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ORIGINAL RESEARCH

Phybrata Digital Biomarkers of Age-Related Balance Impairments, Sensory Reweighting, and Intrinsic Fall Risk

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Objective: To assess the utility of digital biomarkers derived from a head-mounted wearable physiological vibration acceleration (phybrata) sensor to quantify age-related balance impairments, sensory reweighting, and fall risks in older populations.

Methods: Data were collected and analyzed from 516 participants aged 77.7 ± 8.0 yrs (min 51 yrs, max 98 yrs, 334 females, 182 males) in 4 residential senior living communities. Participants first completed a questionnaire that included their fall history in the past 6 months. A 2-minute standing balance test was then carried out for each participant using the phybrata sensor (1 minute with eyes open, followed by 1 minute with eyes closed). Four balance performance biomarkers were derived from the phybrata time series data: eyes open (Eo) and eyes closed (Ec) phybrata powers, average phybrata power (Eo+Ec)/2, and Ec/Eo phybrata power ratio. Sensory reweighting biomarkers were derived from phybrata acceleration spectral density (ASD) distributions. Results are compared for participants with no reported fall history (NF) and those reporting one or more falls (FR) in the previous 6 months.

Results: All four phybrata balance performance biomarkers show significantly higher values for FR participants vs NF participants. As a fall risk biomarker, Ec phybrata power was found to have the strongest statistical correlation with the reported retrospective incidence of falls within the previous 6 months. The Ec phybrata biomarker also showed the strongest statistical difference between F and M participants. Phybrata sensory reweighting biomarkers quantify age-related impairments and sensory reweighting across sensory inputs (visual, vestibular, proprioceptive), central nervous system (CNS) processing, and neuromotor control (vestibulocollic reflex), revealing progressive reductions in visual and vestibular balance regulation and vestibulocollic head stabilization that are offset by an increasing reliance on proprioceptive balance control.

Conclusion: Phybrata digital biomarkers enable rapid objective assessment of progressive age-related balance impairments, sensory reweighting, and fall risks in older populations.

Keywords: presbystasis, age-related balance decline, vestibular, phybrata, wearable sensor, biomarker, balance performance, fall risk, sensory reweighting

Introduction

Age-related balance dysfunction, clinically referred to as presbystasis, is a complex condition characterized by a gradual decline in balance and mobility. This condition not only significantly heightens the risk of falls but also makes it increasingly more difficult to continue living actively, independently, and productively. The economic burden of presbystasis exceeds $280 billion annually in the US, with over $50 billion in direct medical expenses for falls alone.[1] More than $230 billion in additional costs result from spending on long-term care, productivity loss, caregiver burden, and diminished quality of life.[2] Most falls result from a combination of intrinsic/physiological risks (eg impaired postural stability)[3] and extrinsic/environmental risks (uneven surfaces or obstacles, poor lighting, inappropriate footwear, challenging physical activities),[4] but deficits in balance and gait are the most prominent pre-disposing risk factors at the population level.[5–11] Simple tests of balance have been shown to be a good prognostic indicator for risk of all-cause

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mortality in middle-aged and older individuals,[12,13] highlighting the opportunity to combine more detailed and quantitative balance testing with targeted interventions to mitigate adverse health outcomes.

Human balance relies on three primary sensory inputs that provide critical information to the brain regarding the body's movement and orientation to maintain stable balance control. Visual inputs from the eyes inform the brain about relative movements of the body with respect to objects in the surrounding environment, inputs from the vestibular balance organs in the inner ear provide information on the body's own movement by detecting linear and rotational head motion and deviations from earth-vertical (gravity), and proprioceptive and somatosensory inputs from the skin, tendons, muscles, and joints relay information regarding the body's orientation relative to and contact with objects in the surrounding environment. The central nervous system (CNS), which includes the brain and spinal cord, integrates and processes these sensory inputs, generating motor control outputs that are transmitted to the musculoskeletal system via the peripheral nervous system (PNS), enabling the body to stand and move without losing balance. The vestibular system also works closely with the eyes, muscles, and joints to coordinate balance functions automatically[14] through the vestibulo-ocular reflex (VOR), which regulates the eye muscles to maintain gaze during head movements, the vestibulocollic reflex (VCR), which controls the neck muscles to support the head during movements, and the vestibulospinal reflex (VSR), which controls the muscles of the body and limbs to maintain posture and balance.

Although presbystasis is a multifaceted disorder, studies of balance aging have identified vestibular dysfunction as the primary cause of balance decline in more than 55% of adults over age 50, or around 70 million people in the U.S.[5–8] Furthermore, more than 35% of US adults over 40 years of age already suffer from age-related dysfunction in the vestibular balance system,[9] often long before symptoms begin to be observed. This dysfunction impacts both the peripheral vestibular organs in the inner ear and central vestibular processing in the brain,[10] significantly increases fall risk,[11] and has also been linked to the onset and progression of cognitive decline.[15] Part of the normal aging process is the loss of vestibular hair cells, which weakens the sensory signals generated by the vestibular organs and triggers a cascade of additional atrophy effects in the other components of the vestibular system.[8,10,16] These atrophy effects include decrease in the gain of the synapses between the motion sensing cells and the vestibular nerve and decreased conductivity along the vestibular nerve, both of which further weaken the signals received by the brain. These weaker signals can lead to atrophy in those parts of the CNS that integrate and process sensory input and motor control output signals.

A key element of balance-related CNS processing is sensory reweighting (SR), the process by which the brain continuously evaluates the reliability and recalibrates the relative importance, or weighting, that it assigns to visual, vestibular, and proprioceptive sensory inputs.[17,18] SR allows the brain to amplify or attenuate signals from different sensory systems based on their perceived reliability. SR can occur dynamically – in response to changing environmental factors such as poor lighting or uneven surfaces - or it can occur slowly over time – in response to changing physiological factors, such as loss of vestibular hair cells, decline in vision, or peripheral neuropathies that degrade proprioceptive signals. Age-related reductions in the response time or accuracy of the SR process significantly increase fall risks in older people.[19] Evaluation of SR can provide valuable insights into potential underlying causes of balance decline.

Many outcome measures are available for the assessment and treatment of patients with balance and dizziness disorders.[20] Balance researchers and clinical specialists quantify age-related balance and mobility decline, vestibular-specific impairments, changes in SR, and related fall risks using specialized laboratory equipment such as computerized dynamic posturography (CDP) systems.[8,20–25] These systems are costly and require dedicated facilities and trained staff, and they are typically available only in balance and gait research labs or specialized neuromotor clinics that are not widely accessible to most older patients with declining balance and postural control. As a result, most clinicians assessing balance in their older patients day-to-day are limited to visually scored tests or self-reported scales for balance, dizziness, ambulatory performance, and fall risks.[26] While low-cost and easy to perform, their reliability and utility are limited[27] and more than half of elderly patients with balance disorders report vague, inconsistent, or contradictory descriptions of their symptoms.[28] Earlier detection and more effective management of vestibular dysfunction in older adults hinges on the development of more objective and readily available diagnostic methods.

