Pera D, Sova I, Albertini G, et al. Robot-assisted gait training versus treadmill training in patients with Parkinson's disease: a kinematic evaluation with gait profile score. *Funct Neurol.* (2016) 31:163–70. doi: 10.11138/fneur/2016.31.3.163
154. Steib S, Klamroth S, Gaßner H, Pasluosta C, Eskofier B, Winkler J, et al. Perturbation during treadmill training improves dynamic balance and gait in Parkinson's disease: a single-blind randomized controlled pilot trial. *Neurorehab Neural Repair* (2017) 31:758–68. doi: 10.1177/1545968317721976
155. Byl N, Zhang W, Coo S, Tomizuka M. Clinical impact of gait training enhanced with visual kinematic biofeedback: patients with Parkinson's disease and patients stable post stroke. *Neuropsychologia* (2015) 79:332–43. doi: 10.1016/j.neuropsychologia.2015.04.020
156. Grobbelaar R, Venter R, Welman KE. Backward compared to forward over ground gait retraining have additional benefits for gait in individuals with mild to moderate Parkinson's disease: a randomized controlled trial. *Gait Posture* (2017) 58:294–9. doi: 10.1016/j.gaitpost.2017.08.019
157. Bella SD, Benoit C, Farrugia N, Schwartze M, Kotz SA. Effects of musically cued gait training in Parkinsons disease: beyond a motor benefit. *Ann N Y Acad Sci.* (2015) 1337:77–85. doi: 10.1111/nyas.12651
158. Ford MP, Malone LA, Nyikos I, Yelisetty R, Bickel CS. Gait training with progressive external auditory cueing in persons with Parkinsons disease. *Arch Phys Med Rehab.* (2010) 91:1255–61. doi: 10.1016/j.apmr.2010.04.012
159. Frazzitta G, Maestri R, Uccellini D, Bertotti G, Abelli P. Rehabilitation treatment of gait in patients with Parkinsons disease with freezing: a comparison between two physical therapy protocols using visual and auditory cues with or without treadmill training. *Mov Disord.* (2009) 24:1139–43. doi: 10.1002/mds.22491
160. Ganesan M, Sathyaprabha TN, Gupta A, Pal PK. Effect of partial weight–supported treadmill gait training on balance in patients with Parkinson disease. *PM R* (2014) 6:22–33. doi: 10.1016/j.pmrj.2013.08.604
161. Ganesan M, Sathyaprabha TN, Pal PK, Gupta A. Partial body weight-supported treadmill training in patients with Parkinson disease: impact on gait and clinical manifestation. *Arch Phys Med Rehab.* (2015) 96:1557–65. doi: 10.1016/j.apmr.2015.05.007
162. Nocera J, Horvat M, Ray CT. Effects of home-based exercise on postural control and sensory organization in individuals with Parkinson disease. *Parkinsonism Relat Disord.* (2009) 15:742–5. doi: 10.1016/j.parkreldis.2009.07.002
163. Miyai I, Fujimoto Y, Ueda Y, Yamamoto H, Nozaki S, Saito T, et al. Treadmill training with body weight support: Its effect on Parkinsons disease. *Arch Phys Med Rehab.* (2000) 81:849–52. doi: 10.1053/apmr.2000.4439
164. Miyai I, Fujimoto Y, Yamamoto H, Ueda Y, Saito T, Nozaki S, et al. Long-term effect of body weight–supported treadmill training in Parkinsons disease: a randomized controlled trial. *Arch Phys Med Rehab.* (2002) 83:1370–3. doi: 10.1053/apmr.2002.34603
165. Fisher BE, Wu AD, Salem GJ, Song J, Lin C-H, Yip J, et al. The effect of exercise training in improving motor performance and corticomotor excitability in people with early Parkinsons disease. *Arch Phys Med Rehab.* (2008) 89:1221–9. doi: 10.1016/j.apmr.2008.01.013
166. Plotnik M, Shema S, Dorfman M, Gazit E, Brozgol M, Giladi N, et al. A motor learning-based intervention to ameliorate freezing of gait in subjects with Parkinson's disease. *J Neurol.* (2014) 261:1329–39. doi: 10.1007/s00415-014-7347-2
167. Furnari A, Calabrò RS, Cola MC, Bartolo M, Castelli A, Mapelli A, et al. Robotic-assisted gait training in Parkinsons disease: a three-month follow-up randomized clinical trial. *Int J Neurosci.* (2017) 127:996–1004. doi: 10.1080/00207454.2017.1288623
168. Stozek J, Rudzinska M, Pustułka-Piwnik U, Szczudlik A. The effect of the rehabilitation program on balance, gait, physical performance and trunk