Wearable sensor technologies offer a promising approach to enabling more widely accessible instrumented assessments of balance and mobility decline.[29,30] However, current technology typically relies on arrays of multiple

synchronized sensors mounted on different parts of the body to match the quantitative performance of traditional balance research lab solutions.[29] We have previously demonstrated that this limitation can be overcome using a single head-mounted wearable inertial motion unit (IMU)-based physiological vibration acceleration (phybrata) sensor with a simple two-minute test.[31,32] The head-mounted design and tiny mass of the device enable the separation of postural control contributions from visual, vestibular, and proprioceptive inputs along with CNS processing and neuromotor control by mapping them to specific vibrational frequency bands in the phybrata data.[32,33] Previous studies have shown that phybrata-based biomarkers can effectively quantify changes in postural stability, underlying impairments across multiple balance system components, and the resulting sensory reweighting due to head trauma such as concussions,[31,32,34] diseases like multiple sclerosis,[35] and spinal cord injuries.[36] The diagnostic performance of the phybrata sensor has been shown to match that of full-body video motion capture and IMUs mounted on multiple parts of the body in assessing standard balance and gait parameters and postural transitions during activities of daily living.[37,38] The combination of phybrata sensor data and machine learning (ML) has been shown to outperform the diagnostic performance of alternatives such as neurocognitive tests, clinical scales, symptoms checklists, balance and gait testing, MRI, EEG, eye tracking, and blood biomarkers.[34] Comparisons of head-mounted and body-mounted IMUs have demonstrated that for the head-mounted sensor, a 60 second test duration is sufficient for both clinical diagnostic applications and research studies.[38]

The present study investigates the use of digital biomarkers derived from phybrata balance assessments to quantify declining postural stability, underlying impairments across multiple balance system components, the resulting sensory reweighting, and increased fall risks in older adults.

Methods

Participants

Data were collected and analyzed from 516 participants aged 77.7 ± 8.0 yrs (min 51 yrs, max 98 yrs, 334 females, 182 males) during day-long balance clinics held at 4 residential elderly centers in the San Francisco Bay area, California. At check-in and prior to testing, clinical staff at each center measured and recorded each participant's height and weight and recorded their age and the number of falls reported in the past 6 months. Table 1 summarizes participant ages, gender, and fall histories. 329 participants reported no falls (NF) in the previous 6 months (age 76.6 ± 7.9 yrs, min 51 yrs, max 95 yrs, 230 females, 99 males). 187 participants reported falling one or more times (FR) in the previous 6 months (age 79.6 ± 7.7 yrs, min 54 yrs, max 98 yrs, 104 females, 83 males).

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki with research ethics approval under Western IRB Study Number 1188786, and informed consent was obtained for all participants in the study. The participant provided informed consent for publication of the image in Figure 1.

Table 1 Summary of Participants and Reported Fall Histories

	All Participants (516)			Female Participants (334)			Male Participants (182)		
	Total	No Falls Reported	Falls Reported	Total	No Falls Reported	Falls Reported	Total	No Falls Reported	Falls Reported
Number	516	329	187	334	230	104	182	99	83
Mean age (yrs)	77.7	76.6	79.6	77.4	76.5	79.3	78.2	76.7	80
Stnd Dev (yrs)	8.0	7.9	7.3	7.6	7.3	7.7	8.6	9.1	7.8
Min (yrs)	51	51	54	51	51	60	51	51	54
Max (yrs)	98	95	98	98	95	98	98	94	98

Figure 1 Phybrata sensor attached to the mastoid using an adhesive patch.

Measurements

Participants were tested using the previously reported phybrata sensor[31,32,34–37] attached to the patient's mastoid using a disposable medical adhesive, as shown in Figure 1, while standing still for 60 sec with eyes open (Eo) and then again for 60 sec with eyes closed (Ec). During testing, participants were instructed to stand upright in a relaxed position with their feet together and their arms at their sides while maintaining their gaze in a straight-ahead direction focused on a visual target mounted on the wall 10 feet away at eye level. Patients were also instructed not to talk or move during testing. The test administrator always stood by the subjects: (1) to monitor subjects' postural sway throughout the trial; and (2) so that the subjects had no fear of falling during eyes-closed testing. Testing was repeated if any anomalous patient movement was observed during phybrata testing. A smartphone app connects to the phybrata sensor via a Bluetooth low-energy (BLE) wireless link to configure and run tests, collect data, and interface with cloud-based data storage, analytics, and reporting services. The phybrata IMU includes a 3-axis accelerometer to record x (anterior-posterior (AP), or front-back), y (vertical), and z (medial-lateral (ML), or left-right) acceleration time series data in units of *g*. During each 60 sec test, data is recorded at a sampling rate of 100 hz, generating a total of 6000 samples for each of the 3 axes (x, y, z). The accelerometer signals are filtered to remove drift, as in our previous studies with the same device.[31,32] Figure 2 shows sample Eo and Ec x, y, z phybrata time series signals for a participant reporting no falls in the previous 6 months (Figure 2a), a participant reporting one fall in the previous 6 months (Figure 2b), and a participant reporting multiple falls in the previous 6 months (Figure 2c). Figure 3 shows sample Eo and Ec AP/ML phybrata spatial scatter plots and phybrata power bar graphs for the same three participants as in Figure 2.

Data Analysis

For each pair of tests (60 sec Eo followed by 60 sec Ec), four phybrata metrics were calculated from the time series data as previously described:[31,32] Eo and Ec powers (in watts), (Eo+Ec)/2 average power, and Ec/Eo power ratio. Data analyses were carried out using the commercially licensed statistical analysis software package NCSS (NCSS LLC, Kaysville, UT, USA). Data analysis included descriptive statistics, analysis of variance (ANOVA, MANOVA), and receiver operating characteristic (ROC) curves for the 4 phybrata metrics and sub-populations of interest (F vs M, NF vs FR). Eo and Ec distributions generally failed 2 or more of 3 normality tests (Shapiro–Wilk, skewness, kurtosis) and were log-transformed prior to ANOVA/MANOVA. Means and 95% confidence intervals (CIs) were calculated using the bootstrap method. Acceleration spectral density (ASD) frequency analyses of Eo and Ec phybrata time series data were carried out for each participant and used to calculate sensory reweighting profiles as previously described.[32,35,36] Benefits

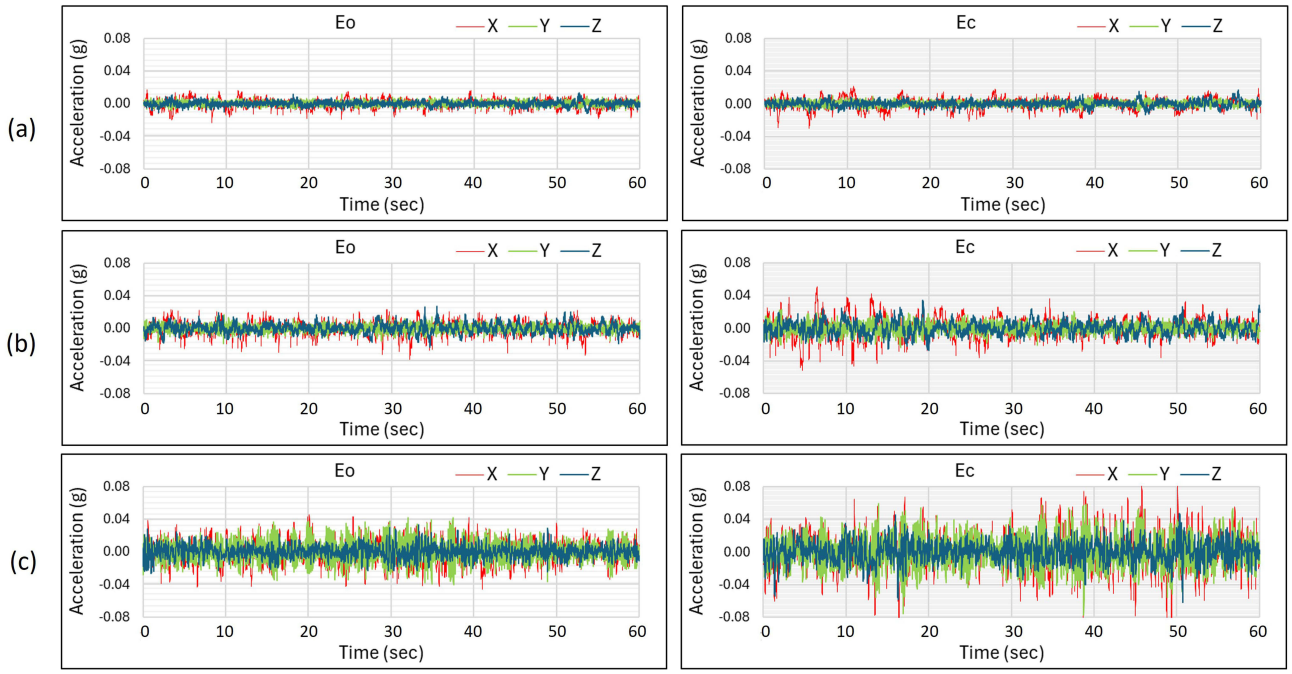

Figure 2 Sample eyes open (Eo) and eyes closed (Ec) x (anterior-posterior, AP), y (vertical), z (medial-lateral, ML) phybrata time series data for participants (**a**) with no reported fall history (**b**) reporting a single fall in the past 6 months (**c**) reporting multiple falls in the past 6 months.

of the direct measurement of acceleration and the use of power-based and frequency-based metrics in the present study include greater sensitivity to differences in Eo vs Ec performance and less sensitivity to sampling duration.[32]

Results

Figure 4 presents box plots comparing the distributions of the 4 phybrata metrics for 329 participants with no reported falls and 187 participants with one or more reported falls (Figure 4a); 230 female participants and 99 male participants with no reported falls (Figure 4b); and 104 female participants and 83 male participants with one or more reported falls (Figure 4c). Corresponding means, 95% CIs, and MANOVA results are presented in Table 2.

All four phybrata metrics show significantly higher values for FR participants vs NF participants (Figure 4a): Eo, $F(1,515) = 149.82$, $p < 0.00001$; Ec, $F(1,515) = 294.10$, $p < 0.00001$; (Eo+Ec)/2, $F(1,515) = 269.85$, $p < 0.00001$; Ec/Eo, $F(1,515) = 97.04$, $p < 0.00001$. The Ec metric shows the strongest correlation with falls status. All four phybrata metrics also show significant differences ($p < 0.05$) between F vs M participants in the NF group (Figure 4b): Eo, $F(1,328) = 5.14$, $p = 0.02$; Ec, $F(1,328) = 19.80$, $p = 0.00001$; (Eo+Ec)/2, $F(1,328) = 15.88$, $p = 0.0001$; Ec/Eo, $F(1,328) = 12.20$, $p = 0.0006$. Three of the four phybrata metrics (Ec, (Eo+Ec)/2, Ec/Eo) showed significant differences between F and M participants in the FR group (Figure 4c): Ec, $F(1,186) = 12.14$, $p = 0.006$; (Ec+Eo)/2, $F(1,186) = 10.44$, $p = 0.002$; Ec/Eo, $F(1,186) = 6.91$, $p = 0.009$.

Figure 5 shows receiver operating characteristic (ROC) curves for the classification of falls history for all 516 participants for all possible cutoff values of the 4 phybrata metrics Eo, Ec, (Eo+Ec)/2, Ec/Eo. Key ROC results are summarized in Table 3. As a metric for clinical assessment of fall risk, Ec achieves area under the curve (AUC) = 0.88 (95% CI = 0.84–0.91), and for a cutoff value of Ec = 0.90 watts, the corresponding sensitivity and specificity are 0.76 and 0.85, respectively. The above cutoff value for Ec (0.90 watts) agrees well with the corresponding box plot distributions in Figure 4a, highlighting the utility of this simple and physiologically intuitive phybrata digital biomarker for rapid diagnostic testing of fall risk. As discussed further below, these ROC results compare favorably with more complex, time-consuming, and expensive approaches for instrumented fall risk assessments. Table 3 also includes ROC results for the classification of falls history for the 334 F participants and 182 M participants for all possible cutoff values of the 4 phybrata metrics. The statistically significant differences observed between M vs F participants in the distributions of the

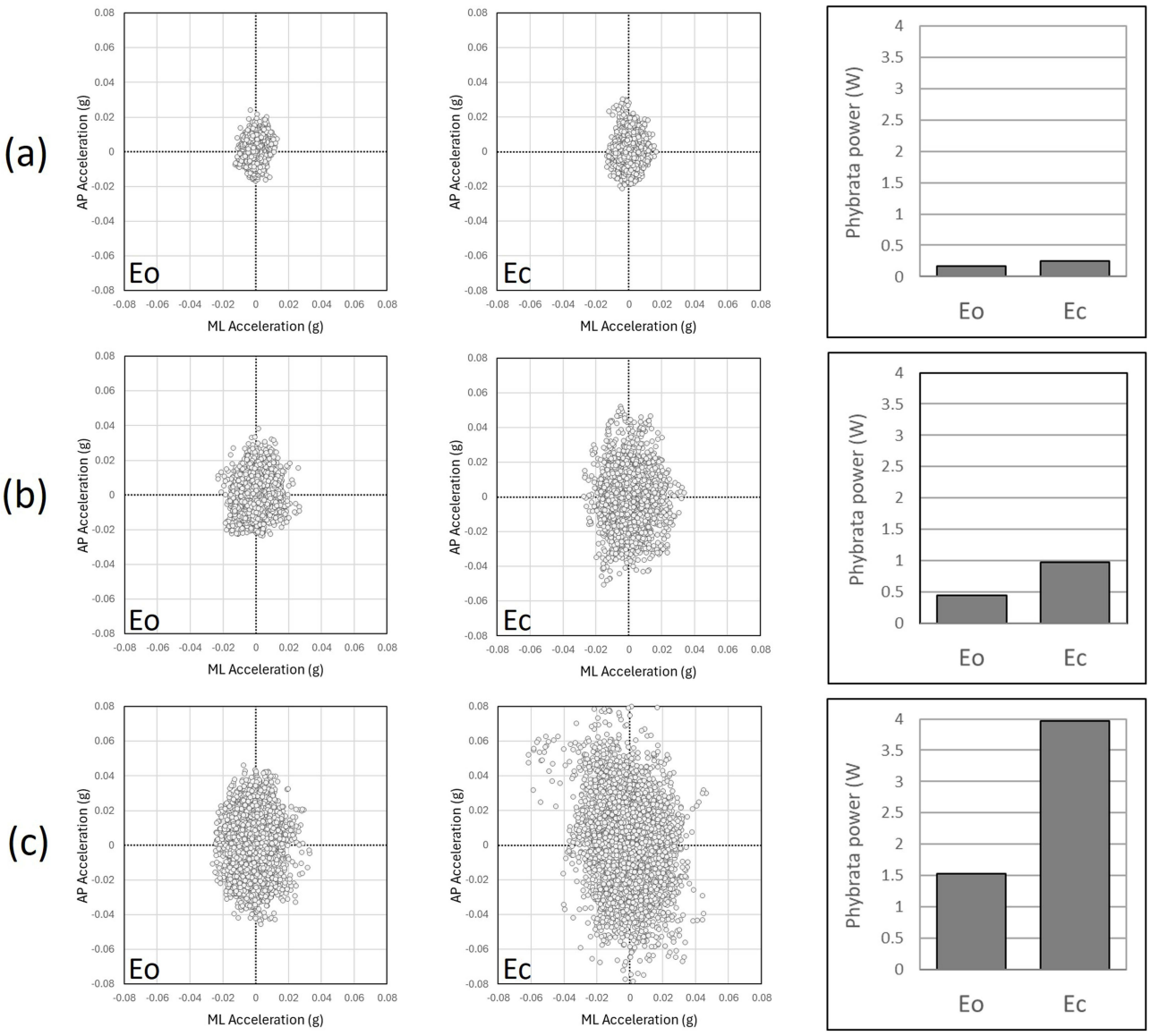

Figure 3 Sample eyes open (Eo) and eyes closed (Ec) AP/ML phybrata spatial scatter plots and phybrata powers for participants (**a**) with no reported fall history (**b**) reporting a single fall in the past 6 months (**c**) reporting multiple falls in the past 6 months.
Abbreviations: Eo, eyes open; Ec, eyes closed; AP, anterior-posterior; ML, medial-lateral.

four phybrata metrics in Figure 4 and Table 2 are reflected in the higher cutoff values for M vs F participants for all four phybrata metrics in Table 3.

Figure 6 presents phybrata sensory reweighting plots for the 20 participants with the lowest values of Ec, the 20 participants with the highest values of Ec, and the 20 participants straddling the Ec = 0.9 falls risk threshold (10 immediately below and 10 immediately above). Separate plots are shown for Eo (Figure 6a) and Ec (Figure 6b). Relative changes in reliance on specific mechanisms of postural control were quantified by calculating relative changes within five frequency bands[32] in the normalized phybrata ASD frequency spectra: 0.02–0.1 hz (visual regulation); 0.1–0.5 hz (vestibular regulation); 0.5–1 hz (CNS participation, both cerebellar and cortical); 1–10Hz (spinal reflexive loops, proprioception, multi-joint and muscle activity); 10–25 hz (vestibulocollic head stabilization). The normalized sensory reweighting plots in Figure 6 are calculated by integrating over time and frequency in each of the five ASD frequency bands for each individual and then averaging each band over the 20 individuals in each of the three groups. Figure 6

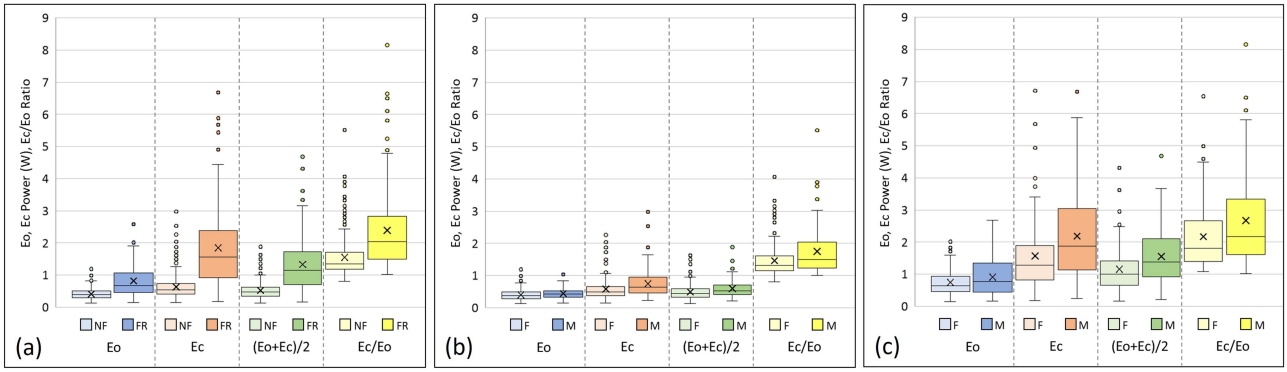

Figure 4 Box plots showing distributions of 4 phybrata metrics for (**a**) 329 participants with no reported falls and 187 participants with one or more reported falls (**b**) 230 female participants and 99 male participants with no reported falls (**c**) 104 female participants and 83 male participants with one or more reported falls.
Abbreviations: F, female; M, male; NF, no falls; FR, falls reported; Eo, eyes open; Ec, eyes closed.

reveals a significant redistribution across the five spectral bands with increasing postural instability and fall risk, with progressive reductions in visual and vestibular balance regulation and vestibulocollic head stabilization that are offset by an increasing reliance on proprioceptive balance control. This observed sensory reweighting is consistent with

Table 2 MANOVA Summary of 4 Phybrata Metrics for 329 Participants with No Reported Falls in the Previous 6 months (NF) and 187 Participants with One or More Reported Falls in the Previous 6 months (FR)

All Participants (516)	**Falls Status**	**Mean**	**95% CI**	**F-Ratio**	**P**
Eo power	NF	0.413	0.394–0.432	F(1,515) = 149.82	<0.00001****
	FR	0.82	0.749–0.894		
Ec power	NF	0.63	0.587–0.666	F(1,515) = 294.10	<0.00001****
	FR	1.845	1.666–2.029		
(Eo + Ec)/2	NF	0.521	0.492–0.548	F(1,515) = 269.85	<0.00001****
	FR	1.336	1.210–1.450		
Ec/Eo	NF	1.55	1.483–1.614	F(1,515) = 97.04	<0.00001****
	FR	2.389	2.205–2.571		
No falls reported (329 participants)	**Gender**	**Mean**	**95% CI**	**F-ratio**	**P**
Eo power	F	0.4	0.377–0.423	F(1,328) = 5.14	0.024*
	M	0.442	0.407–0.475		
Ec power	F	0.579	0.533–0.620	F(1,328) = 19.80	0.00001****
	M	0.749	0.655–0.826		
(Eo + Ec)/2	F	0.49	0.458–0.519	F(1,328) = 15.88	0.0001***
	M	0.595	0.540–0.647		
Ec/Eo	F	1.466	1.397–1.528	F(1,328) = 12.20	0.0006***
	M	1.749	1.579–1.895		

(*Continued*)

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Table 2 (Continued).

Falls reported (187 participants)	Gender	Mean	95% CI	F-ratio	P
Eo power	F	0.748	0.664–0.826	F(1,186) = 3.46	0.065#
	M	0.913	0.791–1.028		
Ec power	F	1.571	1.343–1.772	F(1,186) = 12.14	0.0062**
	M	2.189	1.899–2.474		
(Eo + Ec)/2	F	1.159	1.015–1.295	F(1,186) = 10.44	0.0015**
	M	1.552	1.356–1.739		
Ec/Eo	F	2.166	1.946–2.362	F(1,186) = 6.91	0.0094 **
	M	2.673	2.348–2.964		

Note: #p≥0.05; *p≤0.05; **p≤0.01; ***p≤0.001; ****p≤0.0001.
Abbreviations: F, female; M, male; NF, no falls; FR, falls reported; Eo, eyes open; Ec, eyes closed.

a progressively greater degree of age-related vestibular functional decline in individuals with progressively increasing postural instability and fall risk. A significant increase in the CNS band ($P < 0.05$) is observed for Eo but not for Ec.

Discussion

The present study demonstrates that digital biomarkers derived from a single head-mounted phybrata sensor are sufficiently consistent, reproducible and sensitive to provide objective assessments of progressive age-related balance impairments and sensory reweighting, underlying physiological contributions, and related intrinsic fall risks in older populations. Many previous studies have demonstrated that simple measures of postural sway derived from instruments

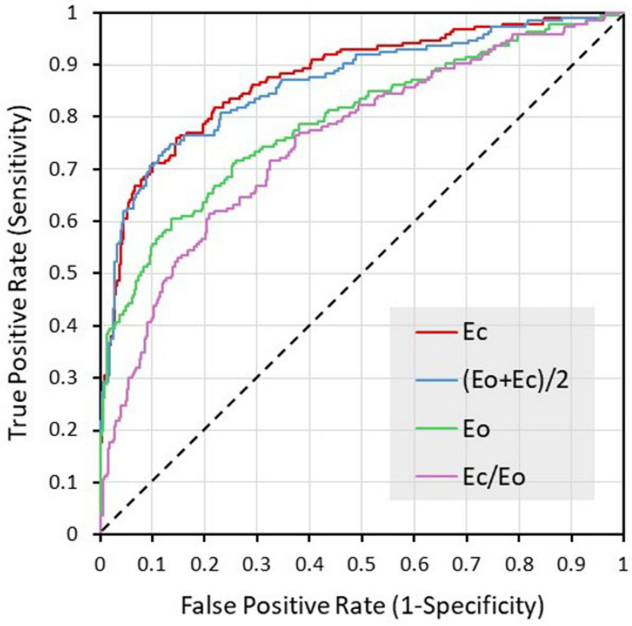

Figure 5 ROC curves for 4 phybrata metrics used for the classification of falls history for all 516 participants.
Abbreviations: Eo, eyes open; Ec, eyes closed.

Table 3 Summary of ROC Results for 4 Phybrata Metrics Used to Classify Falls History for All 516 Participants, for 334 Female Participants, and for 182 Male Participants. Grey Shading Indicates AUC and Cutoff Values for the Ec Metric for Each of the 3 Participant Groups

Phybrata Metric	AUC	95% CI	Cutoff	TP	FP	FN	TN	Sensitivity (TP/TP+FN)	Specificity (TN/TN+FP)	Precision (TP/TP+FP)	Accuracy (TP+TN)/ (TP+FP+FN+TN)	Youden Index	Distance to Corner
All participants (516)													
Eo	0.792	0.745–0.831	0.58	113	45	74	284	0.604	0.863	0.715	0.769	0.468	0.419
Ec	0.876	0.838–0.905	0.90	142	48	45	281	0.759	0.854	0.747	0.82	0.614	0.281
(Eo+Ec)/2	0.865	0.825–0.896	0.74	140	44	47	285	0.749	0.866	0.761	0.824	0.615	0.285
Ec/Eo	0.752	0.704–0.793	1.78	115	69	72	260	0.615	0.79	0.625	0.727	0.405	0.438
Female participants (334)													
Eo	0.793	0.730–0.843	0.58	61	26	43	204	0.587	0.887	0.701	0.793	0.474	0.429
Ec	0.868	0.817–0.906	0.90	75	22	29	208	0.721	0.904	0.773	0.847	0.626	0.295
(Eo+Ec)/2	0.854	0.799–0.895	0.74	74	24	30	206	0.712	0.896	0.755	0.838	0.607	0.307
Ec/Eo	0.753	0.691–0.804	1.78	56	35	48	195	0.539	0.848	0.615	0.752	0.386	0.486
Male participants (182)													
Eo	0.781	0.701–0.841	0.7	46	9	37	90	0.554	0.909	0.836	0.747	0.463	0.455
Ec	0.879	0.816–0.921	1.18	62	8	21	91	0.747	0.919	0.886	0.841	0.666	0.266
(Eo+Ec)/2	0.872	0.806–0.917	0.92	63	9	20	90	0.759	0.909	0.875	0.841	0.668	0.258
Ec/Eo	0.731	0.647–0.797	1.9	56	28	27	71	0.675	0.717	0.667	0.698	0.392	0.431

Abbreviations: Eo, eyes open; Ec, eyes closed; AUC, area under the curve; TP, true positive; FP, false positive; FN, false negative; TN true negative.

such as force plates[39] or wearable IMUs[29,30] are more reproducible and reliable than subjective balance tests[20,26] for the assessment of balance disruptions in older populations. In addition to static balance, head movement kinematics have been shown to enable functional assessments of gait impairments[40–42] and activities of daily living.[43,44] The present study, however, demonstrates the unique ability of the phybrata sensor to map the systematic sensory reweighting across multiple physiological systems that accompanies age-related balance decline and increased fall risk.

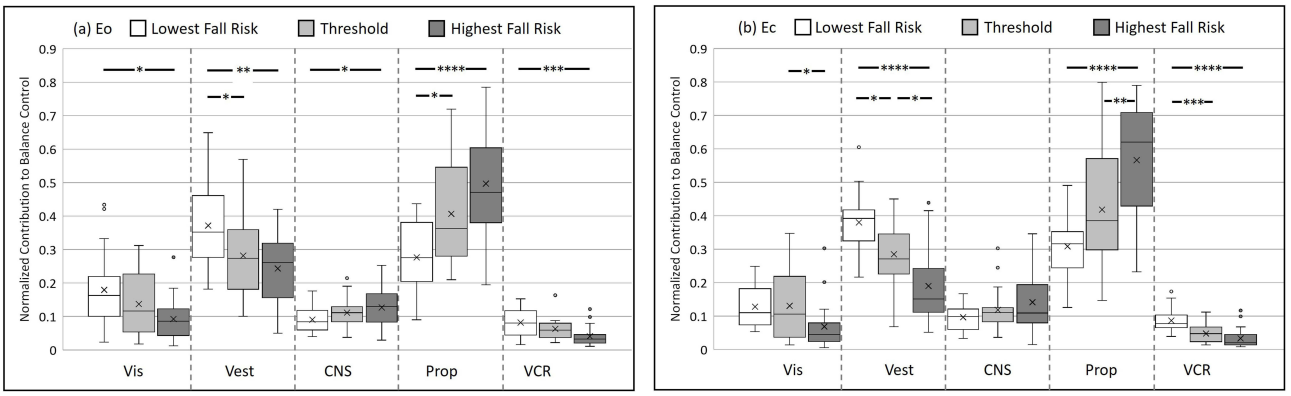

Figure 6 Phybrata sensory reweighting plots for 20 lowest fall risk participants, 20 threshold low/high fall risk participants, and 20 highest fall risk participants (**a**) Eo (**b**) Ec.
Note: *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001; ****p ≤ 0.0001.
Abbreviations: Eo, eyes open; Ec, eyes closed; Vis, vision; Vest, Vestibular; CNS, central nervous system; Prop, proprioception; VCR, vestibulocollic reflex.

The specific phybrata biomarkers discussed here are:

(i) Four balance performance biomarkers derived from the phybrata time series data: eyes open (Eo) and eyes closed (Ec) phybrata powers, average phybrata power (Eo+Ec)/2, and Ec/Eo phybrata power ratio.
(ii) Fall risk biomarker derived from the phybrata time series data: Ec.
(iii) Five SR biomarkers derived from phybrata ASD data to quantify age-related impairments and sensory reweighting across sensory inputs (visual, vestibular, proprioceptive), CNS sensorimotor integration, and neuromotor control (vestibulocollic reflex).

These phybrata biomarkers can serve as:

(i) Physiological biomarkers that assess critical sensory and neuromotor functions related to aging.
(ii) Systems aging biomarkers that identify patterns and pathways in the systemic aging and dysfunctions of the body's integrated neuromotor system.
(iii) Longitudinal and clinical biomarkers of aging that provide insights into the progression of neuromotor aging processes by monitoring individuals over extended periods, allowing researchers to predict health outcomes, understand the dynamics of aging, and develop targeted and personalized interventions to promote healthy neuromotor aging.

Phybrata Balance and Fall Risk Biomarkers

As illustrated in Figure 4a, all four phybrata metrics show significant statistical correlations with reported fall history (FR vs NF). ROC analysis (Figure 5 and Table 3) gives AUC values ranging from 0.75–0.88, which are all higher than the typical AUC range of 0.5–0.7 that have been reported for many other common fall risk assessments.[26] The Ec metric shows the strongest correlation with falls status (AUC = 0.88), although the (Eo+Ec)/2 metric is very close in classification performance (AUC = 0.87). This result is consistent with the observation that, compared to young adults, older adults experience relatively greater difficulty maintaining their balance during sensory feedback perturbations such as standing with the eyes closed or on foam,[45,46] and this behavior has also been correlated with loss of vestibular function.[46] These same four phybrata metrics have previously shown similar significant statistical correlations with the diagnosis of concussion in a study population of 175 individuals aged 7–66 yrs.[32] The (Ec+Eo)/2 metric showed the strongest correlation with concussion diagnosis, although the Ec metric was very close in classification performance. ROC curves demonstrated that Eo and Ec/Eo may be utilized as independent measures to confirm accompanying neurological and vestibular impairments. Phybrata testing and sensory reweighting analysis revealed the significant contribution of vestibular impairment to balance disruption following concussion injuries and allowed subsequent monitoring of improvements throughout treatment and rehabilitation.[31,32] For the diagnosis of concussion, the combination of phybrata sensor data and machine learning models has been shown to enable both binary classification of concussion patients and multiclass predictions of specific concussion-related neurophysiological impairments, outperforming the diagnostic performance of alternatives such as neurocognitive tests, clinical scales, symptoms checklists, balance and gait testing, MRI, EEG, eye tracking, and blood biomarkers.[34] The above similarities in phybrata results highlight the degree to which concussions and other repetitive head impact injuries can lead to "accelerated aging",[47] with impairment profiles that mirror "normal aging", including significant impairments to vestibular function.[48]

As illustrated in Figure 4b, all four phybrata metrics also show significant differences ($p < 0.05$) between F vs M participants in the NF group. As illustrated in Figure 4c, three of the four phybrata metrics (Ec, (Eo+Ec)/2, Ec/Eo, but not Eo) showed significant differences between F and M participants in the FR group. The ROC results in Table 3 also indicate lower thresholds in F vs M for the emergence of fall risk (NF vs FR) for all four phybrata metrics. These results are in contrast to a previous study of the balance performance of 347 healthy college students aged 18–21 years,[31] in which statistically significant differences as a function of gender were observed for Eo and Ec but not for Ec/Eo. In the concussion study discussed above,[32] significant differences in phybrata performance were observed as a function of age in the healthy control participants. Taken together, these results indicate that phybrata testing is sufficiently sensitive to

detect gender-based differences in overall postural control regardless of age (Eo, Ec), the progression of balance decline and fall risk with age (Ec), and the important contribution of vestibular disruptions (increasing Ec/Eo). The observed higher Eo for FR vs NF with no significant difference between M and F may indicate that CNS contributions to age-related balance decline are less dependent on gender in the current study population. Similar trends in age- and gender-related balance performance have also been reported using much more expensive CDP equipment and much more time-consuming test protocols.[49]

Phybrata Sensory Reweighting Biomarkers

The most widely accepted method to quantitatively assess an individual's ability to use visual, proprioceptive and vestibular cues to maintain postural stability during standing balance is the sensory organization test (SOT).[50–52] The SOT uses a sophisticated six-degree-of-freedom CDP motion platform with dual force plates and a wrap-around visual screen to measure changes in a person's balance ability when different combinations of visual, vestibular, and proprioceptive sensory systems are either available or disrupted. Test results include separate scores averaged over three trials of six different SOT conditions, along with an overall equilibrium index score. Multiple studies have used SOT to quantify overall balance decline, underlying sensory system impairments, and fall risk in older population.[21–25] SOT results from a cohort of 34 older adults comparing those with and without elevated fall risks[21] demonstrate qualitative trends similar to those reported here, with elevated fall risk participants recording lower overall equilibrium index scores, lower sensory analysis scores for vestibular and visual function, and higher sensory analysis score for proprioception. ROC curves using the SOT composite score to predict fall risk had an AUC of 0.65,[21] typical of the values ranging from 0.5 to 0.7 that have been reported for many other common fall risk assessments,[26] and much lower than the phybrata Ec results reported here, with AUC = 0.88 (Figure 5). Other SOT studies of balance in older populations consistently report lower overall equilibrium index scores and lower sensory analysis scores for vestibular function.[22–24] The present results are the first to demonstrate clear progressive trends in declining balance performance and sensory reweighting, with decreased vestibular function offset by greater reliance on proprioception, across a large cross-sectional study cohort (N = 516) spanning a wide range of age and balance performance. Compared with SOT, phybrata testing can be completed with much shorter test times and far less complex and expensive apparatus. The portability and ease of use of the phybrata sensor eliminates the need for participants to come to a dedicated balance testing facility.

The phybrata sensor exploits the fact that the head serves as an egocentric reference for balance, walking, and most other voluntary motor activities[53] and centralizes the integrated sensing of physiological signals. Maintaining the biomechanical stability of the head and eyes is thus a fundamental goal of human balance and postural stability control. During quiet stance, body motion increases in order of lower limbs, pelvis, trunk, and head, exhibiting frequency components up to 30 hz at the head due to head-neck stabilization via vestibulocollic reflexes.[54] Direct measurement of head acceleration has been shown to provide much more sensitive detection of body motion across this entire frequency range than is possible using center of pressure (COP) measurements with force plates and CDP systems.[32] ASD is a widely used engineering tool for analyzing random vibrations in complex industrial systems,[55] including the design of robots that can mimic human bipedal motion.[56–58] Physiological vibration has been shown to be inherent to human postural and motor control,[59,60] including components described as tremor,[59,61] rambling and trembling,[60] and head micro-movements.[62] Ensemble-average ASD analyses have been utilized to capture the significant time varying spectral changes that result from intermittent balance control processes that utilize multiple physiological system inputs and outputs,[63,64] and to identify statistically significant spectral features that can distinguish patients vs control groups.[63] In clinical medicine, head-mounted accelerometers have been used to compare normal and pathological passive head acceleration spectra for healthy individuals and those with essential tremor,[65] to compare head and eye tremors for the assessment of vestibulo-ocular impairments,[66] to detect changes in intercranial pulsatility[67] associated with diffuse brain tissue atrophy and white matter degeneration following stroke, and to measure the mechanocardiographic motion of the body[68] resulting from cardiovascular blood flow. Analysis of head micro-movements in MRI image data has been used to classify different neurodevelopmental disorder phenotypes.[62] Acceleration spectral analysis of body center of mass data

has also been utilized to study differences in the complex multi-system postural control process between young children and adults.[69]

Changes in the spectral characteristics of postural control have been observed for many different postural challenges and medical conditions.[17,18,32–36,63,70–85] Age-related changes in specific frequency bands have been observed,[76,77] and it has been proposed as early as 1997 that the analysis of these spectral characteristics during quiet stance may be a clinically useful tool in identifying biomarkers associated with age-related loss of functional balance capacity and increasing fall risk.[77] Spectral analysis of postural sway, sensory impairments, and sensory reweighting due to a wide range of postural challenges and medical conditions reveals that specific frequency bands correspond to distinct postural regulation strategies.[17,18,32–36,71–75,82,84] The present study validates the clinical utility of digital biomarkers derived from phybrata ASD analyses to enable rapid objective assessment of progressive age-related balance impairments, sensory reweighting, and the underlying physiological contributions.

The results presented in Figure 6 are consistent with other studies reporting a general trend toward age-related decline in peripheral and central vestibular function[6–11,15,16,86–89] that is compensated for by a greater reliance on proprioceptive balance control.[89,90] The observed increase in the CNS band for Eo may reflect central vestibular compensation for declining peripheral vestibular function, as has been previously reported in older populations.[91] Recent studies comparing SOT results for sensory-specific changes in balance and MRI results for changes in brain structure[89] have demonstrated the same combination of poorer vestibular function and greater proprioceptive reliance with declining overall balance performance, and shown that these changes are correlated with thinner vestibular cortex, greater gyrification within sensorimotor, parietal, and frontal cortices, and lower free water-corrected axial diffusivity across the corona radiata and corpus callosum. These structural changes are also linked to changes in higher order neurological processes and cognition that play a key role in the regulation of gait and balance in older adults via movement planning, multi-task attention, and response to environmental changes.[92] Another important contribution to higher-frequency proprioceptive postural sway fluctuations in elderly adults is the increased physiological tremor that results from reduced lower extremity muscle strength.[25,93,94] The combination of vestibular deficits and proprioceptive compensation strategies in elderly balance thus reflects multiple disruptions in motor control feedback and correlates well with the observed decline in overall postural stability as individuals are forced to rely more on proprioception.[89,90]

Limitations and Future Developments

The present study is limited to correlating phybrata biomarkers with cross-sectional data from the study population and self-reported retrospective fall histories. Future studies could include longitudinal data collection to directly measure changes in balance performance, vestibular function, and sensory reweighting over time and to track prospective falls incidence, as have been reported in previous longitudinal studies of age-related changes in fall risk and vestibular function.[95,96] The phybrata sensor has also previously been used in longitudinal studies of balance performance in athletes.[31] The lack of direct comparison with other balance assessment tools is another limitation of the present study, which can be overcome by adding more comprehensive vestibular clinical exams and motor, sensory, coordination, and balance testing as in our previous phybrata studies of concussion.[32] A further improvement could be gained by combining phybrata balance testing with instrumented gait analyses to examine the correlation between impairments and sensory reweighting in static balance vs dynamic gait and their relative impacts on fall risk, for a more complete evaluation of age-related decline. The present study does not include direct assessments of specific peripheral vestibular impairments (otoliths vs semicircular canals),[6,10,44,97] the relative contributions of peripheral vs central vestibular impairments,[6,98] or related cognitive impairments.[15,92] These limitations could be addressed in future collaborations with related clinical specialists, as in our previous phybrata studies of motor and cognitive impairments in multiple sclerosis.[35] The frequency band assignments used in the present sensory reweighting analysis rely on previously reported studies. Although the results are consistent with widely reported trends in sensory, CNS, and neuromotor contributions to postural stabilization, future studies should investigate in more detail the potential overlap between these frequency bands, variations across study populations, and individual variations as a function of time, impairments, and interventions.