rotation in Parkinson's disease. *Aging Clin Exp Res.* (2015) 28:1169–77. doi: 10.1007/s40520-015-0506-1
169. Mirelman A, Herman T, Nicolai S, Zijlstra A, Zijlstra W, Becker C, et al. Audio-biofeedback training for posture and balance in patients with Parkinsons disease. *J NeuroEng Rehab.* (2011) 8:35. doi: 10.1186/1743-0003-8-35
170. Hirsch MA, Toole T, Maitland CG, Rider RA. The effects of balance training and high-intensity resistance training on persons with idiopathic Parkinson's disease. *Arch Phys Med Rehab.* (2003) 84:1109–17. doi: 10.1016/S0003-9993(03)00046-7
171. Bhatt T, Yang F, Mak MK, Hui-Chan CW, Pai Y. Effect of externally cued training on dynamic stability control during the sit-to-stand task in people with Parkinson disease. *Phys Ther.* (2012) 93:492–503. doi: 10.2522/ptj.20100423
172. Gandolfi M, Geroin C, Dimitrova E, Boldrini P, Waldner A, Bonadiman S, et al. Virtual reality telerehabilitation for postural instability in Parkinson's disease: a multicenter, single-blind, randomized, controlled trial. *BioMed Res Int.* (2017) 2017:1–11. doi: 10.1155/2017/7962826
173. Yen C-Y, Lin K-H, Hu M-H, Wu R-M, Lu T-W, Lin C-H. Effects of virtual reality–augmented balance training on sensory organization and attentional demand for postural control in people with Parkinson disease: a randomized controlled trial. *Phys Ther.* (2011) 91:862–74. doi: 10.2522/ptj.20100050
174. Shih M, Wang R, Cheng S, Yang Y. Effects of a balance-based exergaming intervention using the Kinect sensor on posture stability in individuals with Parkinson's disease: a single-blinded randomized controlled trial. *J NeuroEng Rehab.* (2016) 13:78. doi: 10.1186/s12984-016-0185-y
175. Atterbury EM, Welman KE. Balance training in individuals with Parkinson's disease: therapist-supervised vs. home-based exercise programme. *Gait Posture* (2017) 55:138–44. doi: 10.1016/j.gaitpost.2017.04.006
176. Mirek E, Kubica JL, Szymura J, Pasiut S, Rudzinska M, Chwała W. Assessment of gait therapy effectiveness in patients with Parkinson's disease on the basis of three-dimensional movement analysis. *Front Neurol.* (2016) 7:102. doi: 10.3389/fneur.2016.00102
177. Hackney ME, Earhart GM. Tai Chi improves balance and mobility in people with Parkinson disease. *Gait Posture* (2008) 28:456–60. doi: 10.1016/j.gaitpost.2008.02.005
178. Landers MR, Hatlevig RM, Davis AD, Richards AR, Rosenlof LE. Does attentional focus during balance training in people with Parkinson's disease affect outcome? A randomised controlled clinical trial. *Clin Rehab.* (2015) 30:53–63. doi: 10.1177/0269215515570377
179. Espay AJ, Baram Y, Dwivedi AK, Shukla R, Gartner M, Gaines L, et al. At-home training with closed-loop augmented-reality cueing device for improving gait in patients with Parkinson disease. *J Rehab Res Dev.* (2010) 47:573. doi: 10.1682/jrrd.2009.10.0165
180. Ginis P, Nieuwboer A, Dorfman M, Ferrari A, Gazit E, Canning CG, et al. Feasibility and effects of home-based smartphone-delivered automated feedback training for gait in people with Parkinsons disease: a pilot randomized controlled trial. *Parkinsonism Relat Disord.* (2016) 22:28–34. doi: 10.1016/j.parkreldis.2015.11.004
181. Geroin C, Nonnekes J, Vries NM, Strouwen C, Smania N, Tinazzi M, et al. Does dual-task training improve spatiotemporal gait parameters in Parkinsons disease? *Parkinsonism Relat Disord.* (2018) 55:86–91. doi: 10.1016/j.parkreldis.2018.05.018