The results presented here highlight many potential applications of phybrata biomarkers for aging biology research, clinical trials, and clinical practice. Current studies of aging focus heavily on molecular and omic biomarkers to quantify the accumulation of age-related molecular damage and other mechanisms of aging, with the goal of identifying interventions that can reduce the consequences.[99,100] A key challenge that remains to be addressed is connecting many of these biomarkers with actionable insights regarding functional decline in healthcare and preventative settings.[101] Phybrata digital biomarkers can address this challenge by directly quantifying the decline in functional mobility that is one of the most profound and directly observable indicators of aging. In addition to sharing the same traditional biomarker clinical goals, digital biomarkers such as those described here contribute new capabilities for continuous longitudinal measurements of more complex physiological systems such as balance.[102]

Phybrata balance assessments can also be extended to IMU-based analysis of gait impairments, which has been shown in multiple studies to enable assessment of age-related decline in balance, mobility, and cognition and the corresponding increase in fall risk.[29,30,95,103] Head movement kinematics derived from IMUs have been shown to enable functional assessments of gait impairments,[40–42] and fall risk predictions using head and neck kinematics during gait testing have been reported to outperform those derived from foot-mounted sensors (AUC = 0.75 vs AUC = 0.68).[40] The combined use of IMUs and camera-based motion capture features has been shown to enhance fall-risk classification, with AUC = 0.88.[104] The fall risk classification performance of standard balance and gait testing approaches can also be improved using machine learning,[105–107] and we have demonstrated that this is also the case for phybrata testing.[34] Decreases in head sway measured using accelerometers in a head-mounted display have been shown to monitor the response to vestibular rehabilitation,[75] highlighting the potential to use phybrata sensors to monitor sensory reweighting during such interventions. Adding postural sway frequency analysis has been shown to improve the sensitivity of SOT for the detection of vestibular dysfunction,[108] and SOT assessments have been combined with gait analysis in a locomotor sensory organization test (LSOT) to study sensory reweighting during ambulatory tasks,[109] highlighting additional potential extensions of phybrata testing.

At the other end of the aging spectrum, CDP has been used to study balance development in children, revealing that the proprioceptive system is fully developed in the first 3–4 years and the visual system by the age of 15, while the vestibular system continues to develop until the age of 16 or later.[110] The role of the vestibular system in early childhood development has also begun to receive significant attention,[111] based on studies revealing that unidentified or untreated vestibular issues in childhood can lead to a number of poor outcomes. In particular, peripheral and central vestibular dysfunction have been identified in children with neurodevelopmental disorders that impact motor coordination, fine motor skills, postural instability, cognitive development and educational performance, and emotional and social behavior.[111,112] Involuntary head micro-movements such as those detected using the phybrata sensor have recently been shown to reflect age-dependent development and decline in human motor stability across a very wide age range.[62] It has been proposed that these head micro-movements may serve as an important biomarker in diagnosing and treating children with developmental disorders.[113]

The above results and discussion highlight the crucial role played by the vestibular system in human development, normal functioning, and aging. The vestibular system provides absolute information about the body's orientation and movement, regardless of external visual cues or the position of other body parts, while vision and proprioception primarily offer relative information based on objects in the surrounding environment and body parts' positions relative to each other. In everyday life, these objects are often moving, forcing us to rely on vestibular inputs as the veridical reference against which other sensory inputs are evaluated when conflicts among multiple sensory inputs occur.[114] The phybrata sensor and biomarkers described here provide a powerful new tool to enable much more frequent and accessible objective assessments of vestibular function at all ages.

Pilot deployments of the above phybrata balance testing, together with a variety of balance rehab solutions, are now underway in multiple healthcare settings, including senior living communities, at-home care delivery, and physical therapy clinics. These pilot deployments include assessments of user training and support requirements, integration into clinical workflows, accompanying enhancements to balance treatment technologies and protocols, benefits to patients across multiple dimensions, and the overall healthcare cost/benefit economics of advanced balance testing and rehab solutions.

Conclusions

Using a head-mounted phybrata wearable sensor, we have developed digital biomarkers that enable rapid objective assessment of progressive age-related balance decline, increasing fall risk, underlying physiological contributions, and sensory reweighting in older populations. The ease of use and simple two-minute test protocol allow the device to be used in any senior care location, including clinical settings, independent and assisted senior living communities, and at home. Phybrata digital biomarkers enable frequent and widely accessible preventive screening to promote healthy neuromotor aging and clinical assessments to develop targeted treatment and rehabilitation strategies that can extend the human healthspan.

Abbreviations

IMU, inertial motion unit; Phybrata, physiological vibration acceleration; Eo eyes open; Ec, eyes closed; ASD, acceleration spectral density; NF, no falls reported; FR, fall(s) reported; ROC, receiver operating characteristic; AUC, area under the curve; CNS, central nervous system; PNS, peripheral nervous system; VOR, vestibulo-ocular reflex; VCR, vestibulocollic reflex; VSR, vestibulospinal reflex; SR, sensory reweighting; CDP, computerized dynamic posturography; ML, machine learning; MRI, magnetic resonance imaging; EEG, electroencephalography; BLE, Bluetooth low energy; AP, anterior posterior; ML, medial lateral; ANOVA, analysis of variance; MANOVA, multiple analysis of variance; CI, confidence interval; SOT, sensory organization test; COP, center of pressure.

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Disclosure

John D Ralston is the co-founder and CEO of Neursantys, Inc., and has a financial interest in the company. In addition, he reports a US provisional patent application 63/741,968 pending to Neursantys Inc. Josh Roper is the co-founder and Vice President of Operations of Neursantys, Inc., and has a financial interest in the company. Scott Stanley is the CEO of Caring Hands Caregivers, and a member of the Neursantys Advisory Board. The authors report no other conflicts of interest in this work.

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