182. Liao Y, Yang Y, Cheng S, Wu Y, Fuh J, Wang R. Virtual reality-based training to improve obstacle-crossing performance and dynamic balance in patients with Parkinson's disease. *Neurorehab Neural Repair* (2014) 29:658–67. doi: 10.1177/1545968314562111
183. Liao Y, Yang Y, Wu Y, Wang R. Virtual reality-based wii fit training in improving muscle strength, sensory integration ability, and walking abilities in patients with Parkinsons disease: a randomized control trial. *Int J Gerontol.* (2015) 9:190–5. doi: 10.1016/j.ijge.2014.06.007
184. Tremblay L, Esculier J, Vaudrin J, Bériault P, Gagnon K. Home-based balance training programme using Wii fit with balance board for Parkinsons's disease: a pilot study. *J Rehab Med.* (2012) 44:144–50. doi: 10.2340/16501977-0922
185. Ribas CG, Silva LA, Corrêa MR, Teive HG, Valderramas S. Effectiveness of exergaming in improving functional balance, fatigue and quality of life in Parkinsons disease: a pilot randomized controlled trial. *Parkinsonism Relat Disord.* (2017) 38:13–8. doi: 10.1016/j.parkreldis.2017.02.006
186. Rogers MW, Hilliard MJ, Martinez KM, Zhang Y, Simuni T, Mille M-L. Perturbations of ground support alter posture and locomotion coupling during step initiation in Parkinson's disease. *Exp Brain Res.* (2010) 208:557–67. doi: 10.1007/s00221-010-2504-z
187. Visser J, Nijhuis LO, Janssen L, Bastiaanse C, Borm G, Duysens J, et al. Dynamic posturography in Parkinson's disease: diagnostic utility of the first trial effect. *Neuroscience* (2010) 168:387–94. doi: 10.1016/j.neuroscience.2010.03.068
188. Abbruzzese G, Marchese R, Avanzino L, Pelosin E. Rehabilitation for Parkinsons disease: current outlook and future challenges. *Parkinsonism Relat Disord.* (2016) 22:S60–4. doi: 10.1016/j.parkreldis.2015.09.005
189. Mirelman A, Rochester L, Maidan I, Din SD, Alcock L, Nieuwhof F, et al. Addition of a non-immersive virtual reality component to treadmill training to reduce fall risk in older adults (V-TIME): a randomised controlled trial. *Lancet* (2016) 388:1170–82. doi: 10.1016/s0140-6736(16)31325-3
190. Dreu MD, Wilk AV, Poppe E, Kwakkel G, Wegen EV. Rehabilitation, exercise therapy and music in patients with Parkinsons disease: a meta-analysis of the effects of music-based movement therapy on walking ability, balance and quality of life. *Parkinsonism Relat Disord.* (2012) 18:S114–9. doi: 10.1016/s1353-8020(11)70036-0
191. Uhrbrand A, Stenager E, Pedersen MS, Dalgas U. Parkinsons disease and intensive exercise therapy – a systematic review and meta-analysis of randomized controlled trials. *J Neurol Sci.* (2015) 353:9–19. doi: 10.1016/j.jns.2015.04.004
192. Herman T, Giladi N, Hausdorff JM. Treadmill training for the treatment of gait disturbances in people with Parkinson's disease: a mini-review. *J Neural Transm.* (2008) 116:307–18. doi: 10.1007/s00702-008-0139-z
193. Robinson AG, Dennett AM, Snowdon DA. Treadmill training may be an effective form of task-specific training for improving mobility in people with Parkinson's disease and multiple sclerosis: a systematic review and meta-analysis. *Physiotherapy* (in press). doi: 10.1016/j.physio.2018.11.007
194. Barry G, Galna B, Rochester L. The role of exergaming in Parkinson's disease rehabilitation: a systematic review of the evidence. *J NeuroEng Rehab.* (2014) 11:33. doi: 10.1186/1743-0003-11-33
195. Ooteghem KV, Frank JS, Horak FB. Postural motor learning in Parkinson's disease: the effect of practice on continuous compensatory postural regulation. *Gait Posture* (2017) 57:299–304. doi: 10.1016/j.gaitpost.2017.06.021

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

APPENDIX

Article Selection Methods

Keyword searches within the PubMed and Google Scholar databases were used to identify articles of interest. Only articles written in or translated into English with full text available were considered. Additional papers of relevance were selected from the citations given by those papers initially found during the literature search.

For section Motor Learning in PD, articles related to "Motor" + "Postural learning" or "Implicit learning" or "Explicit learning" or "learning" + "Parkinson's disease" or "Parkinson disease," "Memory" or "Attention" or "Executive function" + "Motor learning" + "Parkinson's disease" or "Parkinson disease," "Feedback" or "Perception" + "Motor learning" + "Parkinson's disease" or "Parkinson disease," and "Motivation" + "Motor learning" + "Parkinson's disease" or "Parkinson disease" were searched for. Abstracts were read to ascertain whether motor learning deficits of idiopathic PD in human subjects were discussed. For the relevant titles, the full papers were then read to determine methods used and types and definitions of learning analyzed. Because of the wide focus of titles related to motor learning, which considered varying definitions and perspectives of learning and the effects of various other cognitive and perceptual systems, these articles were not synthesized into a systematic review but grouped and discussed with other similar research.

Within section Effect of Training on PIGD, searches were made for "Physical therapy" or "exercise therapy" + "gait" or "balance" + "Parkinson's disease" or "Parkinson disease," "therapy" or "training" + "gait" or "balance" + "Parkinson's disease" or "Parkinson disease," "Perturbation" or "Perturbation training" or "Perturbation training" + "gait" or "balance" + "Parkinson's disease," and "Virtual reality training" + "gait" or "balance" + "Parkinson's disease" or "Parkinson disease." Articles that applied a specific non-pharmaceutical treatment or treatments involving training or therapy, with quantitative measures of overground gait and/or standing balance changes as a primary outcome measure, were selected through abstract review. Perturbation-based studies were also considered if they measured learning effect to trained or generalized perturbations. Review focused on articles relating to individual therapies, not class-based techniques. Articles were not utilized if pharmaceutical, surgical, or other treatments were tested in conjunction with therapy. Only controlled studies, not case studies or series, were considered. Full articles of selected abstracts were then read to ensure relevance. While training methods, intensity, and durations varied too widely for statistical comparison, studies were analyzed and compared (as shown in **Tables 1**, **2**) to note basic trends in effective treatments. Reviews of therapy and training methods in relation to gait and balance were also considered and conclusions discussed in the body of the paper, though only research studies were included in the Tables.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: info@frontiersin.org | +41 21 510 17 00

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership