Balance-controlling mechanism and fall-prevention strategy

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Balance-controlling mechanism and fall-prevention strategy

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Editorial: Balance-controlling mechanism and fall-prevention strategy

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Editorial on the Research Topic
Balance-controlling mechanism and fall-prevention strategy

Falls and fall-related injuries and deaths burden society heavily. Balance and gait disorders are the primary cause of falls in older adults. Currently, evidence-based training regimens are still lacking for some populations with a specific balance disorder, which calls for high-quality interventional studies to facilitate clinical practices. In addition, tackling the challenges of fall prevention demands more in-depth investigations of balance-control mechanisms, which may facilitate the more sensitive assessment of balance impairment and possibly the earlier detection of fall risks. These mechanisms are also expected to provide insights for the earlier, more targeted, and more effective fall-prevention management. We are happy to have published 9 articles in this research topic that advance our understanding of the balance-control mechanisms (He et al.; Jiang et al.; Sato et al.; Xing et al.; Santos et al.; Caronni et al.) and the latest evidence-based fall-prevention management (Xing et al.; Winser et al.; Ho et al.; Elrod et al.).

Probing the balance-control mechanisms

Increasing number of the existing clinical and laboratory tests have been validated for assessing the postural balance. This has facilitated the understanding of how patients' balance performance and fall risks following some neurological impairments are affected. Sato et al. have used the static posturography to evaluate balance during quiet standing in 30 inpatients, who received a radiofrequency ablation neurosurgery to treat the essential tremor. They observed that after the surgery with the tremor symptoms been reduced, the patients could not immediately readjust the center of pressure to the body midline. This potentially suggested the need of rehabilitation, for improving postural balance, in the perioperative period when surgically treating the individuals with essential tremors. Caronni et al. have examined the criterion validities of several clinical tests for balance and gait assessment as measures to differentiate future fall risks in individuals with a neurological disability. The Mini-Balance Evaluation System Test (Mini-BESTest) and the turning duration of the Timed Up and Go (TUG) test were found to be able to predict the participants' fall incidences. These tests have shown promising applications in the fall-risk assessments for the populations with neurological disabilities, although they may inadequately be able to distinguish the fall risks in community-dwelling older adults (1).

In this Research Topic, some studies have also applied advanced methods or have proposed new methods of analyzing the whole-body postural control. Jiang et al. have investigated how the suspensory strategy is affected by the different knee flexion angles in healthy young adults during quiet standing. On top of the conventional assessment of center-of-mass displacement, they have used the time-frequency analysis to evaluate the sensory input and used the sample entropy, one non-linear analysis method of quantifying postural regularity, to evaluate the motor output for maintaining standing balance. Santos et al. have proposed a new parameter to indicate the postural instability in individuals with the Parkinson's Disease (PD), based on the cost-effective motion capture of head movements in quiet standing and the use of movement element decomposition method. The parameter was found to differentiate the individuals among the early stages of PD progression better compared to several other clinical tests for balance performance.

Apart from the analysis of whole-body postural sways, recent studies have delved deeper into the roles of central nervous system and neuromuscular system in balance control. He et al. have used functional near-infrared spectroscopy to investigate the stroke survivors' cortical activation during walking. By comparing healthy walking, functional electrical stimulation (FES)-assisted walking, and non-FES walking, they have observed some asymmetric activation patterns in the investigated cortical areas for stroke survivors. Regarding the motor output pathway, recent studies have investigated the speed of multiple major lower-limb muscles' activation in maintaining reactive standing balance by analyzing the timing and rising rate of electromyographic (EMG) signals, revealing that ankle muscles have the faster response (2, 3). In addition to EMG, with the advancing of wearable technologies, some techniques, such as the ultrasound imaging of muscles, have been available to detect the muscle morphological changes in dynamic situations and assess balance performance (4, 5). Such muscular mechanisms provide new insights for improving balance or relieving the balance and gait disorders.

Exploring the fall-prevention strategies

Since the causes of falls are multi-factorial, effective fall-prevention strategies are not confined to improve the balance and gait performance only (Xing et al.). Winser et al. have conducted a randomized controlled trial to examine the effectiveness and cost of integrated cognitive and balance training (CIBT) on balance and falls in individuals with cerebellar ataxia. The CIBT improved the limit of stability, a measure of volitional balance control, while it did not exhibit better effects on reducing falls compared to the conventional single-task training. Ho et al. have systematically reviewed the effectiveness of robotic-assisted upper-limb rehabilitation in individuals with cervical spinal cord injuries, since the upper-limb reach-and-grasp responses and the arm swings are also important for maintaining balance and avoiding falls. Elrod et al. have reported their case study on the development of academic-community partnerships for delivering fall-prevention programs in an American metropolitan setting. The programs were found successful in reaching the community-dwelling older adults with low to moderate fall risks but not for those at high risk. They have identified some key facilitators and barriers of pragmatic implementation, which may lend experience for the delivery of fall-prevention management in other areas.

In summary, the studies presented in this Research Topic provide updated insights into the clinical applications of balance assessment in specific populations, the state-of-art analysis methods of balance control, and the evidence on the effectiveness and actual implementation of specific fall-prevention programs. We expect that these efforts can facilitate current clinical practices in fall prevention and imply further research on probing balance-control mechanisms.

Author contributions

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Asymmetric cortical activation in healthy and hemiplegic individuals during walking: A functional near-infrared spectroscopy neuroimaging study

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Background: This study investigated the cortical activation mechanism underlying locomotor control during healthy and hemiplegic walking.

Methods: A total of eight healthy individuals with right leg dominance (male patients, 75%; mean age, 40.06 ± 4.53 years) and six post-stroke patients with right hemiplegia (male patients, 86%; mean age, 44.41 ± 7.23 years; disease course, 5.21 ± 2.63 months) completed a walking task at a treadmill speed of 2 km/h and a functional electrical stimulation (FES)-assisted walking task, respectively. Functional near-infrared spectroscopy (fNIRS) was used to detect hemodynamic changes in neuronal activity in the bilateral sensorimotor cortex (SMC), supplementary motor area (SMA), and premotor cortex (PMC).

Results: fNIRS cortical mapping showed more SMC-PMC-SMA locomotor network activation during hemiplegic walking than during healthy gait. Furthermore, more SMA and PMC activation in the affected hemisphere was observed during the FES-assisted hemiplegic walking task than during the non-FES-assisted task. The laterality index indicated asymmetric cortical activation during hemiplegic gait, with relatively greater activation in the unaffected (right) hemisphere during hemiplegic gait than during healthy walking. During hemiplegic walking, the SMC and SMA were predominantly activated in the unaffected hemisphere, whereas the PMC was predominantly activated in the affected hemisphere. No significant differences in the laterality index were noted between the other groups and regions ($p > 0.05$).

Conclusion: An important feature of asymmetric cortical activation was found in patients with post-stroke during the walking process, which was the recruitment of more SMC-SMA-PMC activation than in healthy individuals. Interestingly, there was no significant lateralized activation during hemiplegic walking with FES assistance, which would seem to indicate that FES may help hemiplegic walking recover the balance in cortical activation. These results, which are worth verifying through additional research, suggest that FES used as a potential therapeutic strategy may play an important role in motor recovery after stroke.

KEYWORDS

stroke, hemiplegia, gait, treadmill walking, functional electrical stimulation

Introduction

Stroke is one of the leading causes of disability in adults worldwide. Although most patients can recover their walking ability after rehabilitation treatment, more than 50% of hemiplegic patients with post-stroke in the community cannot walk independently (1). The central pattern generators in the spinal cord play an important role in the generation of rhythmic and repetitive locomotor patterns *via* supraspinal regulation of cerebral neural networks; nonetheless, the neural substrates and associated neurophysiological mechanisms underlying dynamic locomotor control remain elusive (2, 3). To date, the cortical activation mechanism underlying locomotor control during dynamic walking in stroke patients with hemiplegia and healthy individuals have not yet been elucidated. Functional magnetic resonance imaging, which is characterized by high spatial resolution and low temporal resolution, is used to probe cortical activation patterns during finger, ankle, and knee movements; however, it is ill-suited for studying larger locomotor activities, such as walking, due to inherent motion artifacts and structural constraints (4). Positron emission tomography requires the injection of a radioactive tracer and is unsuitable for repeated measurements (5). Electroencephalography (EEG) has high temporal resolution but low spatial resolution, leading to long preparation times and easy human interference (6). Functional near-infrared spectroscopy (fNIRS) imaging technology is not only a good tool for assessing movements, such as walking and postural transitions, but also an effective tool for examining brain activity patterns during real-world activities (7). fNIRS can detect hemoglobin (Hb) oxygenation during human gait and has been utilized as a signal marker of neural substrates underpinning locomotor control in healthy adults (8) and patients with hemiparetic stroke (3).

Treadmill walking (TW) can provide safe, intensive, and task-oriented rehabilitation for patients with dyskinesia after a stroke and is widely used for clinical gait rehabilitation training (9). For the first purpose of our research, we used fNIRS to monitor cortical blood oxygen changes during healthy and hemiplegic walking and to explore differences in brain activation between normal and hemiplegic patterns during walking.

Functional electrical stimulation (FES) is a common representative of the bottom-up peripheral stimulation method for stroke (10). FES has been used to improve foot drop after stroke since 1960 (11) and has been proven to alter circumduction hemiplegic gait patterns, considerably improve the step length and the maximum dorsiflexion and knee flexion angles, and increase the maximum muscle forces of both tibialis anterior and rectus femoris muscles (12). Moreover, the muscular structures of the tibialis anterior, rectus femoris, and gastrocnemius muscles are reversible with long-term FES use, as decreased echogenicity of the tibialis anterior muscle, accompanied by increased muscle size on the paretic side, was found (13). It is most likely that FES provides a different stimulation context for the excitability of the common peroneal nerve, which becomes more susceptible to overuse and fatigue, leading to a decrease in motor-evoked potential (MEP) parameters and motor plasticity (13). However, the decreased excitability of the motor cortex reflected by MEPs cannot prove that FES has a motor plasticity effect. Conversely, previous studies reported that FES did not simply increase the general excitability of the cortex and had specific effects on particular cortical neurons (14). Possibly attributable to a bimodal balance-recovery model, there are different patterns of neural reorganization, such as interhemispheric competition or ipsilateral vicariation, in the injured motor cortex, with different structural reserves (15). However, it remains uncertain how FES affects motor cortical plasticity. Although our previous study found that FES treatment could enhance brain functional connectivity and efficiency in hemiplegic patients, it did not address cortical activation patterns during the locomotor control process (16). As for the second purpose of our research, the present study aimed to explore the possible mechanism of FES in walking rehabilitation by monitoring the effect of FES-assisted walking on brain activation during hemiplegic walking using fNIRS.

Abbreviations: deoxy-Hb, deoxygenated hemoglobin; oxy-Hb, oxygenated hemoglobin; EEG, electroencephalography; FES, functional electrical stimulation; TW, treadmill walking; fNIRS, functional near-infrared spectroscopy; LI, laterality index; MEPs, motor-evoked potentials; PFC, prefrontal cortex; PMC, premotor cortex; M1, primary motor cortex; S1, primary somatosensory cortex; SMC, sensorimotor cortex; SMA, supplementary motor area.

Methods

Participants

Patients with post-stroke who satisfied the following criteria were included in this study: (i) diagnostic criteria for major cerebrovascular diseases in China formulated by the Chinese Society of Neurology, which were applied to diagnose and enroll the patients in this study; (ii) right hemiplegia in the first brain stroke; (iii) subcortical lesions confined to the left hemisphere; (iv) right hemiplegic lower limb function at Brunnstrom stage ≥IV; (v) ability to continuously walk for 10 m for 15 s independently or with the assistance of walking aids, such as ankle foot orthoses and custom-fit insoles for reducing foot drop; and (vi) absence of cognitive impairment and Mini-Mental State Examination (MMSE) score of ≥24 for middle school or higher education and MMSE score of ≥21 for elementary education and no education in order for patients to correctly execute the training test instructions (17). Moreover, the healthy individuals had to satisfy the following criteria: (i) no history of neurological, physical, or psychiatric impairment; (ii) MMSE score ≥24; and (iii) no insomnia, alcohol consumption, or medication usage in the last week. Individuals who had head skin damage or large scar areas, recently used sedatives, or consumed alcohol were excluded. Written informed consent was provided by each participant prior to study commencement, and the study was approved by the Ethics Committee of Xiamen Fifth Hospital (approval number: 2020-XMSDWYY-009).

A total of eight healthy individuals with right leg dominance (male patients, 75%; mean age, 40.06 ± 4.53 years) and six post-stroke patients with right hemiplegia (male patients, 86%; mean age, 44.41 ± 7.23 years; disease course, 5.21 ± 2.63 months) were recruited for this study. There were no significant differences in sex or age between the two groups ($p > 0.05$). All participants had normal cognitive functions, although the MMSE score of healthy individuals was significantly greater than that of hemiplegic patients ($p = 0.01$) (Table 1).

TABLE 1 Basic data of participants.

Variable	Healthy participants	Post-stroke patients
Age (years)	40.06 ± 4.53	44.41 ± 7.23
Time from stroke (months)	/	5.21 ± 2.63
Sex (males, %)	75%	86%
Stroke type (ischemic/hemorrhagic)	/	2/4
MMSE	28.37 ± 1.41	25.17 ± 1.47

Values are presented as mean ± SD or as frequency. MMSE, Mini-Mental State Examination.

Experimental setup

A speed of 2 km/h was found to be a relatively appropriate treadmill speed, which was not too slow for healthy participants to feel comfortable walking while, at the same time, one to which the hemiplegic patients in this study were also able to adapt. The participants walked on a TecnoBody Digital Platform treadmill (ProKin 254P, TecnoBody, Italy) at a speed of 2 km/h while wearing comfortable clothing. Hemiplegic patients wore suspension measures to prevent falls; however, the suspension did not affect their weight. The participants kept their eyes straight and paid attention to a real-time moving image on the screen in front of them while walking. The participants' swinging limbs and torso during walking were displayed at the center of the screen. The walking range of both lower limbs and each foot weight were shown on the lower side of the screen. The participants were instructed to walk in a straight line, to avoid leaning toward one side of the treadmill track, and to keep their shoulders horizontal.

A four-channel FES therapeutic instrument (Model P2-9632, Guangzhou Fanke Medical Equipment Co., Ltd., China) was used. Four groups of muscles—namely, the tibialis anterior muscle, middle and lateral heads of the quadriceps femoris muscle, gastrocnemius muscle, and hamstring muscle—were marked in the movement at the muscle belly point and affixed by four sets of electrodes. The parameter settings were as follows: walking mode; biphasic square wave; frequency of 30 Hz; pulse width of 200 μs; 5-s walking cycle; and current intensity limited to the maximum tolerance of participants.

fNIRS imaging

The fNIRS equipment (Model BS-3000, Wuhan Znion Technology Co., Ltd., Wuhan, China) used 858- and 764-nm wavelengths, and the light intensity data were sampled at 20 Hz. To normalize the fNIRS channels, we applied a 3D digitizer (Nirmap, Wuhan Znion Medical Technology Co., Ltd., Wuhan, China) to record the exact spatial coordinates of four reference points (central zero, nasion zero, AL, and RL) and 24 probes (12 sources and 12 detectors). Subsequently, 37 channels were converted to an estimated Montreal Neurological Institute space (18) by NIRS-SPM (19). Based on the Brodmann probabilistic atlas, all 37 channels were then divided into the following five cortical regions: premotor cortex (PMC), supplementary motor area (SMA), primary motor cortex (M1), and primary somatosensory cortex (S1), among which the M1 and S1 were collectively referred to as the sensorimotor cortex (SMC) (Figure 1 and Table 2).

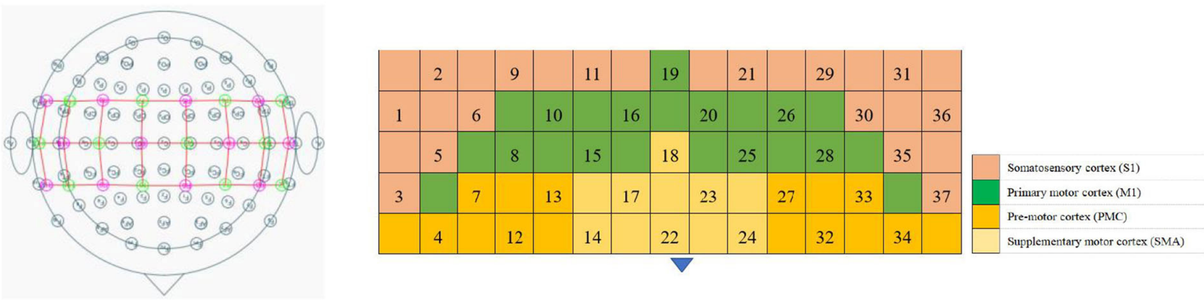

FIGURE 1
Schematic diagram of fNIRS channel registration with brain regions.

TABLE 2 List of fNIRS channels corresponding to Brodmann partitions.

Brodmann areas	Channel number
Primary somatosensory cortex: BA 1, 2, 3	Ch03/05/06/09/11, ch21/29/30/35 /37Ch01/36
Supramarginal gyrus part of Wernicke's area: BA40	Ch02/31
Subcentral area: BA43	Ch3/37
Primary motor cortex: BA4	Ch08/10/15/16/19/20/25/26/28
Premotor cortex: BA6	Ch14/17/18/22/23/24
Supplementary motor cortex: BA6	Ch04/07/12/13/27/32/33/34

fNIRS, functional near-infrared spectroscopy.

Experimental procedure

The whole test process was divided into two stages: preparation and task. During the preparation period, the participants rested in a standing position for 10 s. During the task period, upon hearing the command "walk," the participants first stepped on the right leg and walked alternately for 30 s; when hearing the command "stop," the participants stopped walking and rested in a standing position for 30 s. This process was repeated for five loops (Figure 2).

Data analysis

Light intensity data were converted into changes in oxy-Hb and deoxy-Hb concentrations using a built-in function based on the modified Beer–Lambert law (20). Signal analysis was performed using the MATLAB 2014b toolbox (MathWorks, Inc., Natick, MA, USA).

Cortical activation

NIRS-KIT (registration number for software copyright protection: 2019SR1299168; Beijing Normal University, China) (21) can analyze hemodynamic changes in oxy-Hb and deoxy-Hb concentrations from raw light intensity time series using general linear models. The brain's hemodynamic responses (hmr) to a task condition, including the changes in oxy-Hb and deoxy-Hb concentrations in brain regions (Figure 3) in our study, are assumed to be linearly additive and consistent across trials. This pipeline of task activation detection comprised common and necessary processing steps for fNIRS signal analysis, such as data preparation, quality control, preprocessing, individual-level analysis, group-level statistics, and visualization of results. In the preprocessing step, which consisted of several parts including detrending, the temporal derivative distribution repair (TDDR) motion correction method was adopted for TDDR (22), with bandpass filtering (0.001 to 0.08 Hz) by a third-order infinite impulse response filter. Oxy-Hb levels increased at 3–5 s after the onset of each task, reached a plateau at 10 s, and decreased at 3–5 s after the end of each task; based on this, we acquired images depicting the average from Δoxy-Hb changes, which were obtained *via* block-averaging of five tasks within the time range of 0–35 s minus the baseline hmr level of −5 s before each task began. The MATLAB customized processing method was used to process fNIRS data. A general linear model was used to detect task activation in the individual-level analysis of the task's fNIRS. In group-level analyses, a one-sample t-test was used to test whether the β indices were significantly different (from a given value, e.g., 0) between the healthy and patient groups. The two-sample t-test was used to examine whether the β indices in the healthy and patient groups were significantly different from each other. The paired t-test was used to determine whether the β indices in the treadmill and FES-assisted walking groups were significantly different from each other. The false discovery rate was used to correct for multiple t-testing of fNIRS data in each channel (23). Before the correction, the statistical significance

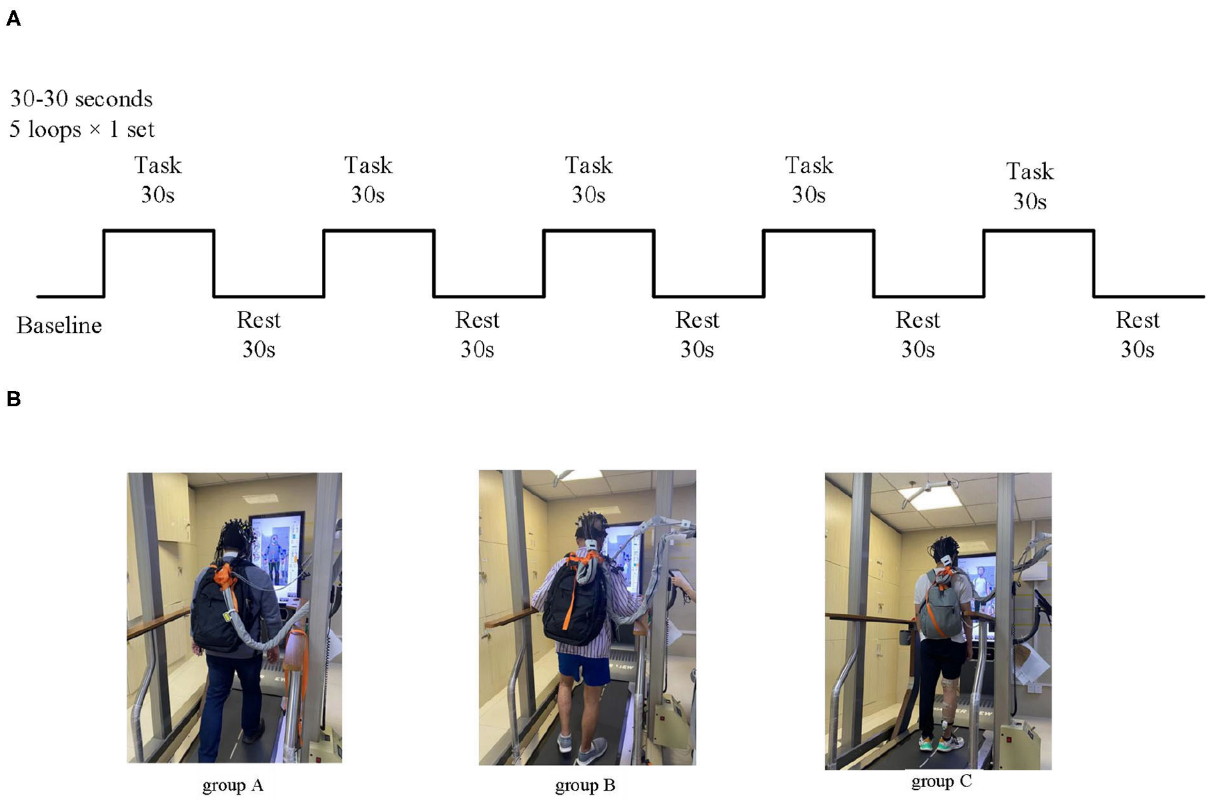

FIGURE 2
Experimental block design for walking modes at a consistent speed. **(A)** Treadmill walking and FES-assisted walking modes. **(B)** Schematic diagram of experimental grouping; Group A: healthy treadmill walking at a speed of 2 km/h; group B: hemiplegic treadmill walking at a speed of 2 km/h; and group C: hemiplegic treadmill walking with FES assistance at a speed of 2 km/h.

level for all comparisons was set at $p < 0.05$ (two-sided). Channel-wise 2D visualization was used to show the task-design fNIRS group-level analysis indices (beta value or contrast value).

Laterality index

The laterality index (LI) was used to evaluate the asymmetry in each region's amount of activation. LI values ranged from −1 to 1; a positive value (0 to 1) indicated right-dominant activation, whereas a negative value (−1 to 0) indicated left-lateralized activation. The oxy-Hb change activation in the brain region of interest was compared using SPSS software version 25.0 (Statistical Product Service Solutions, IBM Corp., USA). The LI was defined as [Δoxy-Hb in the right (unaffected) hemisphere – Δoxy-Hb in the left (affected) hemisphere]/[Δoxy-Hb in the right (affected) hemisphere + Δoxy-Hb in the unaffected hemisphere]; in brief, (R – L) / (R + L) (24). Δoxy-Hb changes were selected in the same time window as the above cortical activation. For the comparison of LI in group-level analysis, we performed a two-way repeated-measures analysis of variance (ANOVA) to test the interactions (3 × 4: type of gait [healthy gait, hemiplegic gait, and hemiplegic gait with FES assistance] × site of cortical regions [S1, M1, SMA, and PMC]). Fisher's least significant difference test was used as a *post hoc* test. Statistical significance was set at a *p*-value of <0.05 for all comparisons.

Results

Cortical mapping of the healthy and hemiplegic gait

Figure 3 presents the trends of hemodynamic changes in oxy-Hb and deoxy-Hb concentrations across all channels under three conditions, which showed several obvious characteristics. Figures 4A, B and Table 3 show the cortical activation patterns during healthy and hemiplegic gait on a treadmill at the group level. Almost no activation in the bilateral M1 and apparent activation in the left PMC (ch33/34) and S1 (ch37) were observed during walking in healthy individuals (Figure 4A). There was more activation in the SMC, including the S1 and M1 (ch8/10/11/15), in the unaffected hemisphere than in the affected hemisphere (ch25/26/28/37). More PMC activation (ch34) in the affected hemisphere was noted during hemiplegic gait

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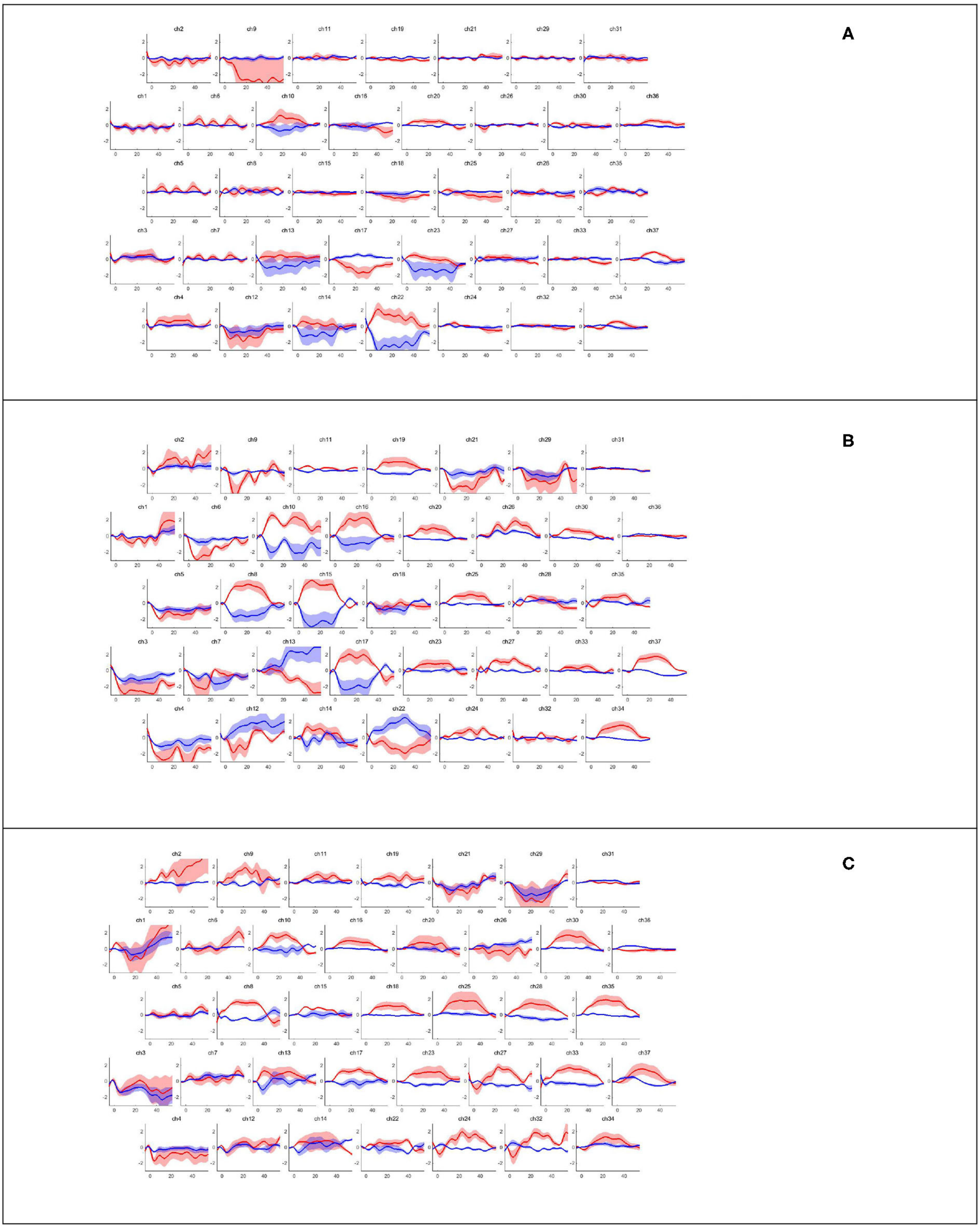

FIGURE 3
Hemodynamic response corresponding to walking task-rest phase by channels. Block averaging of the hemodynamic response (hmrBlockAvg) was designed within the time range of −5 s to 55 s; the baseline hmr level was 5 s before the task began. The oxy-Hb and deoxy-Hb concentrations are indicated by the red and blue lines, respectively. **(A)** Healthy treadmill walking, **(B)** hemiplegic treadmill walking, and **(C)** hemiplegic treadmill walking with FES assistance.

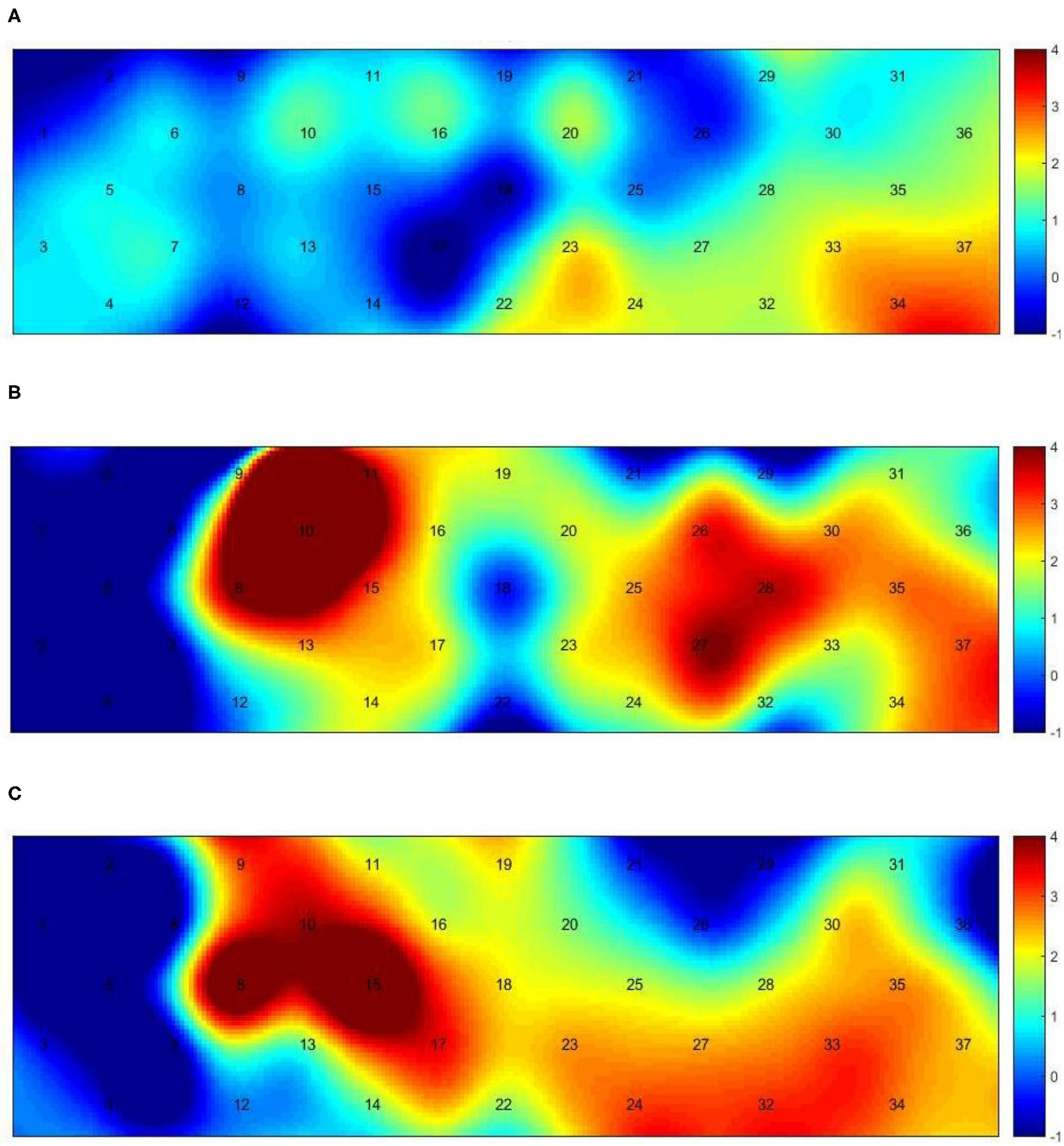

FIGURE 4
Group-level channel activation t-map in the gait task ($p < 0.05$, uncorrected). **(A)** Healthy treadmill walking, **(B)** hemiplegic treadmill walking, and **(C)** hemiplegic treadmill walking with FES assistance.

(Figure 4B). In addition, group differences in cortical activation were observed. The M1 and S1 regions (ch8/15 and ch26/28) in both hemispheres were more activated, and SMA (ch17) and PMC (ch34) activation appeared to be more prominent in hemiplegic patients than in healthy individuals (Figure 5A and Table 3). Generally, the most characteristic finding was the greater locomotor network activation of the SMC-PMC-SMA during the hemiplegic gait than that during the healthy gait.

Cortical activation mapping during FES-assisted hemiplegic walking at the group level is shown in Figure 4C and Table 3. The SMC (ch9, ch8/10/15) was significantly activated in the unaffected hemisphere, whereas the SMA and PMC (ch17/23/24

TABLE 3 List of group-level channel activation in the task (t-value, $p < 0.05$).

	Left	Right
Healthy	Ch33 (2.496, 0.041), ch34 (3.424, 0.011), ch37 (2.514, 0.040)	-
Hemiplegia	Ch25 (2.678, 0.044), ch26 (3.267, 0.022), ch27 (3.983, 0.010), ch28 (3.670, 0.014), ch33 (2.726, 0.041), ch34 (2.843, 0.036), ch37 (3.334, 0.021)	Ch8 (3.800, 0.013), ch10 (14.052, 0.000), ch11 (2.900, 0.034), ch15 (3.188, 0.024)
Hemiplegia with FES	Ch23 (2.667, 0.045), ch24 (3.324, 0.021), ch27 (2.685, 0.044), ch32 (3.379, 0.020), ch33 (3.199, 0.024)	Ch8 (5.003, 0.004), ch9 (3.349, 0.020), ch10 (3.692, 0.014), ch15 (5.726, 0.002), ch17 (3.334, 0.021)
Group differences in cortical activation between healthy and hemiplegic gait	Ch26 (3.030, 0.010), ch28 (2.457, 0.030), ch34 (2.294, 0.041)	Ch8 (2.879, 0.014), ch15 (3.402, 0.005), ch17 (2.515, 0.027)
Group differences in cortical activation between hemiplegic gait with FES and hemiplegic gait without FES	Ch24 (3.229, 0.023), ch33 (4.971, 0.004)	Ch3 (11.342, 0.000), ch9 (61.251, 0.000)

FES, functional electrical stimulation.

and ch27/32/33) were activated in the affected hemisphere. Group differences in cortical activation were also apparent between hemiplegic walking with and without FES assistance. Increased oxy-Hb changes were observed in the S1 (ch3/9) on the unaffected side and in the SMA (ch24) and PMC (ch33) on the affected side during hemiplegic walking with FES, as compared to that without FES (Figure 5B and Table 3). Generally, the most characteristic finding was SMA and PMC activation in the affected hemisphere, but not SMC activation, which was a noticeable change induced by FES.

Cortical activation symmetry during healthy and hemiplegic gait

The LI values (mean ± SD) were 0.120 ± 0.463 in the S1, 0.011 ± 0.547 in the M1, 0.218 ± 0.479 in the SMA, and 0.017 ± 0.620 in the PMC, with a total value of 0.092 ± 0.530 for healthy walking. The LI values (mean ± SD) were 0.584 ± 0.513 in the S1, 0.597 ± 0.184 in the M1, 0.473 ± 0.324 in the SMA, and −0.075 ± 0.335 in the PMC, with a total value of 0.395 ± 0.367 for hemiplegic walking. The LI values (mean ± SD) were 0.428 ± 0.279 in the S1, 0.126 ± 0.387 in the M1, 0.038 ± 0.364 in the SMA, and 0.321 ± 0.630 in PMC, with a total value of 0.228 ± 0.435 for hemiplegic walking with FES assistance. The LI in Figure 6 shows the changes in interhemispheric asymmetry of regional activation during walking among the various groups.

Repeated-measures ANOVA for the LI indicated no significant gait × cortical region interaction ($F_{[6,68]} = 1.578$, $p = 0.167$). A significant main effect for the type of gait ($F_{[2,68]} = 3.172$, $p = 0.048$) was found; in contrast, there was no significant main effect for the site of cortical regions ($F_{[3,68]} = 1.386$, $p = 0.254$). The *post hoc* (least significant difference) test showed that the total positive LI value was greater during hemiplegic gait than during healthy gait ($p = 0.014$), suggesting that the hemiplegic gait induced a relatively greater unaffected (right-dominant) activation than the healthy gait during TW. Moreover, there was a significant difference in the S1 ($t_{[12]} = 2.337$, $p = 0.037$) between hemiplegic gait (0.584 ± 0.513) and healthy gait (0.120 ± 0.463) as well as a significant difference in the M1 ($t_{[12]} = 2.420$, $p = 0.032$) between the hemiplegic gait (0.597 ± 0.184) and healthy gait (0.011 ± 0.547), suggesting that hemiplegia induced a relatively greater bilateral interhemispheric asymmetry in the S1 and M1 in the unaffected (right) hemisphere. Conversely, no significant differences in LI values were detected between the other groups ($p > 0.05$), indicating no significant lateralized activation in healthy or FES-assisted hemiplegic walking.

Furthermore, within the hemiplegic group, the LI values were significantly greater in the S1 (0.584 ± 0.513), M1 (0.597 ± 0.184), and SMA (0.473 ± 0.324) than in the PMC (−0.075 ± 0.335) ($F_{[3,20]} = 9.586$, $p < 0.001$). This suggests that, in the phenomenon of asymmetric cortical activation, the M1, S1, and SMA were predominantly activated in the unaffected hemisphere, whereas the PMC was predominantly activated in the affected hemisphere during hemiplegic walking. No significant difference in LI values was noted in the healthy and FES-assisted hemiplegic walking groups ($p > 0.05$).

Discussion

The present fNIRS study examined cortical activation responses in healthy individuals and hemiplegic patients during treadmill and FES walking at a speed of 2 km/h. In this study, we found that hemiplegic patients exhibited more SMC-SMA-PMC cortical activation during the walking process than healthy individuals. Previous studies have supported the critical role of the locomotor control network in walking. Using fNIRS mapping, Kim et al. demonstrated increased SMC, PMC, and SMA activation during conventional stepping walking, TW, and robot-assisted walking in 14 healthy individuals (25). Miyai et al. found that walking activities on a treadmill were bilaterally associated with increased oxy-Hb levels in the medial primary SMC and SMA in eight healthy individuals (26). Stroke leads to damage to the motor cortices and their descending corticospinal tracts and subsequent muscle weakness (27), so we speculate that patients with post-stroke may need to recruit more locomotor cortical networks in gait locomotion control, in which some

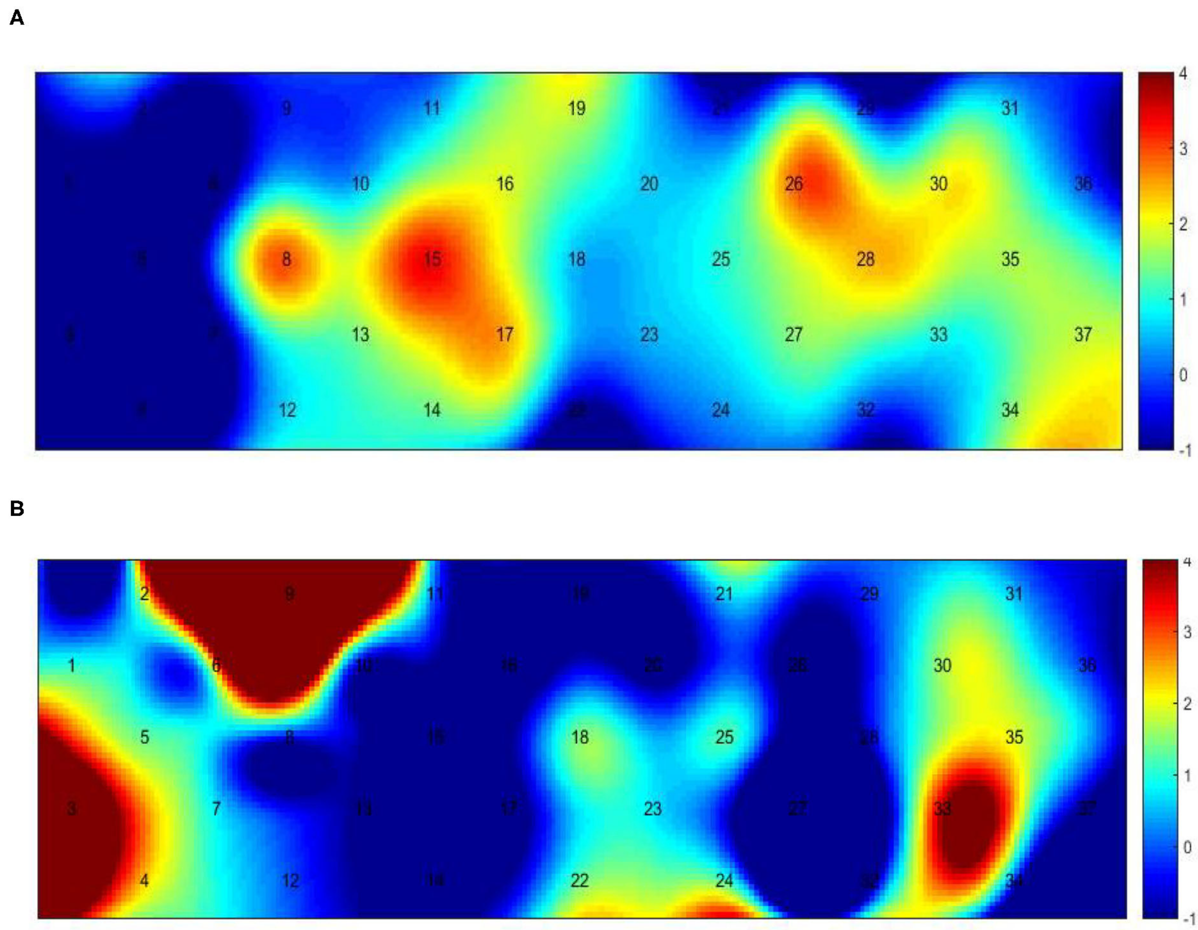

FIGURE 5
Between-group variance of channel activation t-map in the gait task ($p < 0.05$, uncorrected). **(A)** The variance of healthy and hemiplegic treadmill walking. **(B)** The variance of hemiplegic treadmill walking with or without FES assistance.

prominent activation in SMC-SMA-PMC is involved in the hemiplegic walking process.

We observed the obvious feature of almost no activation of the bilateral M1 in healthy individuals during TW. Koenraadt et al. also proved a similar phenomenon in 11 healthy participants; the sensorimotor cortex showed no activation change during walking, whereas SMA showed mainly increased activation before the start of TW tasks (8). The lack of M1/S1 activation during gait may suggest that ongoing gait control mainly relies on subcortical automatisms, such as central pattern generators (28) because it has long been known from animal studies that the M1 is not essential for automated unperturbed gait (29). Our negative findings for the M1 were in line with the results obtained in fNIRS studies by Koen et al. during TW at a speed of 3 km/h (8), by Suzuki et al. at speeds of 3 and 5 km/h (30), by Presacco et al. (31) using EEG at a maximum speed of 2.4 km/h, and by Nordin et al. (32) at different levels of gait speeds (1.8, 3.6, 5.4, and 7.2 km/h), wherein spectral power fluctuations showed reduced left and right sensorimotor alpha and beta EEG waves across the healthy gait cycle. Thus, because the 2 km/h gait speed in the present study lies within the slow speed category, our results contribute evidence of the fact that locomotor speed is largely controlled subcortically (33, 34). Hence, relying on subcortical structures without excessive recruitment of SMC activation is sufficient to support automated movements in healthy individuals.

However, during TW in hemiplegic patients, asymmetric cortical activation was observed as an important feature. The fNIRS mapping showed more SMC activation in the unaffected hemisphere than in the affected hemisphere and more PMC activation in the affected hemisphere. Furthermore, the LI expressing bilateral interhemispheric asymmetry revealed that hemiplegic walking induced relatively greater activation in the unaffected (right-dominant) hemisphere.

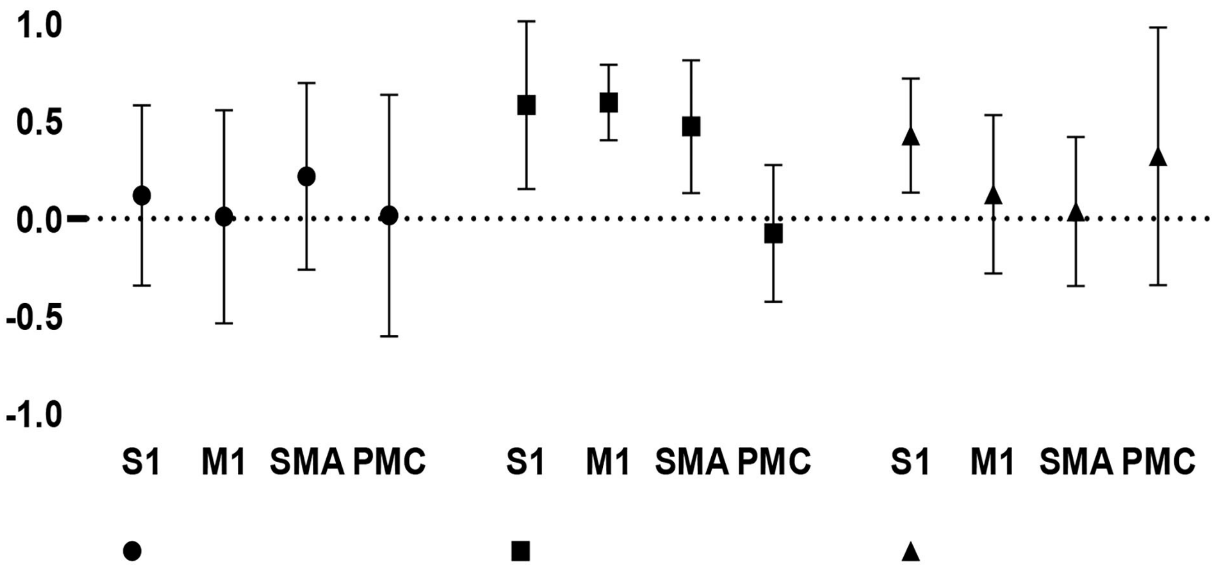

FIGURE 6
Changes in interhemispheric regional activation asymmetry during gait in the three groups, as measured by LI.

The LI regarding inter-regional asymmetry revealed SMC and SMA cortex-lateralized activation in the unaffected hemisphere and PMC-lateralized activation in the affected hemisphere during hemiplegic walking. This was in line with the reports that hemiparetic gait was associated with greater increases in oxy-Hb levels in the medial SMC of the unaffected hemisphere than that in the affected hemisphere (3, 9, 35), possibly related to the inhibitory mechanism of interhemispheric competition.

Obviously, during hemiplegic walking with FES, the noticeable characteristic was SMA and PMC activation in the affected hemisphere, rather than the SMC in the unaffected hemisphere, which seems to be a change induced by FES assistance (Figure 3C). This was similar to the finding that FES-assisted walking training could reduce the MEP latency time of the tibialis anterior muscle and improve the excitability of the corresponding motor cortex (14, 16). Owing to the influence of movement noise, there are few studies on real-time brain functional imaging during FES-assisted walking training. Zheng et al. evaluated the four-channel FES training effect in patients with stroke using fMRI and found that FES increased structural and functional reorganization around the lesion on the affected side (36). Our research focused on the salient activation of the SMA and PMC of the affected hemisphere during hemiplegic walking with FES. Previous research has supported the function of SMA and PMC in the initiation of complex motor activities and postural control (37). In particular, PMC is highly involved in both cognitive and motor dual-task challenges during both healthy and post-stroke adult walking (38). The increased SMA and PMC activation reflects the demand for adaptive locomotion control, compensation, or reorganization of cortical networks, which may represent the intrinsic mechanism of FES that has been proven to promote the rehabilitation of walking and balance functions in patients (39).

Interestingly, there was no significant difference in LI values for bilateral interhemispheric and inter-regional symmetry between healthy walking and FES-assisted hemiplegic walking. It seems that FES may help hemiplegic walking recover the balance in cortical activation. The following reports can also be indicative. Asymmetric cortical excitability has been found in hemiplegic patients, wherein the affected hemisphere had a higher stimulation threshold and lower MEPs than the unaffected hemisphere (40). Moreover, interhemispheric inhibition imbalance aggravated bilateral MEP asymmetry and led to the disappearance of MEPs in the affected motor area (41). As rehabilitation progressed, increased PMC activation was found in the affected side after 2 months of TW training, and the asymmetry of bilateral SMC activation was improved (35). Song et al. reported that cortical activation in patients with stroke was lower in the affected hemisphere than in the unaffected one, while asymmetric activation performance was improved after 3 weeks of robot-assisted gait training (42). Similarly, our research also found asymmetric cortical activation during hemiplegic walking, improved bilateral activation during FES-assisted hemiplegic walking in patients with post-stroke, and speculated that a new interhemispheric balance may be re-established by activating specific brain regions in SMA and PMC on the affected side. FES could be used as a potentially powerful therapeutic strategy, which may play an important role in motor recovery after a stroke. This is worthy of further clinical research and verification.

This study has some limitations. First, the study focused on motor-related cortical regions, including SMC, SMA, and PMC, while the role of the prefrontal cortex (PFC) in gait control was not investigated. PFC activation occurs during normal gait, whereas higher PFC activation occurs during Ekso-assisted walking in patients with stroke (43); in addition, PFC is also activated for longer during precise walking (8). This suggests that more prefrontal cortical metabolism is involved in locomotion control with more complex tasks and when extra attention is required, as in patients with post-stroke and healthy older age people during walking (44, 45). Second, the TW speed of 2 km/h was used in this study to adapt to hemiplegic patients and to ensure safety. Thus, the effect of different walking speeds was not taken into account on brain cortical activation. The literature reports that, as walking speed increases, multiple locomotor network activations are observed and the activation power spectrum increases (25). Conversely, some studies have found that higher walking speeds cause more motor network activation during TW at 3 and 5 km/h (8, 30). These factors should be explored in future locomotor gait control studies.

In conclusion, the present fNIRS study showed that there was more locomotor cortical activation of the SMC-PMC-SMA during hemiplegic gait than during healthy gait. Moreover, in hemiplegic gait, there was more SMA and PMC activation in the affected hemisphere during the FES-assisted task than during the non-FES-assisted task. The LI indicated asymmetric cortical activation during hemiplegic gait, inducing relatively greater activation in the unaffected (right) hemisphere during hemiplegic gait than during healthy walking. Furthermore, SMC and SMA were predominantly activated in the unaffected hemisphere, with PMC being predominantly activated in the affected hemisphere during hemiplegic walking. One obvious feature was that almost no activation in the bilateral M1 was noted during healthy walking, whereas more SMC-SMA-PMC cortical activation was involved in hemiplegic walking, possibly related to the M1. This suggests that M1 may not be essential for automated unperturbed gait in healthy individuals and that patients with post-stroke would need to recruit more locomotor networks to control walking. Asymmetric cortical activation was another important feature of hemiplegic walking, possibly related to the inhibitory mechanism of interhemispheric competition. Increased SMA and PMC activation in the affected hemisphere reflected the demand for adaptive locomotion control, compensation, and reorganization of cortical networks. In this regard, FES-assisted walking appears to increase the activation effect, which is worth verifying through additional research.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Xiamen Fifth Hospital, 2020-XMSDWYY-009. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XKH designed the study. LL, GY, XL, and QQS conducted the study, including patient recruitment and data collection. XKH and SJC contributed to the data analysis. SJC prepared the manuscript draft, with important intellectual input from XKH. All authors approved the final manuscript.

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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.

Publisher's note

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Falls caused by balance disorders in the elderly with multiple systems involved: Pathogenic mechanisms and treatment strategies

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Falls are the main contributor to both fatal and nonfatal injuries in elderly individuals as well as significant sources of morbidity and mortality, which are mostly induced by impaired balance control. The ability to keep balance is a remarkably complex process that allows for rapid and precise changes to prevent falls with multiple systems involved, such as musculoskeletal system, the central nervous system and sensory system. However, the exact pathogenesis of falls caused by balance disorders in the elderly has eluded researchers to date. In consideration of aging phenomenon aggravation and fall risks in the elderly, there is an urgent need to explore the pathogenesis and treatments of falls caused by balance disorders in the elderly. The present review discusses the epidemiology of falls in the elderly, potential pathogenic mechanisms underlying multiple systems involved in falls caused by balance disorders, including musculoskeletal system, the central nervous system and sensory system. Meanwhile, some common treatment strategies, such as physical exercise, new equipment based on artificial intelligence, pharmacologic treatments and fall prevention education are also reviewed. To fully understand the pathogenesis and treatment of falls caused by balance disorders, a need remains for future large-scale multi-center randomized controlled trials and in-depth mechanism studies.

KEYWORDS

balance, fall, elderly, pathogenesis, treatments, mechanism

Introduction

Falls are the leading cause of injury-related mortality among the elderly globally, trailing only traffic accidents in prominence (1), and increasing the mortality rate and disability rate in the elderly. Approximately 27,000 older adults died due to falls in a year (2). Elderly fall victims may endure severe physical harm, including fractures, especially under the circumstance of prior hip surgery or osteoporosis. They may also experience loss of independence and are forced into nursing home admittance (3).

Thus, fearfulness of falling might cause social withdrawal and disengagement (4). Psychological and physical injuries resulting from falls impose a heavy social and financial strain on patients' family, community health services, and economy. Consequently, preventing falls in the elderly is a pressing public health issue.

One of the leading causes of falls in the elderly is balance disorders, which frequently result in harm, disabling conditions, loss of independence, and lowered quality of life (5). With several systems cooperating together to prevent falls, good balance is likely the result of a quick synergistic interplay between diverse physiologic and cognitive factors that enables a speedy and precise reaction to the perturbation (6). Elderly people are more inclined to fall due to balance disorders resulting from the steady reduction of several systems' functions, including musculoskeletal system, the central nervous system and sensory system (7–10). The present review discusses the epidemiology of falls in the elderly, potential pathogenic mechanisms underlying multiple systems involved in falls caused by balance disorders, including musculoskeletal system, the central nervous system and sensory system, as well as some common treatment strategies for balance-disorder-induced falls by regulating different systems.

Epidemiology

Approximately 28 to 35% of individuals over 65 years of age fall each year, and 32–42% of individuals over 70 years of age fall, according to the WHO's (world health organization) survey. This demonstrates that the risk of falling increases with age (11). 20–30% of mild–severe injuries are the results of falls (12), and more than 50% of such injuries require hospitalization for treatment (13). Among them, about 35% of individuals over 70 years of age and 61% of individuals over 80 years of age have suffered from balance disorders (14). With increasing age, greater mobility difficulty, decreased cognitive function, living alone, more concomitant conditions, and the likelihood of experiencing multiple falls increased dramatically (15). A cross-sectional study on the prevalence and risk factors for falls among the elderly indicates that the associated factors of falls among older adults includes impaired balance ability, less physical activity, cognition impairment, mild and moderate depression (16). In conclusion, falls are common in the elderly, which is the result of a complicated pathological process involving a multitude of factors.

Pathogenic factors with multiple systems involved

Balance is the ability to maintain the projected center of mass of the body within the stability limits of support, which has three fundamental properties, such as steadiness, symmetry, and dynamic stability (17). In addition to the aging of physiological functions, balance disorders in the elderly also represents the aggregation of pathology in multiple systems, all of which can result in falls (18). Identifying the pathogenic factors of falls caused by balance disorders in the elderly are the premise and basis for the identification, assessment, and control of dysfunction and loss of independence, which are shown briefly in Figure 1.

Musculoskeletal system

From a biomechanical point of view, when a body is stationary on a plane, its center of mass and pressure are in a vertical projection that touches the support surface (8). While, when the upright balance is lost, with the shifting center on the wrong supporting surface, falls happen (8, 19). The coordination of skeletal muscles throughout the body helps to maintain the forementioned balance dynamically and statically by impacting biomechanical parameters such as body sway, stride length, stride frequency and symmetry (20–23). Thigh and core muscle thickness is favorably connected with dynamic balance and negatively correlated with fall risks (24). However, functional degradation of tendons and joints occurs with aging, which is characterized by decreased muscle mass and reduced contractility, thus leading to falls (25). Elderly people alter the joint torque of their ankle, knee, and hip joints, as well as their body balance, *via* coronal and sagittal adjustments (26). Degenerative spinal deformity, which develops in the elderly due to accumulated degenerative changes, such as asymmetrical disc degeneration, dehydration, and collapse, combined with facet degeneration and ligamentous laxity, can significantly alter the body's center of gravity and cause falls (27).

A study indicates that balance disorders in the severe stage of myasthenia are considerably greater than those in non-myasthenia and pre-myopathy, and the chance of falling is higher, demonstrating a strong correlation between the severity of myasthenia and the risk of balance disturbance (28). Sarcopenia, or the loss of muscle mass with aging, is mostly caused by a decrease in the size of the fast muscle fibers (type II), which results in a higher proportion of slow muscle fibers (type I) in elderly patients (18). Therefore, in older people, the muscles' ability to generate force and their contractile characteristics are more uniform. Aged muscles do, in fact, exhibit a decreased functional working range and are still unable to contract quickly. A study indicates that falls are associated with high levels of muscle activation, which are traits of age-related losses in postural stability (29).

The intake of vitamin D also plays an indispensable role in the balance disorders induced by skeletal muscle. Conventionally, vitamin D plays a major role in regulating calcium and phosphorus metabolism. When vitamin D is deficient, bone density and hardness are reduced, making fractures and falls more likely to happen (30). For the link between muscle and vitamin D, many people have focused on the vitamin D receptor (VDR) although VDR cannot be detected in skeletal muscle (31). However, recent studies have shown that muscles can be regulated by VDR, including atrophy, regeneration, and repairment (32–34). Most studies have shown that vitamin D can predict skeletal muscle health in senior adults and improve lower limb muscle mass and function (35–37). However, it is still unclear how vitamin D functions in muscle, even though it has been documented that muscle function improves after supplementation of vitamin D.

The central nervous system

Besides the muscular and skeletal control in falls, the presence of the central nervous system (CNS) is often not negligible.

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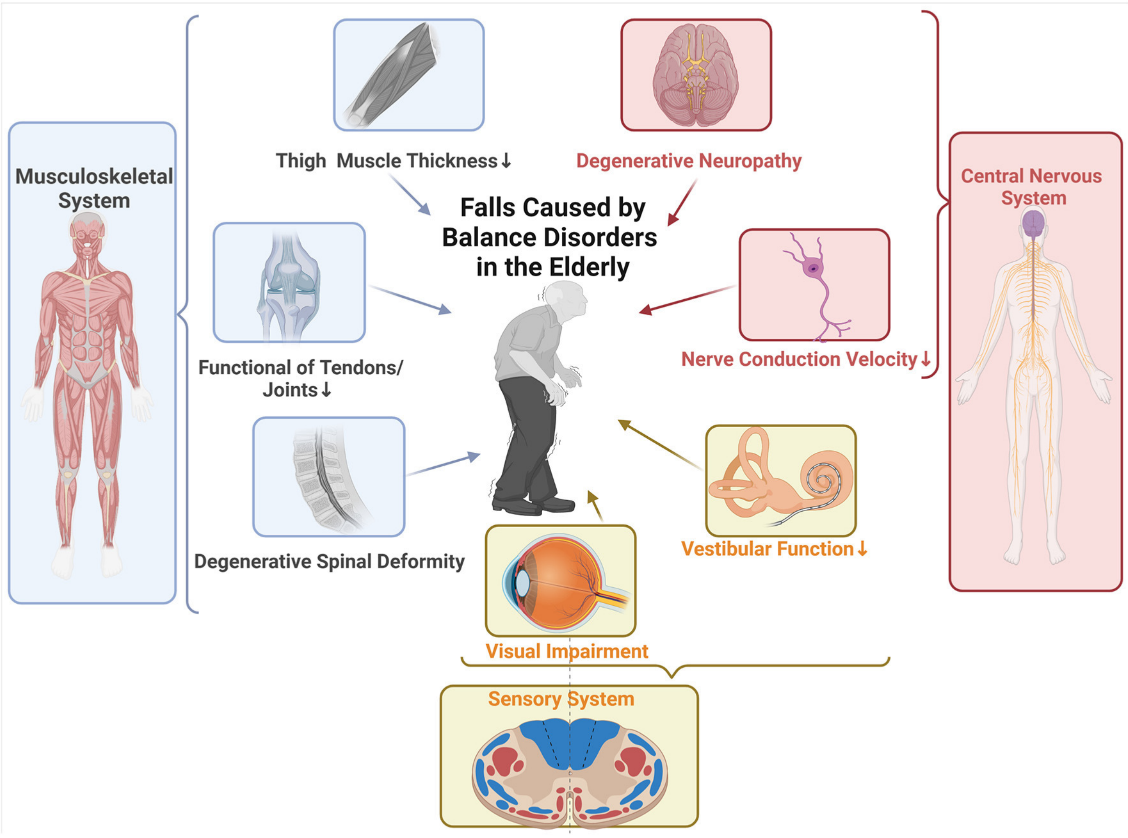

FIGURE 1
Summary of pathogenic factors with multiple systems involved in falls caused by balance disorders in the elderly. Musculoskeletal system: In the elderly, decreased thigh and core muscle thickness is favorably connected with dynamic balance and correlated with fall risk. Functional degradation of tendons and joints occurs with aging, which is characterized by decreased muscle mass and reduced contractility, and thus leads to falls. Degenerative spinal deformity, which develops in the elderly due to accumulated degenerative changes brought on by aging, such as asymmetrical disc degeneration, dehydration, and collapse, combined with facet degeneration and ligamentous laxity, can significantly alter the body's center of gravity and cause falls. Central nervous system (CNS): Aging brings about the spinal networks' structural changes that impair their functionality and motor commanding. Unmyelinated fiber density decreases by 37% in the elderly, while myelinated fiber density decreases by 38%, which is the main culprit of elderly's diminished nerve conduction velocity. Physical balance disorders and an elevated risk of falling are caused by the CNS's degeneration, which makes it more difficult for the body to integrate motor signals. Sensory System: The visual system and vestibular system are like GPS and sentry mod. Older people with visual impairment have a higher incidence of falls than those without visual impairment. The decline in vestibular function with increasing age has been confirmed by many studies and thus can be classified as one of the causes of falls.

When the CNS including afferent and efferent pathways are damaged, such as stroke, spinal cord injury or long-term bedridden, significant changes in the muscle mass will cause myasthenia and eventually lead to falls (38–40). At the same time, the spinal networks' structural changes that impair their functionality and motor command are also brought on by aging. Unmyelinated fiber density decreases by 37% in the elderly, while myelinated fiber density decreases by 38% (41). This is the main culprit of elderly's diminished nerve conduction velocity (42). Physical balance disorders and an elevated risk of falling are caused by the CNS's degeneration, which makes it more difficult for the body to integrate motor signals.

The anterior tibialis muscle, a dorsal foot flexor, is thought to have more efferent pathway degradation than other foot flexors in the elderly, but isometric muscular strength does not appear to be affected until 80 years of age. This is possible because the muscles are collaterally re-innervated by intact nerve endings, which expands the size of the functional remaining motor units (43). The maximum isometric torque (MIT) of the ankle muscles correlates adversely with center of foot pressure (CoP) displacements (43). It is considered that neuropathy-related injury in proprioceptive sensation of ankle and excessive burden of torque development rate in the elderly lead to the decrease of balance function, and thus eventually cause falls (44).

Sensory system

It is now widely known that aging affects the sensory systems involved in the body's orientation and stabilization in space (45). The visual system and vestibular system are like GPS (global positioning system) and sentry mod. As the "GPS" of the human body, the visual system can let us know whether there is danger around us through the input of environmental information, ensure our safe movement, and also predict and give feedback in different directions and spaces (10). A survey of older people in communities found that older people with visual impairment had a higher incidence of falls than those without visual impairment (46). There is also a large proportion of vision loss due to other causes besides aging. Glaucoma, cataract and other diseases that lead to vision loss plague the elderly, which also leads to an increase in falls (47, 48). As the "sentry mod" of the body, the vestibular system is responsible for standing, movement, balance and control of navigation (10). The vestibular system consists of three parts, namely the homogeneous and bony labyrinths, the motion sensors of the vestibular system, and the hair cells (49). The cooperation of extraocular and vestibular functions through the vestibulo-ocular reflex (VOR) helps the body compensate the head and stabilize the image (49, 50). In vestibular-loss patients, when the eyes are closed, it is difficult for the human body to compensate and they are more inclined to fall (51). The decline in vestibular function with increasing age has been confirmed by many studies and thus can be classified as one of the causes of falls (52, 53).

The proprioception and tactility can be complementary to vestibular perception and vision and can also serve as another source of information to the CNS to more accurately control the balance of the body (10, 54). Firstly, muscles, tendons and joints all provide different kinds of information for us to keep our balance and prevent from falling. Muscle spindle is the primary kinesthetic sensor (55). A study of patients with hereditary sensory and autonomic neuropathies (HSANs) found that the absence of functional muscle spindles afferents caused ataxia (56). In addition, the sense of touch is also a subtle but essential part of maintaining balance. Balance scores are also decreased in patients with reduced plantar sensation after stroke, which can be corrected *via* weight transfer between the legs, especially with the eyes closed (57). In patients with diabetes, researchers have found a significant relationship between sensory loss and falls due to peripheral nerve loss in the feet (58). One study of older adults over 60 years old showed that the risk of recurrent falls in patients with loss of sensation was 3.59 times than that of controls (59).

Recent research has shown that multisensory integration plays an important role in balance management as well. In general, the maintenance of balance does not depend on the above parts alone. Balance maintenance should be viewed as a collaborative process involving multiple systems, with different weights assigned to different components in different tasks (60). Multisensory integration is the process through which the nervous system combines data from several perceiving processes, including hearing, feeling, and other somatosensory events, into a single, unified, coherent, and stable multisensory process (61). Studies have shown that, with aging, the multisensory integration is progressively impaired and probably results in falls (62). Insufficient multisensory re-weighting, which is crucial for postural control in senior persons, has been linked to poor balance control in elderly people who are prone to falling (25, 63). A clinical study determining the association of multisensory integration with mobility outcomes in aging indicates that magnitude of multisensory integration is an incremental predictor of incident fall, over and above balance and other known fall risk factors (64). The prefrontal cortico-cortico facilitation, dedifferentiation, and prefronto-thalamo-cortical gatin have been linked to decreased information processing in an aged brain, which may be the cause of this condition (65). Collectively, balance maintenance should be viewed as a collaborative process involving multiple systems.

Treatments

As previously mentioned, falls caused by balance disorders in the elderly are complicated and involve multiple systems. Thus, targeted considerations must be taken when treating and rehabilitating elderly patients with postural balance issues. Treatments of balance-disorder-induced falls by regulating different systems were summarized in this review and succinctly outlined in Table 1 (66–76).

Physical exercise

The most effective method to decrease the rate of falls, enhance gait ability, keep balance, and strengthen performance in physically fragile older persons appears to be a multi-component exercise intervention that combines strength, endurance, and balance training (77). Multi-system physical exercise (MPE) is composed of four parts, including proprioceptive training, muscle strength training, reaction training and postural balance training, which can help to restore the function of musculoskeletal system, the CNS and sensory system. A study has shown that under MPE intervention training even without poorly supervised balance and endurance training (78), elderly people over 65 years old who are at risk of falling show significant improvement in all four aspects and muscle strength is significantly increased, and the fall risk reduced (79). At the same time, Tai Chi (TC) is also helpful for improving balance and can prevent falls in the elderly due to requiring more muscle strength of the lower limb joints. Therefore, the body can develop neuromuscular control strategies to maintain body balance and thus reduce the risk of falls (80). Also intense physical activity boosts levels of brain-derived neurotrophic factor (BDNF), slows down the loss of brain tissue, increases hippocampal capacity, boosts cerebral blood flow, and enhances CNS performance, including executive functions, restoring balance and lowering the risk of accidents (81).

New equipment based on artificial intelligence

New equipment based on artificial intelligence have been introduced to enrich the whole recovering process. Robot assisted training (RAGT) can bring many benefits to patients, including muscle strength, power, range of motion and so on. Patients with poststroke ankle spasms could significantly improve ankle spasms and increase balance after RAGT intervention (82). Virtual reality can be combined with RAGT to improve patients' gait (83). This combination enhances the function of musculoskeletal system, the CNS and sensory system in the elderly. Recently, a large number of fall detection system (FDS) have been developed, which can be divided into the following three categories: video-based (84), ambient sensor-based (85) and wearable sensor-based (86). A study invented the class-imbalanced deep learning fall

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TABLE 1 Summary of studies indicating treatment strategies of balance-disorder-induced falls by regulating different systems in the elderly.

Type	Treatment strategies	Corresponding systems	Assessment indicators	Results	Reference
Physical exercise	Monochromatic infrared energy (MIRE) exposure and Tai Chi exercise	Musculoskeletal system	Berg balance scale (BBS), tinetti clinical scale (TCS), timed up and go test (TUG)	Statistically significant improvements in balance and reduction in the risk of falls in community-dwelling older adults	(61)
	Mobility, strength, coordination, and balance exercise	Musculoskeletal system, central nervous system, and sensory system	Tinetti test and short physical performance battery (SPPB)	Statistically significant improvements in balance and reduction in the risk of falls	(62)
	Chinese fitness dancing	Musculoskeletal system	Maximum muscle strength, fall risk index, and static balance ability of extensor muscle groups in the lower limbs	Statistically significant improvements in muscle strength in the lower limbs and effectively lowered the fall risks	(63)
New equipment based on artificial intelligence	New techniques for retraining based on the feedback technology	Musculoskeletal system, central nervous system, and sensory system	Miniexamen cognoscitivo test, oddball test, attention network test, timed up and go test	Statistically improvements in balance, gait, autonomy, and fall risk	(64)
	Virtual reality (VR) program and motor imagery training (MIT)	Musculoskeletal system, central nervous system, and sensory system	Body center movement area, open and closed eyes balance scores, and fall efficacy	Significant improvements in body center movement area, open and closed eyes balance scores, and fall efficacy	(65)
	Center-of-pressure (COP) controller	Musculoskeletal system, central nervous system	Gait stability and electromyography for muscle activity	Statistically significant improvements in gait stability	(66)
Pharmacologic treatments	Vitamin D	Musculoskeletal system	Berg balance test and biodex balance system (postural stability and fall risk tests)	Statistically significant improvements in balance	(67)
	Antiparkinsonian medication	Central nervous system, and sensory system	12-month incidence rate ratio (IRR) of falls	Antiepileptics were associated with falls [IRR 2.16 (95% CI 1.10-4.24)]	(68)
Fall prevention education	Exercise training combined with education	Musculoskeletal system, central nervous system, and sensory system	Fall efficacy, physical activity, and lower extremity muscle strength	Statistically significant improvements in fall efficacy, physical activity, and lower extremity muscle strength	(69)
	Educational intervention	Musculoskeletal system, central nervous system, and sensory system	Thai Fall Risk Assessment Tool (Thai-FRAT)	Statistically significant reduction in balance impairment, medicine usage, and falls' overall incidence	(70)
	Education and exercise	Musculoskeletal system	Falls efficacy, muscular strength	Significantly fewer falls, less stiffness, less difficulty performing activity; more muscular strength, walking ability, and balance	(71)

detection (CDL-Fall) with a specificity of 91.86%, an F-Score of 98.44%, which is effective on class-imbalanced data and more suitable for real-life application algorithm (87). It has been demonstrated that a novel form of shoe insert called SoleSensor® (U.S. patent issued in 2001, licensed to Hart Mobility, Inc.), can improve the ability of sensory system in the elderly, which is effective in preventing falls (88). In developing novel, cost-effective interventions aimed at identifying specific balancing systems in the elderly, greater attention needs to be paid to target and implement artificial intelligence.

Pharmacologic treatments

Beyond improved bone health, vitamin D helps to prevent falls and fractures. Strengthening muscles with vitamin D helps lowering the risk of falling. According to a meta-analysis, supplementing with vitamin D at a dose of 700 to 1000 IU per day lowers the risk of falling in older people by 19% (89). Before beginning supplementing, the doctor should also find out whether the elderly patient is using any over-the-counter medications that include vitamin D, as too much vitamin D might cause hypercalcemia. The practical strategy is to promote a vitamin D-rich, healthy, balanced diet (90). In the elderly, polypharmacy is quite common, and thus a lot of side effects from clinically drug-drug interaction emerges, including orthostatic hypotension, dizziness, and somnolence, all of which can lead to falls. According to a study, there was a 39% decrease in the rate of falling when psychotropic medicines, such as benzodiazepines, other sleep aids, neuroleptic agents, and antidepressants, were tapered and stopped over the course of a 14-week period (91). Besides, balance disorder induced by neurally mediated hypotension should get specialized treatments and prescriptions (92).

Fall prevention education

The education of fall prevention is a necessary part of the whole strategy and runs through the whole process. A meta-analysis of six fall prevention education (FPE) programs indicated that FPE intervention reduced the incidence of fall-related behaviors among community-dwelling residents (93). The content of the education generally includes: the definition of falls, the prevalence of falls, risk factors, and complications of falls. The final goal is to make patients aware of their current situation and how to adjust and change by themselves, and seek the help of care-giver (93). Especially for the elderly with fear of falling (FOF), the combination of FPE and other therapies has greatly reduced their FOF, thus reducing the occurrence of falls (94).

Summary and outlook

Multiple systems, including the musculoskeletal system, the CNS and sensory system, are all involved in the mechanism underlying the increased occurrence of falls caused by balance disorders in the elderly. Contemporary research, however, has mostly focused on the parallels and correlations between the various systems, rather than the basic processes of falls brought on by balance impairments in the elderly. Few randomized controlled trials and animal model experiments, in contrast, thoroughly examine the mechanism of the efficient treatment approach. Previous research has shown that physical exercise, new technology based on artificial intelligence, pharmacological treatments, and fall prevention education can effectively treat falls caused by balance disorders in the elderly. However, due to varied approaches and a lack of randomized controlled studies with a high sample size, there is currently a lack of useful data supporting the use of these strategies to particularly target certain systems. Future large-scale multicenter randomized controlled trials, in-depth mechanistic research, including big multicenter trials are still required to completely understand the underlying mechanism and management of falls brought on by balance disorders in the elderly.

Author contributions

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

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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.

Publisher's note

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Using an academic-community partnership model to deliver evidence-based falls prevention programs in a metropolitan setting: A community case study

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Background: Prevention is an effective approach for mitigating the negative health outcomes associated with falls in older adults. The Administration for Community Living (ACL) has sponsored the implementation of evidence-based falls prevention programs (EBFPPs) across the United States through cooperative agreement grants to decrease the health and economic burden of falls. Marymount University received two of these grants to deliver three EBFPPs into the northern Virginia region. This community case study describes the development of a collaboration between a university and community-based organizations to adopt and implement multiple evidence-based programming in an area where none previously existed.

Methods: Through an academic-community partnership, EBFPPs were introduced to and implemented by senior-focused organizations. Target adopters were senior and community centers, multi-purpose senior services organizations, recreational organizations, and residential facilities serving older adults. The three EBFPPs were (1) Stay Active and Independent for Life (SAIL), (2) a Matter of Balance (MOB) and (3) Otago Exercise Program (OEP). Key interdependent project elements included: (1) fostering ongoing community organization collaboration, (2) introducing programs in the community, (3) growing and sustaining delivery sites, (4) preparing trained program leaders, and (5) building community demand for the programs.

Results: From August 2016–June 2022, 5,857 older adults participated in one of the three EBFPPs. SAIL classes were offered at 33 sites and MOB workshops at 31 with over 70% of them occurring at community or senior centers. OEP was offered at 4 sites. Factors that influenced the implementation of these programs included having: key advocates at host organizations, programs embedded into site workflows, sufficient capacity and workforce, engaged invested partners, and flexibility in working with a complex set of agencies and systems with different administrative structures.

Conclusion: By connecting academic faculty with various community members from multiple sectors, new initiatives can be successfully implemented. Results from this ACL-funded project indicate that using an academic-community partnership model to build relationships and capacity for ongoing delivery of health promotion programming for older adults is feasible and effective in delivering EBFPPs. In addition, academic-community partnerships can develop a strong network of invested partners to foster continued support of fall prevention activities.

KEYWORDS

older adults, evidence-based programs, fall prevention, academic-community partnership, implementation

Introduction

Falls in older adults are a public health problem as more than 25% of older adults fall each year (1, 2). Although many falls go unreported, they frequently lead to injuries and are associated with substantial health care costs. In 2015, Medicare spent an estimated $28.9 billion for medical costs associated with nonfatal falls in older adults (3). In addition to the direct medical costs associated with falls and fall-related injuries, falls are known to be associated with long-term negative health effects including disability and increased isolation from fear of falling with self-imposed limits on community activity (1, 4, 5). Falls may also contribute to a reduced quality of life.

Risk factors for falls are well-established (6–8) and prevention is an effective approach for mitigating the negative health outcomes associated with falls (9). Evidence-based and community-delivered fall prevention programs that increase awareness of risk factors and engage older adults in falls-prevention targeted exercise and educational activities have been successfully administered in group settings (10–12) and shown to effectively reduce falls, fear of falling, and health care costs (11–13). However, implementing these proven community programs in diverse and varied "real world" settings can be challenging (14–16).

In 2016, community advocates from local senior serving organizations and agencies identified a lack of falls prevention programs in the region as a significant unmet service. Although various community groups hosted a range of general fitness classes, none of the classes were identified as ones that address fall prevention, and there was no public or private senior-serving regional agency to coordinate outreach, implementation, and training across the various jurisdictions. Marymount University (MU) was known for strong community ties across the region and had a history of providing fall prevention lectures and screenings. When the community advocates identified a grant opportunity to build a regional network to offer fall prevention programs, they turned to MU for partnership. MU faculty collaborated with them to write an application for a grant from the Administration for Community Living (ACL).

Since 2014, the ACL has provided funding opportunities aimed at helping communities across the United States implement and sustain community-delivered evidence-based falls prevention programs (EBFPPs) (13). MU received two cooperative agreement grants from the ACL for a project to promote the implementation and sustained delivery of three different EBFPPs in the Northern Virginia region.

Since partnering with communities is a key aspect of health promotion, this community case study describes the development of a collaboration between a university and local community-based organizations to adopt and implement multiple evidence-based fall prevention programs, each one targeting older adults at different levels of fall risk, in a large metropolitan setting. This academic-community partnership serves as a model for ways in which organizations with similar goals can work together to successfully deliver evidence-based programming in an area where none previously existed.

Context

Setting

The initial project, in 2016, included four jurisdictions within Northern Virginia (NoVA): Arlington County, Fairfax County, Loudoun County and the City of Alexandria. These jurisdictions, in the aggregate, are home to nearly 200,000 individuals 65 years of age or older (17). The region is broadly diverse in age, race, ethnicity, economic status, health status, culture, and language (18). The second grant project, in 2018, added the neighboring jurisdictions of Prince William County in NoVA, Montgomery County in Maryland, and the District of Columbia to the target region. Given this expansion, the estimated number of individuals in the target area who were 65 years of age or older increased to over 250,000. These regions were chosen because of their proximity to the university and the need for services identified by community leaders and advocates.

The target population was community-dwelling older adults aged 65 and older who were interested in staying active and minimizing their risk of falling. Community organizations targeted as sites for programs were primarily senior and community centers, multi-purpose senior services organizations, recreational organizations, and senior-focused residential facilities.

Programs offered

Evidence-based falls prevention programs

Although falls are more likely to occur in individuals who are frail, the risk of falling increases with age regardless of one's functional status (19). Thus, three EBFPPs, Stay Active and Independent for Life, A Matter of Balance, and the Otago Exercise Program, were chosen to provide interventions to older adults across a wide range of functional abilities and falls risk. Together these three programs with options for individuals at low, moderate, or high risk of falling have broad reach and applicability.

Stay Active and Independent for Life

Stay Active and Independent for Life (SAIL) is a strength, balance, and fitness program for older adults who are at low to moderate risk for falling. It consists of an hour-long exercise class that meets at least twice weekly and is led by a certified lay leader. The classes are typically provided in 12-week sessions but intended for participants to continue across multiple sessions. Participation in this multi-component exercise and education program leads to improved strength, balance and performance of daily activities in community-dwelling older adults (20, 21).

Matter of Balance

A Matter of Balance (MOB) includes eight 2-hour small group sessions led by two trained leaders. The program uses a cognitive-behavioral approach that focuses on increasing self-efficacy (22, 23). It is designed to reduce the fear of falling and familiarize older adults with balance-focused exercises. Lay leaders are trained as MOB coaches and facilitate workshops in communities. Findings from research studies support its ability to reduce fear of falling and avoidance behaviors, and increase balance confidence (24–26).

Otago Exercise Program

The Otago Exercise Program (OEP) was developed for older adults at high risk of falling (27). It consists of a series of 17 strength and balance exercises with a walking component. Studies have shown it leads to improved balance, lower leg strength, physical fitness, and self-confidence (28). It was originally designed to be delivered in the home by a physical therapist (PT), but in the United States this model encountered multiple implementation challenges because of Medicare reimbursement requirements (29, 30). Newer models of delivery that include community-based group classes have comparable outcomes (31–34).

Academic-community partnership

For this project, the roles of the academic partner, faculty within Marymount University, were to assist the community in implementing their identified needs for fall prevention programs, work collaboratively to establish an implementation and sustainability plan, train EBFPP leaders, provide fidelity checks and annual booster sessions for program leaders, offer community lectures and fall risk screenings to older adults, and maintain a communication mechanism with all partners.

The community partners' roles were to establish community-defined needs, work collaboratively with the academic partner to identify program leaders and sites to host the EBFPPs, participate in regular communication with the academic partner, and foster the sustained delivery of EBFPPs within their sites.

The roles in the academic-community partnership described here are consistent with prior definitions and descriptions of an academic-community partnership as "the coming together of diverse interests and people to achieve a common purpose *via* interactions, information sharing, and coordination activities" (35). Drahota et al. further developed a conceptual definition during their systematic review, "Community-academic partnerships are characterized by equitable control, a cause(s) that is primarily relevant to the community of interest, and specific aims to achieve goals(s), and involves community members (representatives or agencies) that have knowledge of the cause, as well as academic researchers" (36). Academic community partnerships can maximize resources, increase capacity among collaborators and extend the reach of health-focused programming (37). Building partnerships is key to promoting evidence-based programming and identifying policies and practices that can optimize the lives of older adults (38).

Details of project implementation

Five key interdependent project elements included: (1) fostering ongoing community organization collaboration, (2) introducing programs into the community, (3) growing and sustaining delivery sites, (4) preparing trained program leaders, and (5) building community demand for the programs. Success or failure of any one of the five elements impacted the other elements. All five elements required concurrent focus, particularly in the early years of infrastructure building.

Fostering ongoing community organization collaboration

The 17 community partners that collaborated on the initial grant proposal became the Steering Committee for the funded project. These included representatives from each of the four Area Agencies on Aging, two hospital systems, three different Neighborhood Village groups (locally-based networks of neighbors helping neighbors age in place), one residential living community, two senior community centers, two parks and recreation groups, one adult day health center, and several volunteer community advocates. They met quarterly to guide program implementation and to establish a permanent network of community groups to enhance communication and collaboration to support fall prevention efforts. Within 1 year, the group was formalized into the Northern Virginia Falls Prevention Alliance (NVFPA), a member organization, supported by MU, whose mission is *to maximize independence and improve quality of life of older adults by reducing falls and fall-related injuries.* NVFPA is open to all senior-serving groups and individuals interested in facilitating falls prevention efforts. It also became a founding member of the statewide Virginia Arthritis and Fall Prevention Coalition.

Introducing programs into the community

SAIL was the first program to be offered. Many potential sites already provided exercise-based fitness programs to older adults and SAIL fit well with this format. It was initially offered at two senior living communities that were key partners on the project. These sites were well positioned with an interested fitness instructor, a committed administration, space to hold group classes, in-house program marketing capabilities, and a large pool of older adults with generally high participation rates in center activities. MOB was introduced 4 months after SAIL at two different senior community centers. The first OEP program was offered in 2018, 2 years after the start of the project. One assisted living facility and one adult day health center served as the initial sites for OEP.

Growing and sustaining delivery sites

Positive feedback about SAIL and MOB from participants and leaders influenced other organizations to request support to start a program. A part-time program marketing coordinator created a marketing campaign to ensure consistent program and project messaging. This individual, with regular input from the project team, identified and reached out to community-based organizations, initially targeting community sites with a history of implementing health promotion programs. In-person outreach visits (3–4 monthly) to potential delivery sites by project staff served to educate, answer questions, provide fall prevention written material, and problem-solve real or perceived barriers to program implementation. A database of potential and active sites was developed and regularly updated to track all communications and recruitment efforts. Meetings of the NVFPA regularly included time for sites hosting EBFPPs to provide updates, discuss successes and challenges, and solicit advice and guidance.

Preparing trained program leaders

It was essential that a sufficient and ongoing pipeline of trained leaders to support programs was established. SAIL and MOB use a train-the-trainer, lay-leader model for program delivery. A two-step process occurred to meet this need. First, two academic faculty were trained as Master Trainers for SAIL and MOB. Once the Master Trainers were in place, training workshops to prepare leaders were held. The second step was to develop a mechanism to deliver ongoing trainings. The Regional Training Office (RTO) was created to provide and sustain an adequate leader workforce. OEP leader training occurred through an online and asynchronous training program, offered at a modest fee by another university. RTO staff coordinated OEP leader reimbursement of this fee.

Regional Training Office

The Regional Training Office (RTO) was housed at MU. A part-time RTO coordinator assisted with the logistics of setting up trainings, managing communications with interested individuals, and maintaining a registry of trained program leaders in the region. This individual also updated a database of programs that included site, geographic area, leader, days and times offered, start and end dates, and data collected (attendance, pre-program and post-program participant surveys). This information was also used by the coordinator to help promote programs through connections made *via* the NVFPA and postings on their website.

Within the RTO structure, Master Trainers for SAIL and MOB delivered fidelity management and workshops to booster practice along with program leader trainings. Two program updates were provided annually for SAIL and MOB. These were offered to all trained leaders at no cost. The updates included fidelity reminders, program updates or changes, and a report out of successes and challenges experienced by leaders. Services provided *via* the RTO included a training academy for MOB and SAIL, assistance with the implementation of new EBFPPs, a speaker's bureau for community education on falls prevention, and direction for OEP certification. A small fee was charged for leader training, primarily to cover required printed materials.

Master Trainers organized day-long trainings for leaders and assisted them with the implementation of programs. Various mechanisms were utilized to recruit new lay leaders and the training was open to all. Preference was given to leaders who were recruited by a site to become trained so they could lead programs at that site. Project staff also provided short presentations at senior-focused centers, posted flyers throughout the community, and encouraged word-of-mouth sharing. The time and date of training workshops were posted on the NVFPA website and registration was completed online. In addition to seeking EBFPP leaders from the community, university faculty developed a student-focused service-learning course that included training students to serve as a program leader, thus expanding the number of leaders and encouraging intergenerational engagement.

Building demand for programs among older adults

Project staff and the implementation site staff shared the responsibility of marketing the EBFPPs. Project staff provided lectures and fall risk screening activities for older adults, hosted informational booths at health fairs, distributed flyers, and posted announcements on senior-focused websites and newsletters. They also provided Senior Ambassadors (SA) with information about falls and fall prevention programs to share with their community. SAs are trained community volunteers who share information with older adults about community services. Sites implementing EBFPPs also had a major responsibility for marketing to their target audiences and encouraging participation. This included internal marketing of the program, identifying members who could serve as program champions to encourage participation, and advising on the best time of the day/week to hold the program. Many sites had full schedules of activities and therefore needed several months of lead time to add a new program.

Results

All ACL EBFPP grantees were required to enter program data into a national falls data repository. Grantees were provided with data collection forms for this purpose. Program leaders were asked to voluntarily assist in the data collection by administering ACL-provided surveys to each participant and keeping attendance logs. As collection of this data was not a component of the EBFPPs but a request of the grant funding agency, participation by the leaders was encouraged but not required. Data about the type of site was collected for the organization hosting the EBFPP. The project was approved by the university's institutional review board.

Participants

The target population was community-dwelling older adults aged 65 and older who were interested in staying active and minimizing their risk of falling. From August 2016–June 2022, 5,857 older adults participated in one of the three EBFPPs. Table 1 displays key participant characteristics, by program, of those who completed the pre-program participant survey: 93% were 65 years of age or older (average age = 76.6); 64% had ≥2 chronic conditions. Overall, 33% of participants completed the pre-program participant survey. Completion rates varied greatly by program and during the COVID-19 pandemic vs. pre COVID-19 time periods. COVID-19 isolation precautions required all programs to unexpectedly and immediately transition from in-person to remote delivery. Pre COVID-19, 83% of MOB participants completed the pre-program survey compared to 41% during the pandemic. Similarly, 45% of SAIL participants completed the pre-program survey prior to the COVID-19 pandemic but only 4% during it.

Additionally, during the first 4 years of the project, MU's IRB committee required written informed consent from participants as well as the immediate availability of a project team member to answer any participant questions during the review and consent process. This negatively impacted data collection efforts. This requirement was removed in year 5, allowing program leaders to read an ACL derived falls prevention program group leader script that described how the de-identified data was to be used prior to requesting completion of the survey forms.

Leaders

From 2016 through June 2022, 385 SAIL leaders and 141 MOB leaders were trained, and 16 individuals reimbursed for OEP certification training. For SAIL and MOB, there were 25 and 15 leader trainings held with an average attendance of 15 and 9, respectively.

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TABLE 1 Participant characteristics.

	SAIL (*n*=1,317)	MOB (*n*=465)	OEP (*n*=53)
At or over 65 years of age	92%	94%	92%
At or over 80 years of age	37%	37%	45%
Lives alone	46%	51%	20%
Seldom active/prefers sedentary activities	9%	19%	27%
2 or more chronic conditions	62%	65%	80%
4 or more chronic conditions	13%	17%	45%
Self-reported health as excellent or very good	44%	40%	35%
Self-reported health as fair or poor	12%	12%	10%
Fell in the last 3 months	13%	34%	24%
Fall resulted in injury	9%	15%	42%
Self-reported fear of falling as 'a lot' or 'somewhat'	35%	52%	33%
Concerns about falling interfered with social activities (extremely, quite a bit, moderately)	22%	32%	25%
History of depression	12%	18%	30%

Trained individuals included paid staff from sites hosting programs, independent contractors and volunteers. Some sites trained multiple people to allow flexibility in scheduling and staff availability. Training was open to all and not all leaders were from the region or had specific plans to offer a program. Natural attrition occurred over time with leaders changing jobs or work responsibilities, retiring, or moving.

Program sites

Initially, in 2016, there were 0 sites that offered EBFPPs in the targeted region. By July of 2022, 157 SAIL sessions had been offered at 33 sites, and 57 MOB workshops at 31 sites. Seventy-three percent (73%) of the SAIL sessions and 72% of the MOB workshops were held at either community or senior centers. OEP was offered at a community day health program, senior center, and residential living facilities. Table 2 provides a full list of site locations.

Program adoption was operationally defined as a site that hosted the same program 3 or more times during the target period of July 2016–June 2022. Given this definition, 20 of the 33 SAIL sites adopted SAIL (61%); 7 of the 31 MOB sites adopted MOB (23%); and 0 of the 4 OEP sites adopted OEP. Only 2 sites adopted both SAIL and MOB.

Community partners

By the end of the project time period NVFPA had over 135 members. Table 3 describes the organizational characteristics of the members. To enhance communication across all community partners, the NVFPA maintained a website (www.novafallsprevention.com) where members of the community, as well as area professionals, could find updated information on current programs, services, and events; falls prevention education and awareness resources; and links to member organizations. The group distributed an electronic newsletter 3–4 times a year and led the region in annual Falls Prevention Awareness Week activities each September.

Discussion

Using an academic community partnership model, academic faculty and community partners built the infrastructure for nearly 6,000 older adults to participate in one of three EBFPPs: MOB, SAIL, or OEP. SAIL was adopted at a much higher rate than MOB, and OEP was not successful in being offered with any consistency. Key lessons learned from the implementation of this project are summarized below.

1. Secure strong organizational support.

Challenges existed in convincing sites to include new programs in their weekly workflow. While senior and community centers are a natural fit for hosting these programs, issues such as staff time, startup concerns with new initiatives, space constraints, and lack of a consistent pool of trained leaders prevented many sites from adopting the programs. Organizations that used paid staff as leaders or those that had an administrator that was a champion of the initiative were more successful in offering and adopting EBFPPs. Local champions have been shown to be key for program adoption, as they can work internally to facilitate organizational support (39, 40). Having staff view leading a program as a part of their work facilitated continued delivery of programs (41). Volunteer leaders were also used by community-based organizations to fill workforce needs. Although effective, this strategy can be problematic as a long-term solution given the inconsistencies associated with volunteer leader attrition (42).

2. Provide mechanisms to show organizations the benefits of offering EBFPPs.

Data collected from the pre-program and post-program surveys were compiled by RTO staff into one-page summaries for each host organization. This helped to illustrate the impact of their particular program on the participants' health, quality of life indicators and satisfaction with the program. The program summaries provided individualized data to show administrators that supporting the

TABLE 2 Setting characteristics.

	SAIL		MOB		OEP	
	Sites (*N*=33)	Programs held at sites (*N*=157)	Sites (*N*=31)	Programs held at sites (*N*=57)	Sites (*N*=4)	Programs held at sites (*N*=5)
Community center	7	12	7	13	0	0
Nonprofit adult daycare	0	0	0	0	1	1
Educational institution	1	8	1	1	0	0
Faith-based organization	0	0	2	2	0	0
Fitness organization	1	1	1	1	0	0
Health care organization	2	3	3	8	0	0
Local neighborhood village	1	7	1	1	0	0
Multipurpose social services	1	2	1	1	0	0
Nonprofit service organization	1	8	0	0	0	0
Residential facility	4	15	6	10	2	3
Senior center	15	101	9	20	1	1

TABLE 3 NVFPA membership: types of organizations.

Type of organization	Number of organizations
Community-based nonprofit	13
Home care (Unskilled)	12
Physical therapy/occupational therapy	10
Community center	8
Individual	8
Area agency on aging	6
Academic institution	6
Assisted living community	6
Hospital system	4
Low-income housing	4
County health department	3
County parks and recreation department	3
Senior housing	3
Media	1
Nonprofit adult daycare	1
State health department	1

program was worthy of their time and resources. Program leaders were also encouraged to collect testimonials from participants to be used in newsletters and promotional materials.

3. Determine how building and maintaining workforce capacity will be achieved early in the implementation process.

Building and maintaining sufficient training capacity and workforce was led by the RTO. Factors that influenced the implementation of the EBFPPs included offering a sufficient number of trainings to support new programs, assuring time for Master Trainers to conduct fidelity checks in the field and mentor newly trained leaders, and determining a feasible cost structure for the trainings. Through the relationships built within the community, partner sites offered their space at no cost for the leader trainings. Because of grant funding and a desire to entice host organizations to support having their staff trained, the fees for the leader trainings were set to cover the cost of materials only. Changes in the availability of volunteer leaders and employment or job responsibilities of staff members leading programs resulted in a continual need to replenish leaders. Thus, being diligent in continuing to secure new leaders is crucial to ensure sufficient availability to meet current and new program needs (43). Not only is it necessary to have a mechanism to train leaders, it is also critical to have enough Master Trainers to lead the trainings. The Master Trainers also need to have time allotted within their workload to mentor new leaders and ensure they are maintaining fidelity to the EBFPP.

4. Develop internal spreadsheets to manage and track communications between project team members regarding outreach to community-based organizations.

As each jurisdiction in the project area functioned in different ways, it was challenging to find a streamlined mechanism to engage with all of them collectively. This complexity required multiple processes for connecting with and assisting organizations to successfully deliver EBFPPs. What worked well in one county or city did not necessarily work well in another area. This held true in marketing and advertising, recruiting participants, utilizing referral sources, and finding staff and volunteers leaders. Internal spreadsheets provided a mechanism to take notes and document individualized needs across the diverse host organizations. Templates were made for marketing materials and recruiting leaders. As the community became more aware of the EBFPPs and delivery processes, this challenge diminished.

5. Consider incentives for completion of data collection forms.

Collecting data about participants and the impact of participation in the program is a powerful tool for demonstrating effectiveness and supporting permanent adoption of the programs. As this project was funded by the ACL, part of the leader training was to educate leaders on the process for requesting participants to complete the data collection forms and on the voluntary nature of participation. The protocol included reading an oral script that served as informed consent at the beginning of each program and then administration of the surveys. Given the limited time and busy schedules of program leaders, over time leaders teaching multiple programs were less likely to follow this request for voluntary participant form completion. Possible solutions include providing incentives (to sites, leaders and/or participants), having RTO staff and graduate students more consistently assist in the data collection, and using technology to improve adherence (e.g., use Google forms instead of paper to improve the process).

6. Develop and nurture a strong community connection.

The NVFPA, from its early days as a steering committee to its current robust membership, served as the communication hub for connecting local community organizations. NVFPA members were critical in identifying interested program leaders and host sites. The quarterly meetings included an education component, project updates and networking. While meetings were held in-person prior to the COVID-19 pandemic, they transitioned to virtual following it, which allowed for greater participation. Members anecdotally reported that the meetings keep them engaged and provided a mechanism to promote falls prevention activities in the community. Project staff maintained a website for the NVFPA, which included detailed listings of current programs, resources for trained leaders and the general public, and links to member websites and regional events. This helped to foster cross-agency collaboration in an effort to increase awareness of falls prevention efforts while minimizing duplication of services.

Limitations

Limitations discovered through the development of this academic-community partnership can be used to improve similar programmatic efforts as well as focus areas of future work for the project team. Collecting detailed data is a key component of assessment and for this initiative it was limited by the willingness of community partners and leaders to provide data and have surveys completed. Barriers to evaluating implementation models include lack of adherence to data collection (44). Future efforts must include implementing new strategies, including incentives, to improve the readiness of organizations to build data collection into their workflow.

Although EBFPPs continue to be delivered within the region, many unanswered questions remain about program adoption. Analysis of factors associated with sites that have adopted programs from those who have not, as well as what characteristics are associated with maintaining these programs over time is needed. It would also be beneficial to develop a mechanism to capture which trained leaders actually led programs and determine the staff and staff setting variables that separate adopters from non-adopters. Understanding which entities are likely to adopt programs will minimize barriers and frustration, and maximize resources when attempting to deliver EBFPPs.

Delivery of the EBFPPs during the project time period was disrupted by the COVID-19 pandemic. A hiatus in offerings occurred as EBFPP implementation sites stopped all in-person programming. Since older adults were not partaking in programming, data collection halted as well. While not being able to offer in-person classes limited the ability of older adults to participate in beneficial health promotion programs and the project team to meet its goals, it did foster the creation of alternative delivery methods. Virtual programming for MOB and SAIL, a product of the pandemic, continued to be offered in addition to in-person classes, widening opportunities for more older adults to participate in falls prevention activities.

Finally, a desire of the project team was to target older adults at different levels of fall risk. The initiative was successful in reaching community-dwelling older adults with low to moderate risk for falls, but not for those at high risk. OEP was chosen by the project team to provide a program for ambulatory older adults that had a high risk of falling (27, 28). Challenges with reimbursement from Medicare became an obstacle to implementation of the physical therapist-led version of the program, and concerns over liability and participant safety became an issue for local organizations with the lay-leader, community-based format where sites could only provide limited professional oversight. Continued work is needed to identify strategies and supports to implement community-accessible falls prevention programs for individuals at high risk for falls or to make health professional guided programs, such as OEP, more accessible (31, 33).

The location of the project in a large metropolitan area and the implementation strategies employed likely impacted its successes and challenges. Despite these limitations, the overall lessons learned from this community case study provide insights that may encourage and guide others toward delivering multiple EBFPPs in their communities.

Conclusion

This ACL-funded project had a goal of delivering multiple EBFPPs that have been proven to reduce falls, fear of falling, and fall-related injuries in older adults in a region in which none previously existed. The initial results indicate that using an academic-community partnership model to build relationships and capacity for ongoing delivery of evidence-based programming was successful in achieving this goal. Community-based initiatives such as this one are critically important components of a comprehensive fall prevention strategy.

This academic-community partnership model successfully delivered two EBFPPs in a metropolitan setting, introduced a third, implemented a mechanism to train program leaders, and built a network of invested partners to foster continued support of fall prevention activities and programming. Although all three EBFPPs were made available to all sites, only two sites adopted multiple programs.

Collaborating with community partners is the foundation for this academic-community partnership model. Individuals using it seek to connect research and other academic initiatives with various community members from multiple sectors including public health, health care, for-profit and nonprofit, faith-based and others (45, 46). This work entails being open to partners' wishes and agendas. Success comes from the collective desire to build capacity to meet community-identified needs.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Marymount University's Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

CE led the development and writing of the manuscript. RW provided substantial conceptual input and CE, SP and RW wrote components of it. All authors critically reviewed the manuscript, suggested revisions, and approved the published version.

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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.

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Displaced center of pressure on the treated side in individuals with essential tremor after radiofrequency ablation: a longitudinal case–control study

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Background: Essential tremor (ET) is a common involuntary movement disorder (IMD). Radiofrequency ablation (RFA) targeting the ventral intermediate nucleus (Vim) of the thalamus is a stereotactic neurosurgery performed in individuals with ET when pharmacotherapy is no longer effective. Though the reasons remain largely unclear, certain adverse events are known to appear post-RFA. These may be due to functional changes in the Vim, related to RFA-induced tremor reduction, or an adverse reaction to compensatory movement patterns used to perform movements in the presence of tremor symptoms.

Objective: This study aimed to understand the characteristics of post-RFA symptoms in individuals with ET.

Methods: In a longitudinal case–control study, we compared post-RFA symptoms between individuals with ET who underwent Vim-targeted RFA and those with IMD who underwent non-Vim-targeted RFA. Symptoms were compared preoperatively and 1-week and 1-month postoperatively. Quantitative assessments included center-of-pressure (COP) parameters, grip strength, Mini-Mental State Examination, two verbal fluency tests, and three types of physical performance assessments (upper extremity ability, balance ability, and gait ability).

Results: Individuals with ET after RFA showed horizontal displacements of the COP to the treated side (the dominant side of the RFA target's hemisphere) at 1-week postoperatively compared to the preoperative period. The horizontal COP displacement was associated with balance dysfunction related to postural stability post-RFA. Other COP parameters did not significantly differ between the ET and IMD groups.

Conclusion: COP displacement to the treated side may be due to a time lag in adjusting postural holding strategies to the long-standing lateral difference in tremor symptoms associated with tremor improvement after RFA.

KEYWORDS

center-of-pressure, essential tremor, post-operative symptoms, radiofrequency ablation, ventral intermediate thalamic nucleus

1. Introduction

Essential tremor (ET) is a common neurological disorder, affecting people of all ages, with a worldwide prevalence of 4.6% in people aged ≥65 years as reported in a meta-analysis (1). It is characterized by postural and motion tremors (4–12 Hz), involving the hands, forearms, and head (2) often affecting activities of daily living. ET has recently been recognized as a monosymptomatic disorder; however, it is also associated with other symptoms, such as gait disturbance, balance impairment, and non-motor symptoms (3–5).

Treatment for ET generally begins with lifestyle guidance, including stress management. Patients with inadequate response are switched to pharmacotherapy, particularly when symptoms are sufficiently severe to interfere with activities of daily living (ADLs) and social participation. Rehabilitation for tremors has been reported as an intervention for movement disorders (6), which includes a selection of adaptive self-help devices for tremors and training to use them (7). In patients who fail to improve with conventional pharmacologic therapy, chemo-denervation with botulinum toxin, and stereotactic neurosurgery may significantly ameliorate ET. There are two common types of stereotactic neurosurgeries: stimulation and coagulation. Deep brain stimulation (DBS) is a technique, in which a stimulating electrode is implanted in the targeted brain nucleus. Radiofrequency ablation (RFA) is a coagulative technique (8), involving stereotactic insertion of electrodes into the ventral intermediate thalamic nucleus (Vim), the target site, to create RFA foci to improve tremor symptoms.

DBS is currently the mainstay of treatment because of the possibility of postoperative stimulation adjustments for symptoms and complications (9). However, certain patients develop bacterial infections with the implantation of the device or do not respond to DBS stimulation. In those cases, RFA, which shows a long-time effect, is handy as a salvageable option as an alternative to DBS. Swelling surrounding the permanent brain lesion during the RFA process was reported to be a transient neurological deficit related to the neural network involved in the Vim, leading to ataxia, hemiparesis, dysarthria, and cognitive decline (10–19), which may require postoperative rehabilitation other than those for tremors. Although it makes sense to advance our understanding of post-RFA symptoms, only the appearance of symptoms has been investigated and not fully verified. Understanding the characteristics of post-RFA symptoms can help to clarify priorities for intervention during postoperative rehabilitation and to identify signs that require intensive intervention.

This study, therefore, investigated the characteristics of symptoms occurring after RFA for ET by quantitatively appropriate endpoints. To explain postoperative symptoms, we compared perioperative symptoms among ET individuals who underwent Vim-targeted RFA and individuals with involuntary movement disorders (IMDs) who underwent RFA targeting other regions.

2. Materials and methods

2.1. Study design

This was a single-center, longitudinal case–control study. It was approved by the Ethical Review Committee of the Tokyo University of Health Sciences (TPU-20-004), the institution where the research was conducted, and by the Sanai Hospital Ethical Review Committee (21-s001), which was the hospital responsible for conducting the surgeries and collecting data before and after surgery. All participants provided written informed consent after being given a complete description of the study.

2.2. Sample size

Since we were unable to find any previous report that quantitatively evaluated the complication symptoms and motor and non-motor functions before and after surgery in individuals with ET or IMD, we calculated the sample size using G Power 3.1 (https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower), with the following assumptions: effect size (f) = 0.25, significance level (p) = 0.05, power = 0.8, and measurement time-points = 3. The calculated minimal number of participants in each group was 14 (28/2). We set the number of participants to 15 per group, taking dropouts into account.

2.3. Participants

The participants were inpatients who underwent RFA at Sanai Hospital in Saitama City between February and December 2020. The inclusion criteria were individuals with ET, among whom Vim was the targeted RFA site (ET group, 15 patients), and those with other IMDs, such as dystonia, among whom non-Vim regions, such as the ventral oral nucleus (Vo), globus pallidus internus (GPi), and pallido-thalamic tract (PTT), were the RFA targets (IMD group, 15 patients). Exclusion criteria were apparent cognitive impairment (Mini-Mental State Examination [MMSE] scores ≤ 24) and previous stereotactic brain surgery.

One neurosurgeon (T.T.) performed all surgeries and prescribed rehabilitation.

2.4. Evaluations

Evaluations were performed on the day before surgery (pre-op) within 1 week postoperatively (1wpost-op) and approximately 1 month postoperatively (1mpost-op). One physical therapist (K.K.) and one occupational therapist (T.A.) performed all evaluations. The method of instruction during the evaluations was manualized and implemented so that there would be no discrepancies between the examiners.

2.4.1. Tremor function, ADL, and quality of life in ET individuals

The Essential Tremor Rating Assessment Scale (TETRAS) comprises a 9-item performance subscale (TETRAS-PS) and a 12-item ADL subscale (TETRAS-ADL) (20). The Quality of Life in Essential Tremor Questionnaire (QUEST) is a self-reporting questionnaire consisting of five domains (communication, work and finances, hobbies and leisure, physical, and psychosocial) comprising 30 items (21). The higher the score, the more severe the tremor symptoms and the lower the ADL ability and quality of life (QOL). These scales were used to assess individuals in the ET group only.

2.4.2. Motor symptoms

The quantitative postural assessment was performed using a force platform (UM-BAR II, UNIMEC, Usmate Velate, Italy) that measures the center of pressure (COP), which corresponds to the center of gravity response (Figure 1A). The COP using the platform was selected based on previous studies (22–24). We measured the root mean square area, the total path length of COP (COP-RMA and COP-LNG, respectively), and the displacement of the COP in the X- and Y-axis directions (COP-X and COP-Y, respectively). Participants were instructed to stand on the force platform with their feet together, eyes open, and look at the gazing point (marked with a red X) on the wall in front of them (Figure 1B). For comparison with the COP displacement to the treated side (for instance, the dominant limb side of the cortical hemisphere operated on as the RFA target), positive values were assigned to the displacement on the treated side.

Grip strength (muscle strength) was determined using a hand dynamometer as the average of three measurements on the treated side (dominant limb of RFA target's cortical hemisphere) and non-treated side (same limb side of RFA target's cortical hemisphere).

2.4.3. Non-motor symptoms

As a non-motor symptom, cognitive dysfunction was assessed using the MMSE and two types of verbal fluency tests: category-cued (VF-c) and phonologically cued (VF-p) tests. We recorded the MMSE score, the number of words expressed per minute on the VF-c (listing vegetable names) and on the VF-p (listing words beginning with "ka").

2.4.4. Physical performance

Gait ability was measured using the 10-meter walk test (10-MWT). The time required by participants to walk 10 m as fast as possible was measured (25). The walking distance before the measurement was 3 m, used in Japanese clinical practice, instead of the original 5 m (25). Balance ability was tested using 14 tasks in the Berg Balance Scale (BBS) (26). Upper extremity performance was evaluated using the Simple Test of Upper Extremity Function (STEF), a Japanese standardized test of 10 items scored from 0 to 10 for each hand (total score: 0–100). We obtained STEF scores for both sides (27). A higher score indicated better upper limb manipulation ability.

2.5. Statistical methods

We compared the preoperative age, disease duration, and age of onset in the ET and IMD groups using Student's t-test. We compared sex distribution using Fisher's exact test. Multiple imputations (the Markov chain Monte Carlo [MCMC] method) were used to address missing data, assuming that data were missing at random. To ensure internal validity, five datasets with missing values were created and analyzed using SPSS (ver. 27.0; IBM Inc., Armonk, NY, USA). The average values obtained in these datasets were assigned as the missing values for the analyses.

We conducted a linear mixed model analysis to detect improvement in tremor symptoms after RFA, using the TETRAS-PS, TETRAS-ADL, and QUEST scores as dependent variables and the measurement time-point as the independent variable (pre-op, 1wpost-op, and 1mpost-op), including age and sex as covariates and participants as random effects. After confirming that the created model was statistically more significant than the null model, a test was performed to reveal substantial differences in the dependent variables according to the measurement time-point.

To analyze changes in motor symptoms (COP and grip strength), non-motor symptoms (MMSE, VF-c, and VF-p), and physical performance (10MWT, BBS, and STEF) after RFA, we also evaluated interactions between measurement time points and group and also the main effects of each measurement time-point and group. A linear mixed model was used to examine changes from before to after RFA, including age and sex as covariates (with weight added as a covariate for grip strength), and participants as random effects. After confirming that the created model was statistically more significant than the null model, a test was performed to detect significant differences in the interaction and main effect of group (ET vs. IMD) and measurement time-point (pre-op, 1wpost-op, and 1mpost-op) on the objective variable.

To demonstrate the relationship between physical performance decline and the items of motor or non-motor symptoms that showed interaction in the linear mixed model, we analyzed correlations using the amount of change in the measurements from the preoperative level in each group.

Unless otherwise stated, statistical analyses were performed using Jamovi ver. 1.6.23 (https://www.jamovi.org/download.html). Statistical significance was defined as a p-value of < 0.05.

3. Results

The mean age and disease duration among the groups were significantly different: the mean age was higher, and the duration of the disease was longer in the ET group than in the IMD group (Table 1).

3.1. Evaluations

Complete data were available for 24 participants. For six participants, some data were missing. One participant had no data at 1wpost-op, and two participants had no data at 1mpost-op. Three participants had no data on non-motor symptoms at any time point, and the other had no data on 10-MWT at 1mpost-op.

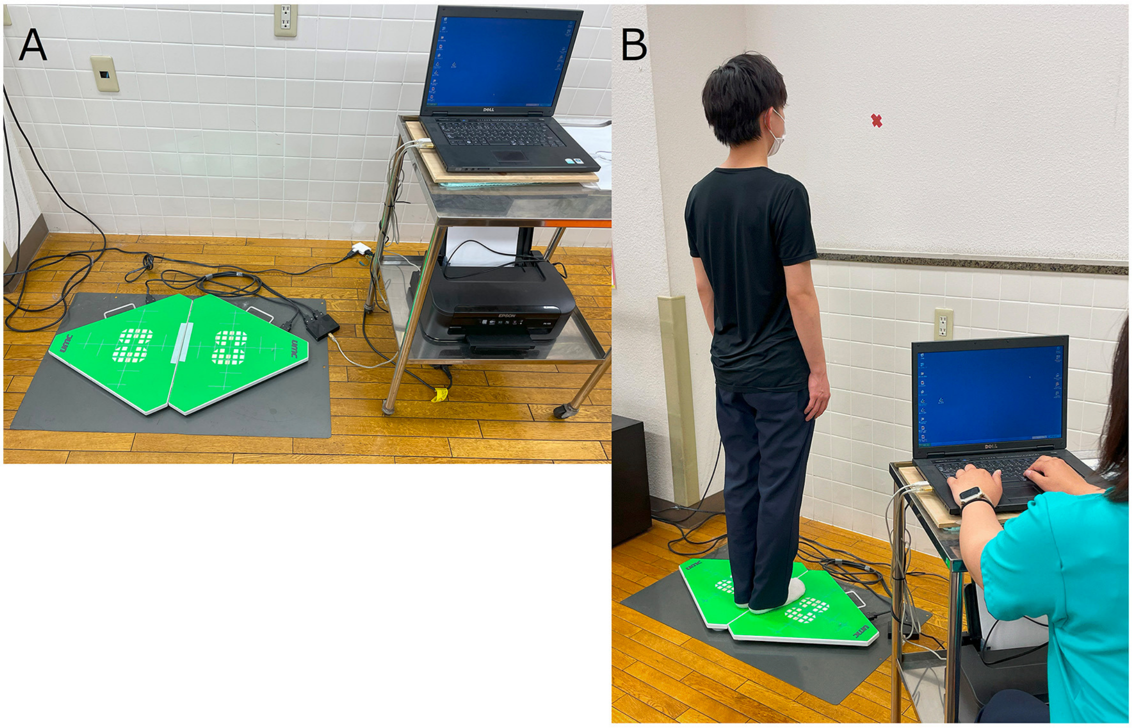

FIGURE 1
Methods for the measurement of the center of pressure (COP). **(A)** Force platform used in the study. **(B)** Arrangement for COP measurement.

TABLE 1 Demographic and clinical characteristics of participants with ET and IMD.

	ET ($n = 15$)	IMD ($n = 15$)	P-value
Age, Mean (SD) years	56.5 (18.2)	43.7 (15.3)	**0.046**[a]
Female, n (ratio %)	6 (40.0)	11 (73.3)	0.139[b]
Diagnosis, n			
(Essential tremor/cervical dystonia/writer's cramp/trunk dystonia)	15/0/0/0	0/4/9/2	—
Onset age, mean (SD) years	34.7 (21.9)	36.2 (14.4)	0.830[a]
Duration of disease, mean (SD) years	24.3 (15.1)	7.4 (9.7)	**0.001**[a]
Target site, n (right/left)	4/11	3/12	>0.999[b]
Target, n (Vim/Vo/PTT/GPi)	15/0/0/0	0/9/3/3	—

ET, Essential tremor with Vim-targeted radiofrequency ablation; GPi, globus pallidus internus; IMD, Involuntary movement disorders with non-Vim-targeted radiofrequency ablation; PTT, pallidothalamic tract; SD, Standard deviation; Vim, ventral intermediate thalamic nucleus; Vo, ventral oral. [a]t-test, [b]Fisher's exact test, —: No data. The number of individuals with ET in terms of onset age and duration of disease was 14 because the onset age of one participant was unknown. Bold font indicates significant correlations.

We used the MCMC method to impute missing values and then conducted linear mixed models.

3.2. Tremor function, ADL, and QOL in ET individuals

A main effect of measurement time-point in the tremor assessment was observed for all three endpoints in the ET group (TETRAS-PS: $F = 39.76$, $p < 0.001$, TETRAS-ADL: $F = 35.70$, $p < 0.001$, and QUEST: $F = 17.955$, $p < 0.001$). Performance in both the TETRAS and QUEST had improved at 1wpost-op and 1mpost-op than that pre-op (t-value range: 4.40–7.918, all p-values $p < 0.001$), as shown in Table 2.

3.3. Motor symptoms

For motor symptoms, a significant time-point × group interaction was found for an eccentric COP-X displacement to the treated side ($F = 4.563$, $p = 0.015$) and grip strength on the treated side ($F = 4.990$, $p = 0.010$) (Table 3). In the simple main effect results, the ET group showed a significantly greater eccentric COP-X displacement to the treated side at 1wpost-op than at pre-op

TABLE 2 Tremor function, ADL, and QOL in participants with essential tremor post-radiofrequency ablation.

Variables above: mean (SE) below: estimated marginal mean (SE)	Pre-op	1-week post-op	1-month post-op	Main effect of measurement time-point	*Post-hoc*
TETRAS-PS	21.3 (2.02) 20.75 (1.84)	5.86 (1.87) 5.34 (1.84)	5.03 (1.84) 4.51 (1.84)	**$F_{(2,28)}$ = 39.76 p < 0.001**	**pre-op vs. 1wpost-op (t = 7.512, p < 0.001) pre-op vs. 1mpost-op (t = 7.918, p < 0.001)**
TETRAS-ADL	18.9 (1.93) 18.43 (1.75)	7.51 (1.92) 7.07 (1.75)	6.62 (1.69) 6.19 (1.75)	**$F_{(2,28)}$ = 35.70, p < 0.001**	**Pre-op vs. 1wpost-op (t = 7.030, p < 0.001) pre-op vs. 1mpost-op (t = 7.576, p < 0.001)**
QUEST	33.1 (3.86) 32.5 (4.09)	17.9 (4.40) 17.3 (4.09)	13.4 (3.88) 12.7 (4.09	**$F_{(2,28)}$ = 17.955 p < 0.001**	**pre-op vs. 1wpost-op (t = 4.40, p < 0.001) pre-op vs. 1mpost-op t = 5.72, p < 0.001)**

ADLs, activities of daily living; QOL, quality of life; TETRAS, The Essential Tremor Rating Assessment Scale; QUEST, Quality of Life in Essential Tremor Questionnaire Linear mixed model included the measurement time-point (preoperatively [pre-op], 1-week post-operatively [1wpost-op], and 1-month postoperatively [1mpost-op]) as independent variables, age and sex as covariates, and participants as random effects. Bold font indicates significant correlations.

(t = 4.871, p < 0.001) and significantly reduced displacement at 1mpost-op than at 1wpost-op (t = −3.601, p < 0.001), as shown in Figure 2A. In comparison, grip strength on the treated side in the IMD group showed a more significant decrease at 1wpost-op than at pre-op (t = −4.935, p < 0.001), as shown in Figure 2B.

A main effect of time of measurement, but no interaction, was seen for COP-LNG. COP-LNG was more prolonged at 1wpost-op than at 1mpost-op (t = −2.658, p = 0.031). There was no statistically significant change from pre-op to 1wpost-op (t = 1.872, p = 0.199) or 1mpost-op (t = −0.787, p > 0.999) (Table 3).

3.4. Non-motor symptoms

Significant time-point × group interactions were seen among non-motor symptom outcomes for VF-p and VF-c. The VF-p score in the IMD group at 1wpost-op was lower than that at pre-op (t = −5.625, p < 0.001) and at 1mpost-op (t = 3.010, p = 0.004). The VF-c score did not change significantly in either group. The MMSE scores showed a main effect of the measurement time-point but no interaction. The MMSE score at 1mpost-op was significantly improved than that at pre-op (t = 2.887, p = 0.017) and at 1wpost-op (t = 3.284, p = 0.005) (Table 3).

3.5. Physical performance

The 10-MWT, STEF scores on the treated and non-treated sides and the BBS score did not show any statistically significant interaction or effects on the measurement time-point. The STEF scores on the treated side were significantly improved at 1mpost-op than that at 1wpost-op (t = 3.44, p = 0.003). While both STEF scores showed main effects on the group, STEF scores on the treated and non-treated sides in the ET group were significantly worse than those in the IMD group (F = 12.126, p = 0.002 and F = 19.5081, p < 0.001, respectively) (Table 3).

3.6. Correlation of motor and non-motor symptoms with physical performance decline

Correlation analyses were analyzed between the pre-op or 1wpostop motor or non-motor symptoms with changes due to RFA. The ET group had a correlation between COP-X and BBS (r = −0.661, p = 0.007). In the IMD group, grip strength on the treated side correlated with STEF on the treated side (r = 0.520, p = 0.047) and VF-c correlated with the 10-MWT (r = −0.696, p = 0.004) (Table 4).

4. Discussion

In this case–control study, we evaluated the symptoms of individuals with ET, treated with Vim-targeted RFA, during the perioperative period compared to individuals with IMD treated with RFA targeting non-Vim areas. We found that individuals with ET who underwent Vim-targeted RFA showed improvement in tremors, ADLs, and QOL. However, they showed a significant shift in COP-X toward the treated side (dominant side of the RFA target's hemisphere) 1 week after RFA compared to the preoperative period. To the best of our knowledge, this is the first study to elucidate functional decline after RFA using quantitative measures in patients with ET as compared to control participants. The COP-X displacement can help to assess symptoms other than tremors arising after RFA and can provide valuable information as a clinical indicator of response to rehabilitation methods and outcomes.

The Vim is innervated by the dentato-rubro-thalamic tract of the dentate nucleus of the cerebellum, which has neural connections to the primary motor cortex in the cerebrum, forming the cerebellar-thalamo-cortical network (CTC) (28). CTC network abnormalities in ET are primarily attributable to pathophysiology (29) and swelling surrounding the permanent brain lesion after RFA. However, the COP displacement to the tremor side cannot be fully explained based on the effect of the Vim-targeted RFA on the CTC network. The total trajectory length and rectangular area, which directly measured the amount of center-of-gravity motion,

TABLE 3 Motor and non-motor symptoms and physical performance in participants with ET and IMD, post-radiofrequency ablation.

	Essential tremor (ET)			Involuntary movement disorders (IMD)			Linear mixed model		
Variables above: mean (SE) below: estimated marginal mean (SE)	Pre-op	1-week post-op	1-month post-op	pre-op	1-week post-op	1-month post-op	Interaction group × measurement time-point	Main effect of measurement time-point	Main effect of the group
Motor symptoms									
COP RMA	87.5 (13.5) 83.3 (48.6)	175 (40.0) 170.6 (48.6)	114 (21.4) 109.4 (48.6)	140 (48.7) 145.5 (50.3)	179 (79.9) 184.8 (50.3)	131 (39.0) 136.6 (50.3)	$F_{(2,56)} = 0.3437$ $p = 0.711$	$F_{(2,56)} = 2.6223$ $p = 0.082$	$F_{(1,26)} = 0.2886$ $p = 0.596$
COP LNG	267 (21.8) 253 (36.3)	327 (30.9) 313 (36.3)	253 (17.6) 239 (36.3)	281 (30.3) 300 (37.6)	304 (60.6) 324 (37.6)	261 (32.1) 280 (37.6)	$F_{(2,56)} = 0.384$ $p = 0.683$	**$F_{(2,56)} = 3.730$ $p = 0.030$**	$F_{(1,26)} = 0.478$ $p = 0.495$
COP-X	1.63 (2.55) 1.9487 (2.82)	18.3 (2.82) 18.6195 (2.82)	5.97 (2.39) 6.2965 (2.82)	0.44 (2.34)−0.0149 (2.89)	3.26 (1.96) 2.8051 (2.89)	1.92 (3.81) 1.4651 (2.89)	**$F_{(2,56)} = 4.563$ $p = 0.015$**	**$F_{(2,56)} = 8.544$ $p < 0.001$**	**$F_{(1,26)} = 5.981$ $p = 0.022$**
COP-Y	−7.49 (3.44) −7.637 (3.37)	−10.7 (2.75) −10.865 (3.37)	−5.93 (3.52) −6.080 (3.37)	−1.64 (2.66) −1.032 (3.47)	−7.16 (3.53) −6.552 (3.47)	−0.253 (3.45) 0.355 (3.47)	$F_{(2,56)} = 0.1123$ $p = 0.894$	$F_{(2,56)} = 2.5476$ $p = 0.087$	$F_{(1,26)} = 2.1780$ $p = 0.152$
Grip strength on treated side	27.6 (2.13) 26.2 (1.32)	27.1 (2.51) 25.7 (1.32)	27.2 (2.19) 25.8 (1.32)	25.0 (2.72) 28.5 (1.34)	20.5 (2.18) 24.0 (1.34)	22.1 (2.63) 25.6 (1.34)	**$F_{(2,56)} = 4.99023$ $p = 0.010$**	**$F_{(2,56)} = 7.72901$ $p = 0.001$**	$F_{(1,26)} = 0.00646$ p = 0.937
Grip strength on the non-treated side	25.5 (2.23) 24.3 (1.26)	25.2 (2.27) 24.0 (1.26)	26.0 (2.43) 24.9 (1.26)	22.8 (2.42) 26.1 (1.28)	20.9 (2.04) 24.2 (1.28)	23.1 (2.53) 26.4 (1.28)	$F_{(2,56)} = 0.8668$ $p = 0.426$	$F_{(2,56)} = 2.7482$ p = 0.073	$F_{(1,25)} = 044009$ $p = 0.513$
Non-motor symptoms									
MMSE	28.5 (0.361) 28.6 (0.537)	28.2 (0.564) 28.4 (0.537)	29.3 (0.356) 29.5 (0.537)	27.6 (0.622) 27.4 (0.555)	27.6 (0.698) 27.4 (0.555)	28.9 (0.385) 28.7 (0.555)	$F_{(2,56)} = 0.150$ $p = 0.861$	**$F_{(2,56)} = 6.426$ $p = 0.003$**	$F_{(1,26)} = 2.115$ $p = 0.158$
Verbal fluency-category	12.2 (0.865) 12.4 (1.08)	12.9 (0.866) 13.0 (1.08)	13.2 (0.682) 13.3 (1.08)	17.6 (0.881) 17.1 (1.12)	16.0 (1.66) 15.6 (1.12)	14.8 (1.2) 14.3 (1.12)	**$F_{(2,56)} = 4.720$ $p = 0.013$**	$F_{(2,56)} = 1.116$ $p = 0.319$	$F_{(1,26)} = 3.492$ $p = 0.073$
Verbal fluency-phoneme	7.82 (0.693) 7.92 (0.952)	6.98 (0.683) 7.07 (0.952)	8.3 (0.871) 8.40 (0.952)	13.7 (1.03) 13.63 (0.984)	8.67 (1.08) 8.56 (0.984)	11.4 (0.952) 11.27 (0.984)	**$F_{(2,56)} = 5.71776$ $p = 0.006$**	**$F_{(2,56)} = 11.24005$ $p <$ 0.001**	**$F_{(1,26)} = 7.55014$ $p = 0.011$**
Physical performance									
10MWT	5.26 (0.167) 5.29 (0.247)	5.88 (0.169) 5.91 (0.247)	5.67 (0.3) 5.71 (0.247)	4.85 (0.174) 4.75 (0.255)	5.77 (0.344) 5.68 (0.255)	5.2 (0.226) 5.10 (0.255)	$F_{(2,56)} = 0.6371$ $p = 0.533$	**$F_{(2,56)} = 9.7459$ $p <$ 0.001**	$F_{(1,26)} = 2.2021$ $p = 0.150$
BBS	55.3 (0.371) 55.4 (0.586)	52.8 (0.719) 52.9 (0.586)	54.1 (0.524) 54.2 (0.586)	55.3 (0.347) 55.3 (0.605)	54.7 (0.836) 54.7 (0.605)	55.0 (0.468) 55.0 (0.605)	$F_{(2,56)} = 2.353$ $p = 0.104$	**$F_{(2,56)} = 6.466$ $p = 0.003$**	$F_{(1,26)} = 1.330$ $p = 0.259$
STEF on treated side	91.7 (1.61) 91.6 (1.59)	85.5 (1.7) 85.5 (1.59)	90.0 (1.72) 89.9 (1.59)	98.7 (0.599) 98.8 (1.65)	93.9 (1.66) 94.1 (1.65)	96.1 (1.39) 96.2 (1.65)	$F_{(2,56)} = 0.7679$ $p = 0.469$	**$F_{(2,56)} = 16.3252$ $p <$ 0.001**	**$F_{(1,26)} = 12.1260$ $p = 0.002$**
STEF on the non-treated side	91.4 (1.83) 90.9 (1.47)	88.6 (2.04) 88.1 (1.47)	90.6 (1.9) 90.0 (1.47)	98.9 (0.446) 99.4 (1.53)	98.3 (0.575) 98.8 (1.53)	98.1 (0.661) 98.6 (1.53)	$F_{(2,56)} = 1.8724$ $p = 0.163$	**$F_{(2,56)} = 3.1987$ p = 0.048**	**$F_{(1,26)} = 19.5081$ $p < 0.001$**

BBS, Berg Balance Scale; COP, center of pressure; ET, essential tremor with Vim-targeted-radiofrequency ablation; IMD, Involuntary movement disorders with non-Vim-targeted-radiofrequency ablation; LNG, length; MMSE, Mini-Mental State Examination; RMA, root mean square area; SE, standard error; STEF, simple test for evaluating hand function; 10MWT, 10-meter walk test. Linear mixed model included Group (ET and IMD) × Measurement time-point (preoperatively [pre-op], 1-week post-operatively [1wpost-op], and 1-month postoperatively [1mpost-op]) as independent variables, age and sex as covariates (with weight added as a covariate for grip strength), and participants as random effects. Bold font indicates significant correlations.

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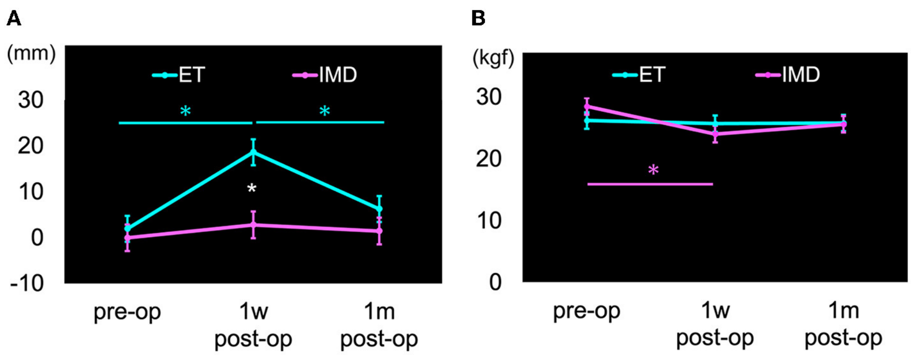

FIGURE 2
Motor symptoms with significant differences in time-group interaction. Cyan color: Essential tremor group (ET), Magenta color: Involuntary movement disorders group (IMD), Error bars: standard errors (SE), *$p < 0.05$. **(A)** Center of pressure horizontal displacement (COP-X). The direction of displacement to the treated side was calculated as a positive value. The ET group had significantly displaced COP-X to the treated side at 1wpost-op than at pre-op and significantly reduced displacement at 1mpost-op than at 1wpost-op, as shown in cyan color asterisks (*). The displacement in the ET group at 1wpost-op was significantly displaced compared to the IMD group, as shown by white color asterisk (*). **(B)** Strength grasp on the treated side. The grip strength on the treated side in the IMD group significantly decreased at 1wpost-op than at pre-op, as shown in magenta color asterisk (*).

TABLE 4 Correlations of the amount of change between preoperative and 1-week postoperative motor and non-motor symptoms with physical performance decline in ET and IMD.

Values mean (SE)	STEF on treated side −6.19 (1.78)	STEF on non-treated side −2.78 (1.78)	10-MWT 0.623 (0.139)	BBS −2.42 (0.752)
(A) ET				
COP X 16.7 (3.93)	r = 0.304 p = 0.271	r = −0.338 p = 0.217	r = 0.310 p = 0.261	**r = −0.661 p = 0.007**
(B) IMD				
Values mean (SE)	STEF treated side −4.73 (1.42)	STEF non-treated side −0.533 (0.446)	10-MWT 0.927 (0.304)	BBS −0.600 (0.623)
Grip strength on treated side−4.53 (1.31)	**r = 0.520 p = 0.047**	r = 0.514 p = 0.050	r = −0.462 p = 0.083	r = 0.164 p = 0.560
Verbal fluency–category−1.51(1.18)	r = 0.318 p = 0.248	r = 0.184 p = 0.512	**r = −0.696 p = 0.004**	r = 0.437 p = 0.103
Verbal fluency–phenomenon –**5.07 (1.06)**	r = 0.070 p = 0.803	r = 0.175 p = 0.534	r = −0.270 p = 0.330	r = 0.118 p = 0.676

BBS, Berg Balance Scale; ET, Essential tremor with Vim-targeted-radiofrequency ablation; IMD, Involuntary movement disorders with non-Vim-targeted-radiofrequency ablation; SE, standard error; STEF, simple test for evaluating hand function; 10-MWT, 10-meter walk test. Pearson's product-moment correlation coefficients. Bold font indicates significant correlations.

did not change significantly between the pre- and post-surgery period in this study.

We hypothesized that tremor symptom improvement after RFA occurred as a shift in balance retention and postural strategy. Pre-operatively, individuals with ET adjusted the center of gravity to the median direction by applying torque in the direction of the treated side to maintain balance against the presence of unbalanced tremor symptoms. Since postoperative measures to maintain posture reduced the symptoms of tremors, it would be necessary to readjust the torque to the tremor side. ET individuals were reported to have impaired motor learning, which caused a functional disturbance of olivo-cerebellar circuits in the pathogenesis of ET (30). Therefore, this readjustment takes time due to impaired motor learning, the torque toward the tremor direction may be excessive until the patient adapts, and the center-of-gravity may shift in the tremor direction.

In individuals with IMD who underwent non-Vim-targeted RFA, treated-side grip strength and phonic VF worsened 1 week after surgery. The targets of RFA were the Vo, GPi, or PTT, which are included in the basal ganglia–thalamocortical (BTC) network (29). The BTC network, linked to both the RFA targets used in IMD individuals and to the gray matter of the supplementary motor cortex, is associated with smooth motor coordination (31) and has also been shown to regulate grip strength (32). It is reasonable to conclude that RFA-induced changes in the BTC network cause a perioperative decline in grip strength in individuals with IMD. In this study, the IMD group consisted of dystonia patients with RFA targets other than Vim, and neither the dystonia site nor the RFA target was controlled. The postoperative changes of each dystonia site were consecutive. We consider that individuals with cervical dystonia might have differed from the other types (Supplementary Table 1). Further investigation of the relationship between the dystonia site and the RFA target is necessary to determine the cause of the decrease in grip strength after RFA surgery.

A systematic review of the neural basis of VF using functional magnetic resonance imaging (fMRI) suggested that phonic-related VF is more associated with the dorsal left inferior frontal gyrus than meaning-related VF (33). In comparison, the GPi, one of the RFA targets in IMD, is located in the cognitive loop, involved in the cortico-basal ganglia circuits. We speculated that the low VF-p score at 1w-postop in the IMD group was due to the inability to inhibit the habitual response of using words according to their meaning, due to the deterioration of the prefrontal cortical loop, similar to the VF-p results seen in Parkinson's disease patients who have undergone GPi-targeted DBS (34).

Physical disabilities may occur due to craniotomy, and they can also be interpreted as disabilities due to the different neural mechanisms associated with each targeted RFA site. The current results of the correlation analyses between the COP-X and BBS in the ET group, and between the treated-side grip strength and STEF in the IMD group, supports this interpretation. Perioperative physical disabilities were not found to be specific to the RFA target, and both groups had worse physical performance post-treatment than preoperatively. Therefore, we propose that rehabilitation for physical disabilities in the perioperative period should consider the impact of functional impairment on the target site. Future studies should include symptom progression, deep somatosensory function, and limb muscle strength to strengthen the findings of the present study.

The current study had three limitations for generalizing post-RFA symptoms in individuals with ET. First, we investigated patients with ET who underwent RFA performed by a surgeon at a single institution. Second, the current data included imputed missing values due to missing data points for some participants. Third, to make the relationship between post-RFA symptoms and physical performance decline, a more robust finding and a large sample size are needed to allow multivariate regression analysis in a future study.

5. Conclusion

We compared symptoms after RFA treatment between individuals in ET, among whom the Vim was targeted, and individuals with IMD, among whom other brain regions were targeted, in a longitudinal case–control study, with measurement performed at 1-week and at 1-month post-RFA. We showed that individuals in the ET group showed improvement in tremors, ADL, and QOL at 1-month post-RFA. However, the COP showed horizontal displacement to the treated side at 1-week post-RFA. This COP displacement was associated with balance dysfunction related to postural stability post-RFA. Our theory is that the shift in the center of pressure toward the treated side may be caused by a delay in adapting to the long-term differences in tremor symptoms, which improve after RFA. We propose that the horizontal displacement of the center of pressure can be used to evaluate non-tremor symptoms that occur after RFA, providing important information as an indicator of the effectiveness of rehabilitation methods and their results.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Review Committee of the Tokyo University of Health Sciences in Tokyo University of Health Sciences (TPU-20-004) and the Sanai Hospital Ethical Review Committee in Sanai Hospital (21-s001). The patients/participants provided their written informed consent to participate in this study.

Author contributions

The study was designed by AS and TI with contributions from TH and MK. Patient identification and surgery were carried out by TT. Subjects recruitment and data collection were carried out by KK and TA. Data analysis was carried out by AS and TI. The article was primarily written by AS and TI, and reviewed by all the authors. All authors contributed to the article and approved the submitted version.

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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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1182082/full#supplementary-material

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The effectiveness of robotic-assisted upper limb rehabilitation to improve upper limb function in patients with cervical spinal cord injuries: a systematic literature review

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Background: Spinal Cord Injury (SCI) damages corticospinal tracts and descending motor pathways responsible for transmitting signals from the brain to the spinal cord, leading to temporary or permanent changes in sensation, motor function, strength, and body function below the site of injury. Cervical SCI (cSCI), which leads to tetraplegia, causes severe functional upper limb (UL) impairments that increase falls risk, limits independence, and leads to difficulties with activities of daily living (ADLs). Robotic therapy (RT) has been developed in recent decades as a new treatment approach for people with cervical spinal cord injuries (cSCI). The present review aimed to explore current available evidence and studies regarding the effectiveness of RT for individuals with cSCI in improving UL function, identify current research gaps and future research directions.

Method: This review was conducted by searching PubMed, CINAHL, Medline, Embase, and APA PsycInfo for relevant studies published from January 2010 to January 2022. Selected studies were analyzed with a focus on the patients' self-perception of limited UL function and level of independence in activities of daily living. In addition, the JBI Critical Appraisal checklist was used to assess study quality.

Results: A total of 7 articles involving 87 patients (74 males and 13 females) were included in the analysis, with four studies utilizing exoskeleton and three studies utilizing end-effector robotic devices, respectively. The quality of these studies varied between JBI Critical Appraisal scores of 4 to 8. Several studies lacked blinding and a control group which affected internal validity. Nevertheless, four out of seven studies demonstrated statistically significant improvements in outcome measurements on UL function and strength after RT.

Conclusion: This review provided mixed evidence regarding the effectiveness of RT as a promising intervention approach to improve upper limb function in participants with cSCI. Although RT was shown to be safe, feasible, and reduces active therapist time, further research on the long-term effects of UL RT is still needed. Nevertheless, this review serves as a useful reference for researchers to further develop exoskeletons with practical and plausible applications toward geriatric orthopaedics.

KEYWORDS

limb activation, robot-assisted therapy, spinal cord injury, exoskeleton, adults

1. Introduction

Spinal cord injury (SCI) is a devastating, life-changing event that occurs due to trauma of the vertebral column or its surrounding tissue, which causes damage to corticospinal tracts and descending motor pathways and ascending sensory pathways are responsible for transmitting signals from the brain to the spinal cord (1–3). Often, this can leads to temporary or permanent loss in sensation, motor function, strength, and body function below the site of injury (4). Previous demographics showed the annual incidence rate of SCI in the United States was 54 cases per million population (5), with the prevalence rate of 721 to 906 per million people (6). Among these SCIs, cervical SCI (cSCI) is the most common occurrence. It makes up around 62% of all SCIs to cause severe functional upper limb (UL) impairments and difficulties with activities of daily living (ADLs) (7). This may also lead to tetraplegia. Hence, through the restoration of UL function, including range of movement (ROM) and muscle strength in the arms and hands, patients can regain independence and improve their quality of life (8, 9).

Our arm plays an important role to maintain balance following a postural disturbance (10). Disturbance of arm swing in non-impaired adults during walking have resulted to alter temporal–spatial gait parameters and interrupt natural pelvic-thoracic motion (11). Importantly, bilateral arm swing restriction have been shown to increase the metabolic cost of walking, impairing stability and increasing fall risk through inducing physical fatigue (12, 13). Hence, the arms are important for locomotor stability and preventing falls by controlling whole-body angular momentum, redirecting the body's center-of-mass, and providing support to arrest descent.

Recent approaches in allied-health interventions have demonstrated modest evidence to preserve the range of motion and enhance mobility skills in the UL. Currently, there are more than 120 devices being developed for UL rehabilitation toward patients affected by neurologic disability (14). These rehabilitation regimes comprise of repetitive movement patterns, functional exercises, verbal and visual feedback, and task-oriented training are considered effective in improving upper limb function (15). However, these newer interventions, such as robotic-assisted upper limb rehabilitation, remains to be accounted as experimental (16). This is owing to the variation of the training characteristics, the type of training and the absence of specific outcome measures to limit the applicability of evidence. In addition, the optimization of robotic-assisted upper limb rehabilitation for maximizing functional improvements (i.e., ADLs, quality of life, activities, and participation) and preserving and/or increasing such progress over time is still an open question. Moreover, the characterization of the type of patient that could benefit from the treatment with different robotic systems remains poorly explored. Although Lu et al. outlined current rehabilitation options to improve UL function in patients with spinal cord injuries, further research are still needed to determine the effectiveness of robotic rehabilitation (17).

Robotic assisted UL rehabilitation, or robotic therapy (RT), facilitates UL function by assisting in repetitive labor-intensive manual therapy normally administered by a physiotherapist (PT) or occupational therapist (OT) (18). Such that, UL robotic devices increase the number of motor repetitions to aid patient recovery and provide consistent training to measure performances outcomes (19). Unlike traditional hands-on therapy, RT would not lack frequency and intensity due to labor limitations and cost (20). Additionally, traditional hands-on rehabilitation outcomes may differ based on the variation in practice between therapists. Robotic devices are either categorized as end-effector-based or exoskeletons. End-effector-based devices are adaptable to patients of various sizes, and exoskeleton-based devices require specific modifications due to optimal joint adaptations (21). While for exoskeletons, they can be classified into grounded exoskeletons and wearable exoskeletons (22). These design approaches affect the level of control over the interaction as well as the output impedance of the device and the ability to modulate this impedance through control. These requires large reduction ratios and results in high inertia and friction at the output where the patient is attached, which can partially be compensated through control. Many researchers have investigated UL rehabilitation according to the facilitation approach with increased physical therapy, electrical stimulation, and passive manipulation (23–25). Toward the clinical evaluations, these include scales for the upper limb function (e.g., using the Fugl-Meyer and the Motricity Index), spasticity, and health-related quality of life questionnaires toward daily activities (26, 27). And the evaluation of muscle strength and the finger pinch are common instrumental assessments (28, 29). Despite various robotic assisted therapy devices being developed since the 1990s, there are still no standardized protocols around the use of these devices in patients with spinal cord injuries. Additionally, while systematic reviews focusing on robotic lower limb rehabilitation were widely published, reviews appraising relevant evidence around the effectiveness of upper limb robotic rehabilitation for individuals with cSCIs are still lacking.

Even though there was a published systematic review around the use of UL robotic devices, the inclusion of low quality appraised studies affected the overall quality of the review (30). Though Morone et al. also have published a comprehensive review toward the state-of-the-art clinical applications around UL robotic training in motor and functional recovery for cSCI patients (31), the search strategy was not explicit due to the limited inclusion and exclusion criteria. Herein, the present review aimed to explore current available evidence and studies regarding the effectiveness of robotic-assisted therapy for individuals with cSCI in improving UL function, and to identify current research gaps for future research directions.

2. Methods and methods

The current systematic review was conducted according to the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement (32). No ethical approval was needed because all analyses were based on published evidence.

2.1. Data sources and search strategy

The systematic literature review was performed by searching the following database: PubMed, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Medline, Embase, and APA PsycInfo. To understand the changes for the past decade, we included relevant articles published from January 2010 to January 2022. The following keywords were used for the literature search: ("Robotic therapy or Robotic assisted training or robotic assisted therapy or robot* or exoskeleton or telerobot* or wrist-robot* or robotic upper limb rehabilitation") AND ("adult* or patient or individual* or young person* or young adult* or person or elderly or aged or older or elder* or geriatric* or elderly people or old people or older people or senior*") AND ("cervical sci or cervical spine cord* or central cord syndrome or central spinal cord or central spinal cord injur* or ccs") AND (upper limb or upper limb function or arm function or hand function or upper extremit* or upper extremity function). The full search strategy and key search terms can be found in Supplementary 1. Subsequently, the reference lists were manually screened by two independent expert observers to reach a common agreement on relevant studies.

2.2. Study eligibility criteria

Studies were included when the following criteria were met: (1) articles that report findings regarding the effectiveness of robotic-assisted therapy application in human subjects; (2) allied health prescribed robotic therapy to aid upper limb training; (3) quantitative investigation on the outcome of improving upper limb function; and (4) peer-reviewed articles published in English before 1 February 2022. Studies were excluded if the retrieved item (1) was a review study, qualitative study, a single case report, an editorial comment, a meta-analysis of prior studies, or clinical trials under review; (2) animal study; (3) studies included children or patients aged above 75; (4) interventions for lower limb robotics or the use of lower limb exoskeletons and related robotic devices; (5) no investigation on the upper limb function as an outcome; (6) subjects with brain or neurological injuries other than cSCI; (7) consisted of abstracts with no associated full article published in a peer-reviewed English-speaking journal.

2.3. Study selection and data extraction

The titles and abstracts were imported into EndNote X9 to remove duplicated studies. After the removal of duplications, all records were manually screened by titles and abstracts to exclude irrelevant articles by two authors independently. Then, the same two authors independently performed a comprehensive extraction of key data points from those studies that met the eligibility criteria. All data were then extracted using a standard data collection form. Any discrepancies during the data extraction process were adjudicated by a third author. The following data were recorded using a table from each eligible article: (1) the name of the first author, (2) year of publication, (3) study design, (4) number of patients, (5) patient characteristics, (6) intervention, (7) type of robotic device, (8) outcome measured, (9) SCI stage and level, and (10) findings.

2.4. Quality assessment of individual studies

The selected studies were appraised by two independent reviewers (JSWH and GCWM) for methodological quality prior to inclusion in the overview, using a standardized critical appraisal tool, JBI Critical Appraisal Checklist for Systematic Reviews and Research Synthesis (33). Any disagreements that arise between the two reviewers will be resolved through consensus and discussion or guidance from a third reviewer (SWL) will be employed. A narrative summary of the results of the critical appraisal of systematic reviews will be presented and supported by relevant supporting tables. A score of 0–3 representing very low-quality; a score of 4–6 representing a low-quality; a score of 7–9 representing a moderate-quality; and a score of 10–11 will be considered as high-quality.

2.5. Data presentation and data analysis

Due to the methodological and clinical heterogeneity of patient groups, data pooling and meta-analysis were not performed. Various variables collected with absolute numbers and corresponding percentages were displayed for each study. A descriptive statistical analysis of the data collected was performed.

3. Results

This systematic review includes items published from January 2010 to January 2022. After the removal of duplicates and articles that did not meet selection criteria, a total of 7 studies (of which four case series, one randomized controlled trial (RCT), and two quasi-experimental studies) were included, concerning a total of 87 subjects. The PRISMA 2020 flow diagram of the search process is shown in Figure 1.

3.1. Study selection and characteristics

In the preliminary search using the specified keywords on the databases, 995 articles were identified. After removing the duplicates and screening the titles and abstracts, 18 items (2%) were retained for full-text analysis by our two expert reviewers, of which 11 (61%) were excluded because they failed to meet inclusion/exclusion criteria. Of the 11 excluded items, they were removed due to various reasons (Figure 1). Among the 7 included studies, the sample size ranged from 4 to 34 participants. Characteristics of the included studies are summarized in Table 1.

3.2. Quality assessment

Studies were critically appraised using study-specific Joanna Briggs Institute (JBI) critical appraisal tools (CATs) to assess the methodological quality of studies in allied health literature. The 7 included studies were critically appraised by two independent reviewers using the JBI checklist. Of the 4 case studies (maximum quality score 10), 2 studies were assigned a score of 7 (35, 37), one

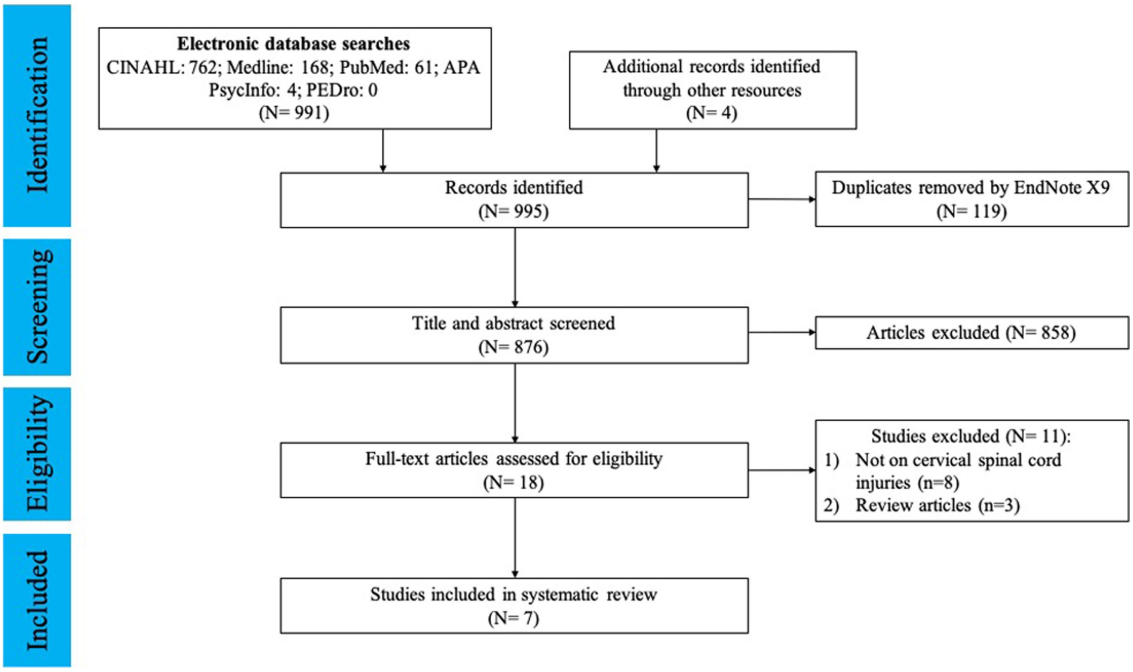

FIGURE 1
PRISM flowchart.

study scored 6 (36), and another study scored 4 (38). The RCT studies scored 8 (maximum quality score 13) (39), while the two quasi-experimental studies (maximum quality score 9), the studies scored 6 (34), and 4 (40), respectively. Failure in blinding subjects and blinding therapists are the two most common methodological limitations in all included studies. The detailed results of the methodological quality assessment done with JBI assessment are shown in Tables 2–4.

3.3. Subjects: demographic and individual considerations

Taken together, all studies included a total of 87 subjects of both genders (72 men and 13 women), gender remained unclear or unreported for 2 subjects. Most patients were male (85%) and patients' age ranged from 19 to 75 years old (mean average age at recruitment = 49 years old). Among these subjects recruited, 25 subjects were classified as having chronic SCIs, 19 subjects with sub-acute SCIs and 43 subjects with sub-acute to chronic SCIs. Whereas, the majority of the SCIs was found to be at C4–C5 (58.8%). These subjects were mainly recruited through rehabilitation centres' databases, inpatient or outpatient units, research institutes' referrals, or volunteering.

3.4. Intervention delivery

Robotic devices and training protocols varied across all studies. Interventions included the use of the following robotics: fabric-based robotic soft glove ($n = 1$), InMotion 3.0 wrist robot ($n = 1$), MAHI Exo-II exoskeleton ($n = 1$), Haptic Master ($n = 1$), Armeo Power ($n = 1$), and Armeo Spring ($n = 2$). Four robots are exoskeletons connected to multiple joint axes, which require modifications due to joint adaptations, and three robots are end effector devices connecting to distal parts of the joints, and are adaptable to those of various body sizes. In addition, three studies with both subacute and chronic patients in inpatient settings received co-therapy along with robotic therapy (34, 39), while other studies reported to receive only robotic therapy and did not specify if co-therapy was included. Robotic intervention was administered and supervised by physiotherapists ($n = 2$) or occupational therapists ($n = 3$), but 2 studies did not specify the background of their therapists and assessors (35, 38). The duration of the treatments ranged from 4 weeks to 6 weeks, and the length of training sessions between 30 min to 3 h. In addition, the characteristics and outcome parameters used in these studies were different (Table 1).

3.5. Outcome measures and statistics

Four studies focused on assessing the feasibility, safety, and effectiveness of UL RT in cSCI patients (34, 35, 37, 38). Another study focused on investigating the effectiveness of UL RT combined with conventional OT (39). The remaining two studies focused on the impact of UL RT in assisting upper limb functional activities for participants with decreased hand strength (36, 40).

Based on the evidence from two studies, it showed greater functional outcomes in participants that received RT in addition to conventional therapy (39, 40). One of these studies administered routine OT across both groups (39). An assessor blinded RCT was conducted to assess the effectiveness of robotic therapy to improve upper limb function in individuals with cSCI. The result showed intervention group showed small improvements in motor strength and SCIM-III scores in the RT group after 4 weeks of RT combined with conventional OT, but no statistically significant differences were identified between groups. Additionally, the study had an unequal

TABLE 1 Characteristics and outcomes of studies included in the systematic review.

Article	Study Design	Aim	Sample Size (dropouts)	Participant characteristics	Intervention	Type of robotic device	Rehabilitation program	Outcome measures for robotic therapy	SCI stage and level	Findings
Zariffa et al. (34)	Multi-center Pilot Study	Establish feasibility of using robotic device in SCI inpatient setting and gather preliminary data on device's efficacy	15 (3 dropouts)	14 M, 1 F 19–75 years	1 h × 3–5 days/wk. x 6 weeks along with combined conventional PT and OT exercises	Armeo Spring Training mode: Passive assist	Robotics with varying rehabilitation program	GRASSP Action Research Arm Test Grip Dynamometry ROM	C4-6 subacute	Armeo spring increased the amount of rehabilitation training and reduced the time required from therapists but showed few functional benefits.
Cortes et al. (35)	Case Series	To assess feasibility, safety, and effectiveness of robotic assisted training of upper limb in chronic SCI	10	8 M, 2 F 17–70 years	6 week wrist-robot training protocol (1 h/day × 3 times/wk)	InMotion 3.0 Wrist Robot Training mode: Passive, assistive, active, resistive	Robotics with varying rehabilitation program	Motor performance: Upper extremity motor score Pain Level (VAS) Spasticity (Modified Ashworth Scale)	C4-6 chronic	Robotic assisted training is feasible and safe that can enhance movement without affecting pain or spasticity in chronic SCI.
Vanmulken et al. (36)	Case Series	To assess feasibility and effectiveness (arm-hand function and performance) of haptic robotic technology	5 (2 dropouts)	4 M, 1 F 25–70 years	1 h × 3 days/wk. x 6 wks	Haptic Master Training mode: Passive assist, active assist	Complex system with varying rehabilitation program	IMI and CEQ	C4-7 chronic	The haptic master is easy to work with and is feasible to use in patients with cSCI.
Francisco et al. (37)	Case Series	To demonstrate feasibility, tolerability and effectiveness of RT in incomplete cSCI	10	8 M, 2F 19–60 years	Single degree of freedom upper limb exercises for 3 h per session, 3 times/wk. for 4 wks	MAHI Exo-II exoskeleton Training mode: Passive assist, active assist	Robotics with fixed rehabilitation program	Arm and Hand Function tests: Jebsen-Tylor Hand Function Test, Action Research Arm Test Upper Limb Strength: Upper limb motor score, grip, pinch strength Independence in Daily Activities: Spinal Cord Independence Measure II	C2-7 chronic	Repetitive training of arm movements with MAHI Exo-II is safe and has the potential to be used as rehabilitation intervention for patients with mild to moderate SCI upper limb impairments.

(Continued)

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TABLE 1 (Continued)

Article	Study Design	Aim	Sample Size (dropouts)	Participant characteristics	Intervention	Type of robotic device	Rehabilitation program	Outcome measures for robotic therapy	SCI stage and level	Findings
Cappello et al. (38)	Case Series	To offer a fabric-based soft robotic glove as an assistive solution for participants with limited hand strength	9	8 M, 1 F 20–68 years	Administration of the Toronto Rehabilitation Institute Hand function test x2, once without glove for baseline line and once while wearing the glove	Fabric-based soft robotic glove Training mode: Passive assist, active assist	Robotics with fixed rehabilitation program	Upper Limb Function: TRI-HFT	C4-7 Subacute/chronic	The fully portable robotic glove showed significant average object manipulation improvement and upper limb lift force.
Kim et al. (39)	RCT	To investigate the efficacy of upper extremity robotic rehabilitation as an adjunctive treatment to conventional OT in patients with tetraplegia.	34 (4)	28 M, 6 F RT: 56.7 + 13.6 years OT: 47.1 + 14.9 years	RT: OT with 30 min Armeo Power/day OT: OT with additional 30 min OT/day	Armeo Power Training mode: Passive assist, active assist	Complex system with varying rehabilitation program	Key muscles: Medical research council scale Trained arm: UEMS SCIM-III	C2-8 Subacute/chronic	Small improvements in muscle strength and SCIM-III scores in RT group, but no statistically significant differences.
Sorensen et al. (40)	Single-Subject Study (B-C-B)	To explore the impact of robotic training on upper limb function, ADL and training experience in subacute tetraplegic inpatients.	4	4 M 19–62 years	Six weeks total – two weeks of baseline OT followed by two weeks RT + PT then OT 11 sessions RT, 60 min each	Armeo Spring Training mode: Passive assist	Robotics with varying rehabilitation program	Arm and Hand Function: GRASSP ADL: SCIM-III Training Experience: 13-item Questionnaire	C4-7 subacute	Study could not confirm improvements were due to robotic intervention.

ADL, activities of daily living; CEQ, credibility and expectancy questionnaire; cSCI, cervical spinal cord injury; EMG, electromyography; GRASSP, the graded redefined assessment of strength, sensation and prehension; IMI, intrinsic motivational inventory; OT, occupational therapy; PT, physiotherapy; RT, robotic therapy; ROM, range of motion; SCIM-III, spinal cord independence measure; TRI-HFT, Toronto Rehabilitation Institute Hand Function Test; UEMS, upper extremity motor score; VAS, visual analog scale.

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TABLE 2 JBI critical appraisal checklist for case series.

Author	1	2	3	4	5	6	7	8	9	10	Total	Quality
Cappello et al. (38)	U	Y	U	N	Y	U	U	U	Y	Y	4/10	Low
Cortes et al. (35)	Y	Y	U	N	Y	Y	U	Y	Y	Y	7/10	Moderate
Francisco et al. (37)	Y	Y	Y	N	Y	Y	U	N	Y	Y	7/10	Moderate
Vanmulken et al. (36)	Y	Y	N	N	Y	Y	U	U	Y	Y	6/10	Low

Key: Y, yes; N, no; U, unclear. Questions: 1. Were there clear criteria for inclusion in the case series? 2. Was the condition measured in a standard, reliable way for all participants included in the case series? 3. Were valid methods used for identification of the condition for all participants included in the case series? 4. Did the case series have consecutive inclusion of participants? 5. Did the case series have complete inclusion of participants? 6. Was there clear reporting of the demographics of the participants in the study? 7. Was there clear reporting of clinical information of the participants? 8. Were the outcomes or follow up results of cases clearly reported? 9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information? 10. Was statistical analysis appropriate?

TABLE 3 JBI critical appraisal checklist for quasi-experimental studies.

Author	1	2	3	4	5	6	7	8	9	Total	Quality
Sorensen et al. (40)	Y	U	Y	N	U	N	Y	Y	N	4/9	Low
Zariffa et al. (34)	Y	Y	Y	Y	Y	N	Y	U	N	6/9	Low

Key: Y, yes; N, no; U, unclear. Questions: 1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e., there is no confusion about which variable comes first)? 2. Were the participants included in any comparisons similar? 3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest? 4. Was there a control group? 5. Were there multiple measurements of the outcome both pre and post the intervention/exposure? 6. Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analyzed? 7. Were the outcomes of participants included in any comparisons measured in the same way? 8. Were outcomes measured in a reliable way? 9. Was appropriate statistical analysis used?

TABLE 4 JBI critical appraisal checklist for randomised controlled trials studies.

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	Total	Quality
Kim et al. (39)	Y	N	Y	N	N	Y	Y	U	Y	Y	U	Y	Y	8/13	Moderate

Key: Y, yes; N, no; U, unclear. Questions: 1. Was true randomization used for assignment of participants to treatment groups? 2. Was allocation to treatment groups concealed? 3. Were treatment groups similar at the baseline? 4. Were participants blind to treatment assignment? 5. Were outcomes assessors blind to treatment assignment? 6. Were outcomes assessors blind to treatment assignment? 7. Were treatment groups treated identically other than the intervention of interest? 8. Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analyzed? 9. Were participants analyzed in the groups to which they were randomized? 10. Were outcomes measured in the same way for treatment groups? 11. Were outcomes measured in a reliable way? 12. Was appropriate statistical analysis used? 13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

distribution of participants between groups due to small sample sizes, where the number of acute patients were greater than chronic ones.

Two other studies (34, 40) showed slight improvements in upper limb function and independence with ADLs after RT, as well as patient satisfaction and enjoyment. However, they could not conclude that robotic rehabilitation brought functional benefits. The small number of participants and the lack of a control group limited the generalizability of findings.

Four case series (35–38) concluded that repetitive training of the affected arm using a robotic device was feasible and safe in enhancing upper limb movement in both subacute and chronic patient groups. While three of these studies found statistically significant improvements in motor performance, upper limb motor scores, grip and pinch strength, lift force, and ADLs after 6 weeks of robotic assisted training, a study from Vanmulken et al. (36) noticed diverse scores in intrinsic motivation, credibility, and expectancy among participants, potentially affecting their engagement with the robotic-assisted device. Additionally, some studies did not discuss their study limitations, and the long-term results of RT were unknown.

As all studies aimed to investigate the effectiveness of RT in improving upper limb function, between-group analyses were essential to compare the performance of both intervention and control groups pre- and post-treatment. All studies reported the patients' baseline characteristics using descriptive statistics along with the mean and standard error (SE) or standard deviation (SD). Only 3 studies showed statistically significant data with p-values less than 0.05 (35, 37, 39). However, these studies failed to report CIs and only reported the p-values, increasing the likelihood of data misinterpretation and potential errors in accepting or rejecting the null hypothesis.

4. Discussion

This review was based on 7 studies that met the inclusion criteria. Among four out of these seven studies, participants with cSCIs demonstrated significant improvements in UL function, strength, grasping, and overall motor function with the implementation of RT as a primary intervention. Additionally, these studies found that repetitive UL arm training is feasible and safe for both subacute and chronic patient groups. Interestingly, patients with mild to moderate impairments showed better improvements in outcome measures when undergoing repetitive UL arm training than those with severe impairments.

Previous reviews mainly provide a broad overview on the clinical application, feasibility, and outcomes of RT alone (30, 31). They summarized that robotic assisted therapy (RAT) was shown to be feasible, safe, reduced therapists' active assistance, and had positive effects on arm function and movement quality when compared to conventional therapy alone. However, they concluded that little to no clinically significant improvements in muscle strength, grip strength, ROM, and functional activity. Although our review also showed similar findings, we also focused on the importance of implementing RT into allied health rehabilitation.

The findings from this review suggested that Allied Health Professionals (AHPs) should implement RT alongside conventional therapy as part of their rehabilitation program. This can be implemented by instructing participants to perform UL functional exercises with the use of upper extremity robots providing resistance and movement assistance to the affected limb (9). Though there are difficulties in reaching a consensus regarding the appropriate dose, frequency and optimal robot for rehabilitative training, the effectiveness of RT may impact current guidelines that do not have recommendations for robotic rehabilitation in the management of cSCI.

To minimize active-therapist time required and resources, long-term follow-ups can be utilized in group sessions to increases efficiency in care delivery. Clinical research can also help to reinforce the importance of patient-centered interventions and determines the effectiveness of treatment given (41). Engaging with developments in research, the evidence provided can help to introduce new clinically and cost-effective ways to respond to patients' needs. As PT practice aims to select and plan appropriate interventions to facilitate and restore movement and function and OT practice aims to help patients lead independent and productive lives, the findings of this review would can benefit current practice by providing AHPs with valuable insight into the effectiveness of RT as potential intervention for cSCI.

Concerning the type of intervention proposed, a very high variability was recorded in terms of robotic devices, the number of sessions per day, session duration, frequency, and joint involvement. Despite this, the lack of CIs in all studies would also increase the likelihood of statistical errors in data interpretation to decrease the credibility of the studies' findings. Although Kim et al. (39) found small improvements in motor strength and functional independence in the RT group, the differences between the groups was not statistically significant. Similarly, Sorensen et al. (40) and Zariffa et al. (34) failed to demonstrate correlation between RT and UL function. Importantly, the lack of long-term follow-up in most studies can led to challenges in determining the continuous effects of RT or lasting changes of UL function. Hence, further study should focus on the long-term effects of RT as support toward clinical benefit. Likewise, by implementing long-term follow-ups by re-assessing participants through a variety of objective measures, it can allow AHPs to observe changes in UL strength and overall performance. As supported by Cortes et al. (35), it demonstrated RT allows functional gain to be retained over time. Additionally, understanding the participants' and caregivers' perceptions of RT using qualitative methods, such as focus groups and interviews, will help to supplement a clearer view of service users' personal experiences.

Uncertainty and debating opinions around optimal robotic design limits the relevance and accessibility of robotic interventions for cSCI rehabilitation. Such factors include cost, patient satisfaction, user friendliness, comfort, convenience, time required for device set up, and its accuracy in providing repetitive UL training would need to be accounted. Implementing patient-centered designs by understanding the service users' needs allows the multidisciplinary team to design new robots or modify existing ones to tailor the needs of AHPs and service users. Robotic devices that are cost-effective, quick to setup, and allow multi-joint training are highly preferred for cSCI rehabilitation design (17). Hence, future studies should adopt rigorous outcome measures to gain deeper insight into the cost-effectiveness and accessibility of RT amongst AHPs as an intervention for participants with cSCI. Additionally, educational opportunities including training courses and in-hospital teaching seminars, and multidisciplinary team discussions regarding the development of RT can be incorporated to further equip AHPs with the knowledge and resources needed to implement RT in cSCI rehabilitation.

Furthermore, there does not seem to be sufficient research tackling on the effectiveness of RT in improving UL function in specific population groups, especially in elderly patients with central cord syndrome, the most common incomplete cSCI. To address this, conducting clinical trials with larger sample sizes focusing on elderly patient groups is highly recommended to ensure more well-rounded evidence. On the other hand, Ross et al. (42) have identified potential barriers in RCT recruitment that may lead to difficulties in recruiting specific cSCI patient groups for conducting such setup. Such that, participants with strong preferences in receiving the intervention or conventional therapy may drop out from the study when knowing they might be placed into the "sham control group" when randomization is involved. Crossover studies randomize patients to a sequence of treatments may facilitate intra-individual comparisons. This study design often requires a smaller sample size for the same statistical power compared to parallel designs, and are thus less costly. However, crossover studies are only feasible when the condition being studied is relatively stable and the intervention has a short-term effect (43). While for most robotic rehabilitation for sSCI, the intervention might not be direct to show relative stability and might require a long duration to observe such effect. Additional expenses or inconveniences, such as travelling costs and transportation difficulties, may also lead to barriers that affect participants with disabilities. Further studies should tailored on patient recruitment in accordance with the participants' needs, experiences and environment to minimize the number of dropouts and allow active patient participation in clinical trials (e.g., gender and ethnicity) (44). Moreover, researchers should also convey study information in a combination of oral, written and video methods along with professional advice from clinicians to ensure patients' understanding toward the study procedures and associated risks (45).

5. Limitations

The strength of this review was the implementation of a thorough search strategy across five databases. In addition, the JBI manual provided a comprehensive guide to conducting this systematic review. However, there remains a number of limitations that should be mentioned when interpreting our results. Firstly, the current review only includes studies published in English. The results from relevant studies published in other languages were not accounted for and could affect the outcomes of our analyses and interpretations. Secondly, the small sample sizes and lack of control groups in selected case series and non-RCTs may lead to difficulties in assessing the methodological quality, risk of bias, and generalizability of results. Thirdly, as most of the included studies were retrospective and prospective in design, the limited RCT and experimental studies can limit the identification of cause-and-effect relationships between factors. Moreover, the studies included were mainly appraised as low-quality data which can inherently lead to review bias.

6. Conclusion

This scoping review provided an overview of evidence relevant to the effectiveness of AHP-prescribed RT in improving UL function for individuals with cSCI. Among the three seemingly average quality studies, it showed no significant effects on treatment outcomes. However, short-term results from selected studies demonstrated improvements in muscle strength and UL function. This may indicate the potential of AHPs to be incorporated as RT during cSCI rehabilitation. And from the findings in three medium quality studies, it appeared that robotic therapy coupled with strengthening exercises or conventional physiotherapy can yield greater significant improvement than RT alone. However, further study with control group and proper blinding protocol would still be needed. In addition, further research on the long-term effects of UL RT, its cost-effectiveness and accessibility, protocol development, and service users' experience, would be essential to provide clinicians with a well-rounded perspective of both the clinical effectiveness and service users' experience prior to incorporating UL RT as a standard clinical regime.

Author contributions

Material preparation, data collection, and analysis were performed by JH, KK, SL, and GM. The first draft of the manuscript was written by JH and GM. SL and GM supervised the study. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1126755/full#supplementary-material

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Pay attention: you can fall! The Mini-BESTest scale and the turning duration of the TUG test provide valid balance measures in neurological patients: a prospective study with falls as the balance criterion

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Background: Balance, i.e., the ability not to fall, is often poor in neurological patients and this impairment increases their risk of falling. The Mini-Balance Evaluation System Test (Mini-BESTest), a rating scale, the Timed Up and Go (TUG) test, and gait measures are commonly used to quantify balance. This study assesses the criterion validity of these measures as balance measures.

Methods: The probability of being a faller within nine months was used as the balance criterion. The Mini-BESTest, TUG (instrumented with inertial sensors), and walking test were administered before and after inpatient rehabilitation. Multiple and LASSO logistic regressions were used for the analysis. The diagnostic accuracy of the model was assessed with the area under the curve (AUC) of the receiver operating characteristic curve. Mobility measure validity was compared with the Akaike Information Criterion (AIC).

Results: Two hundred and fourteen neurological patients (stroke, peripheral neuropathy, or parkinsonism) were recruited. In total, 82 patients fell at least once in the nine-month follow-up. The Mini-BESTest (AUC = 0.69; 95%CI: 0.62–0.76), the duration of the TUG turning phase (AUC = 0.69; 0.62–0.76), and other TUG measures were significant faller predictors in regression models. However, only the turning duration (AIC = 274.0) and Mini-BESTest (AIC = 276.1) substantially improved the prediction of a baseline model, which only included fall risk factors from the medical history (AIC = 281.7). The LASSO procedure selected gender, disease chronicity, urinary incontinence, the Mini-BESTest, and turning duration as optimal faller predictors.

Conclusion: The TUG turning duration and the Mini-BESTest predict the chance of being a faller. Their criterion validity as balance measures in neurological patients is substantial.

KEYWORDS

falling risk, neurological rehabilitation, psychometrics, criterion validity, gait assessment, balance assessment, inertial measurement unit

1. Introduction

Falls are a leading cause of injury, disability, and injury-related death (1), and an increased risk of falling afflicts people with neurological impairments (2). Hence, balance, i.e., the ability not to fall (3), is paramount in medicine, particularly in neurology and rehabilitation.

Evaluating the patient's stance, gait, and transferring ability is fundamental in assessing balance (1, 4). Once patients with poor balance are identified, treatments are available to reduce the balance impairment, eventually reducing their fall risk (5, 6).

Several rating scales have been developed for balance assessment. In these scales, clinicians rate the patient's performance in different balance tasks. Scores are typically low if the patient cannot complete the item or when the chance of falling during testing is high (7).

The Mini-Balance Evaluation System Test (Mini-BESTest) (8) is a rating scale with high content and construct validity as a balance measure. Regarding the former, any clinician likely considers the Mini-BESTest items as good balance indicators. About the latter, the Mini-BESTest complies with the Rasch analysis requirements (9–12), thus returning high-quality, unidimensional balance measures.

Timed clinical and instrumental mobility tests are also used to assess balance.

Gait speed can predict several adverse events (including falls, hospitalization, and mortality), earning the "vital sign" title (13). An increased duration of the Timed Up and Go (TUG) test (14), in which the time a person takes to rise from a chair, walk a few meters, turn, walk back to the chair and sit down is measured, can indicate an increased risk of falls (1, 6).

In recent years, an instrumented version of the TUG test has been developed (i.e., the instrumented TUG, ITUG) (15) in which patients complete the TUG donning an inertial measurement unit. With these tools, many mobility measures can be obtained from the TUG test, with some of them, such as those from the turning phase, suitable for balance assessment (16–19).

Even if different rating scales, gait, and TUG test measures have shown validity as balance measures, there is still a real need to assess their criterion validity in greater detail. In this regard, studies using the risk of falling as the balance criterion standard seem particularly valuable.

The need for further investigations is particularly true for the ITUG measures, given the relatively young age of these devices. However, this also holds for well-referenced mobility tests since results have been inconsistent from study to study [e.g., (20)]. Moreover, the same measure can predict the risk of falling in a specific population but not in another (21).

The current work aims to assess if different mobility measures, including the Mini-BESTest, gait parameters, and measures from the ITUG, have satisfactory criterion validity as balance measures in neurological patients. The probability of becoming a faller, assessed prospectively within 9 months, was used as the balance criterion.

2. Methods

This is a longitudinal, prospective, observational study. From October 2018 to September 2020, participants were recruited among those admitted to the inpatient rehabilitation unit of Casa di Cura del Policlinico (Milan, Italy) because of a neurological disability. The local ethics committee approved the study (Comitato Etico Milano Area 2; 568_2018bis), and participants gave their written consent to participate. The current work reports the primary analysis of the project.

The study's inclusion and exclusion criteria are listed below.

Inclusion criteria:

- Age > 18 years;
- Hemiparesis secondary to a stroke (ischaemic or haemorrhagic), peripheral neuropathy of the lower limbs, Parkinson's disease, or vascular parkinsonism;
- Consent to participate in the study.

Exclusion criteria

- Concomitance of two neurological diagnoses (e.g., hemiparesis and Parkinson's disease);
- The inability to complete the TUG test and the 10 m walking test without touching assistance on admission and discharge;
- A TUG duration longer than 30 s on discharge;
- Severe visual impairment or hearing loss;
- Rare neurological diseases.

The study only included stroke, peripheral neuropathies, and parkinsonism [and excluded rarer diseases also known to cause a balance and gait impairment, such as neuromuscular disorders (22)] since they represent three widespread and prototypical motor syndromes affecting gait and gross motor functions. In plain words, these three motor syndromes are common causes of increased risk of falling.

In detail, hemiparetic walking was represented by stroke patients, ataxic gait by peripheral neuropathies, and the gait disorder of the rigid-akinetic syndromes by Parkinson's disease and vascular parkinsonism.

All hemiparetic patients included here had a clinical stroke diagnosis with brain imaging (i.e., CT scan or MRI) compatible with intracerebral hemorrhage or ischaemic stroke (23). All these participants suffered persisting focal neurological deficits (i.e., hemiparesis) at the time of their inclusion in the study (23).

The criteria by Postuma et al. (24) were used for diagnosing Parkinson's disease. Vascular parkinsonism was diagnosed in case of significant signs of vascular encephalopathy in the brain CT or MRI scan associated with a clinical diagnosis of rigid-akinetic syndrome, i.e., in the case of parkinsonian features, presumably of vascular origin (25). Based on the above, patients with atypical, degenerative parkinsonism were excluded [e.g., (26)].

The peripheral neuropathy of the lower limb was diagnosed after a nerve conduction study. The peripheral neuropathy in the patients included here was axonal, sensory-motor, and length-dependent (18, 27). Diabetes was among the polyneuropathy most-frequent risk factors (18).

All patients completed 5 to 6 weeks of physiotherapy (two sessions/day, 45 min each, 5 days/week) and occupational therapy (one session/day, 45 min each, 3 days/week). The rehabilitation program followed recommendations for reducing the fall risk [e.g., (28); details can be found in (18)].

The study's sample size was calculated as follows: in line with previous reports on the risk of falling in neurological patients [e.g., (29)], it was estimated that about 50% of participants would fall within 1 year. Based on this estimate, considering that each participant was followed up for 9 months and that the logistic regression was used for the primary analysis, we planned to recruit at least 213 patients. In this way, it was reasonable to expect at least 80 fallers in the nine-month study, a total number of cases that permits simultaneously assessing up to seven predictors in the logistic regression models (30). In estimating the maximum number of predictors simultaneously testable in a (logistic) regression model (here, seven plus the regression intercept), the "10 events per variable" rule of thumb was applied (31).

The STROBE checklist for reporting cohort studies was followed (32).

2.1. Falls recording

Falls, i.e., events "during which a person inadvertently comes to rest on the ground or other lower level" (1), were recorded 9 months after the rehabilitation discharge.

Participants received a monthly paper calendar and were asked to annotate on this calendar if a fall occurred and the day it happened (33). Moreover, research staff contacted all participants at the end of the first, second, third, sixth, and ninth months from discharge to maximize compliance.

Participants were classified into non-fallers, fallers, and recurrent fallers according to the number of falls they experienced in the observation period. In particular, fallers fell just once, and recurrent fallers were those with two or more falls in the follow-up period (34).

2.2. Participants' gait and mobility testing

The Mini-BESTest (8), the 10 m walking test (35), and the ITUG (15) were administered to each participant at rehabilitation admission and discharge.

The three-meter variant of the TUG test (14) was performed here (turning point marked by a traffic cone) and recorded with an inertial measurement unit (mHT-mHealth Technologies, Bologna, Italy) secured to the participant's back (15, 17, 18).

The Mini-BESTest balance measure (36) was expressed in logits (the higher, the better the balance), the measurement unit from the Rasch analysis.

The patient's disability was measured with the Functional Independence Measure (FIM) (37) in both assessment sessions (motor and cognitive domains). Finally, additional participants' information was collected on admission only, including age, gender, and diagnosis.

Details on the measures collected here are given in Supplementary appendix 1.

2.3. Statistical analysis

The criterion validity of the Mini-BESTest, gait, and ITUG measures was assessed by testing their ability to predict the probability of being a faller within 9 months after discharge. Multiple logistic regression and the Least Absolute Shrinkage and Selection Operator (LASSO) logistic regression were used.

Overall, 12 variables were assessed as potential faller predictors, including five features from the medical history:

1. age (years),
2. gender (male vs. female),
3. acute vs. chronic condition,
4. cognitive impairment (present vs. absent) and
5. urinary incontinence (present vs. absent).

Acute patients were those transferred to rehabilitation from an acute hospital. Chronic ones were admitted from the community (19). Cognitive impairment was diagnosed from the total score of the FIM cognitive domain (no impairment if the cognitive domain total score was $\geq$33). Urinary incontinence was also derived from the FIM scale (no incontinence if item 7 was $\geq$6).

Four gait and mobility measures were tested as predictors:

6. GS: gait speed (m/s),
7. WR: walk ratio (cm/number of steps/min),
8. MB: Mini-BESTest interval measure (logits) and
9. TUG: the total duration (s) of the TUG test.

Finally, three measures from the ITUG test were assessed:

10. STW: duration (s) of the sit-to-walk phase,
11. Turn: duration (s) of the first turning phase,
12. ω: peak angular velocity (°/s) along the vertical axis during the first turning phase.

All predictors, except variables 1–3 from the medical history, came from the discharge assessment.

2.3.1. Criterion validity assessment

First, a multiple logistic regression model was arranged with variables 1–5 as predictors and faller status as the response variable. This model, nicknamed "h" since it only contains variables from medical history, was the reference model.

Next, balance and gait measures were added to model h. The following models, called "h+," were evaluated:

1. h + GS, i.e., containing all the variables included in model h plus gait speed (GS);
2. h + WR;
3. h + MB;
4. h + TUG;
5. h + STW;
6. h + Turn;
7. h + ω.

A mobility measure had criterion validity if (i) it was a significant predictor of the faller status per the likelihood ratio test and (ii) the AIC of its h + model was smaller than the one of model h, with a difference >2 in absolute value (38).

The AIC difference was also calculated to compare the criterion validity of the different balance and gait measures. AIC differences <2 indicate that the two models are equally good. Differences >4 suggest that the model with the smallest AIC is sensibly better than the candidate model.

The diagnostic accuracy of model h and models h + was assessed by calculating the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. The AUC's 95% confidence intervals (95% CI) were calculated with bootstrap (10^4 replicates).

LASSO logistic regression was used to investigate criterion validity further (39). The variables subdued to the LASSO regression were all the variables from model h plus the mobility measures from h + models whose AIC difference to model h was >2.

If the mobility measures were selected as predictors by the LASSO procedure, this was considered confirmatory evidence of criterion validity. Note that this analysis assessed gait and mobility measures simultaneously rather than separately, as done previously.

A secondary analysis was run with recurrent faller as the response variable (i.e., participants who have fallen at least twice vs. non-fallers or fallen only once). For sample size reasons, only the LASSO logistic regression was used for this analysis.

Finally, simple logistic regression was employed to provide reasonable cut-offs for the clinical application of the measures with good criterion validity. In detail, three probabilities of being a faller (i.e., 0.25, 0.50, and 0.75) are used to identify as many balance measure cut-offs and define four ranges of balance impairment. Patients whose balance measure (upper cut-off, say of the Mini-BESTest interval measure) is associated with a probability of being a faller <0.25 are considered to suffer a mild balance impairment. Those whose balance measure is associated with a faller probability between 0.25 and 0.50 are considered to have a moderate balance impairment. Finally, those with a severe and markedly severe balance impairment have a balance measure associated with a faller probability between 0.50 and 0.75 and >0.75, respectively. A sensitivity and specificity analysis was eventually calculated on the measurement cut-offs.

Like any regression, logistic regression is susceptible to extreme observations. In the current study, the duration of the turning and sit-to-walk phases presented some "far-outs" (40), and their distribution was right-skewed, similar to other TUG duration measures [e.g., (41, 42)]. Regarding the far-out observations, these were defined according to Tukey (40) as the observations more extreme than the third (or first) quartile plus (or minus) three times the interquartile range. Because of far-outs and skewness, turning and sit-to-walk durations were ln-transformed before entering the regression models, a solution that effectively worked out this statistical issue.

The median and the first to third quartile (1st–3rd Q) were used as central tendency and dispersion measures, respectively. The Wilcoxon test was used to test paired comparisons (e.g., change in the mobility measures before and after rehabilitation).

R version 4.2.0 was used for statistics and graphics. See Supplementary appendix 1 for details on the LASSO logistic regression.

3. Results

Of the 353 patients included in the study, 214 were retained for the primary analysis (Figure 1). Most participants (57.0%) had hemiparesis secondary to a stroke, followed by patients with peripheral neuropathy (24.3%; Table 1).

During the nine-month follow-up, 166 falls were recorded from 82 patients. Forty-two participants were recurrent fallers. Most falls caused no injury, while 38 were injurious falls. Of these, 25 caused a contusion, and seven a contused lacerated wound. Five resulted in a limb fracture, including a hip fracture, and one in a subdural haematoma.

A full description of the sample is given in Supplementary appendix 2.

3.1. Criterion validity analysis: fallers identification

The AUC of model h was 0.66 (95% CI: 0.59–0.74), pointing out some ability of this model to distinguish fallers from non-fallers. The AUC of h + models was also larger than 0.5 and negligibly higher than that of model h (Table 2).

When h+ models were contrasted with model h (likelihood ratio test), the Mini-BESTest ($p = 0.006$), TUG ($p = 0.040$), and turning duration ($p = 0.002$) and the peak angular velocity during turning ($p = 0.023$) were significant faller predictors.

Figure 2 shows the AIC of model h and h+ models. Considered altogether, significance testing and the AIC analysis indicated that turning duration and the Mini-BESTest were the mobility measures with the highest criterion validity for fall risk assessment.

The LASSO logistic regression substantially confirmed these findings. The Mini-BESTest measure and the turning duration were the only mobility measures selected as predictors of being a faller by the LASSO procedure, alongside gender, chronicity, and urinary incontinence (Figure 3A).

The AUC of this model was 0.69 (95%CI: 0.62–0.76).

According to the LASSO logistic regression, the chance of being a faller was higher for female patients than male patients, chronic than acute patients, and patients with urinary incontinence. Participants with low Mini-BESTest scores and high turn duration had a higher probability of becoming a faller.

3.2. Criterion validity analysis: identification of recurrent fallers

Figure 3B shows the results of the LASSO logistic regression with recurrent faller status as the response variable.

The LASSO procedure only selected chronicity, cognitive impairment, and the Mini-BESTest measure as optimal predictors (AUC: 0.71; 95%CI: 0.62–0.79).

3.3. Will my patient fall? Tentative cut-offs for fall risk assessment

Figures 4A,B show the relationship, from simple logistic regression, between the Mini-BESTest measure and the probability of being a faller and a recurrent faller, respectively. For application in the clinic, the

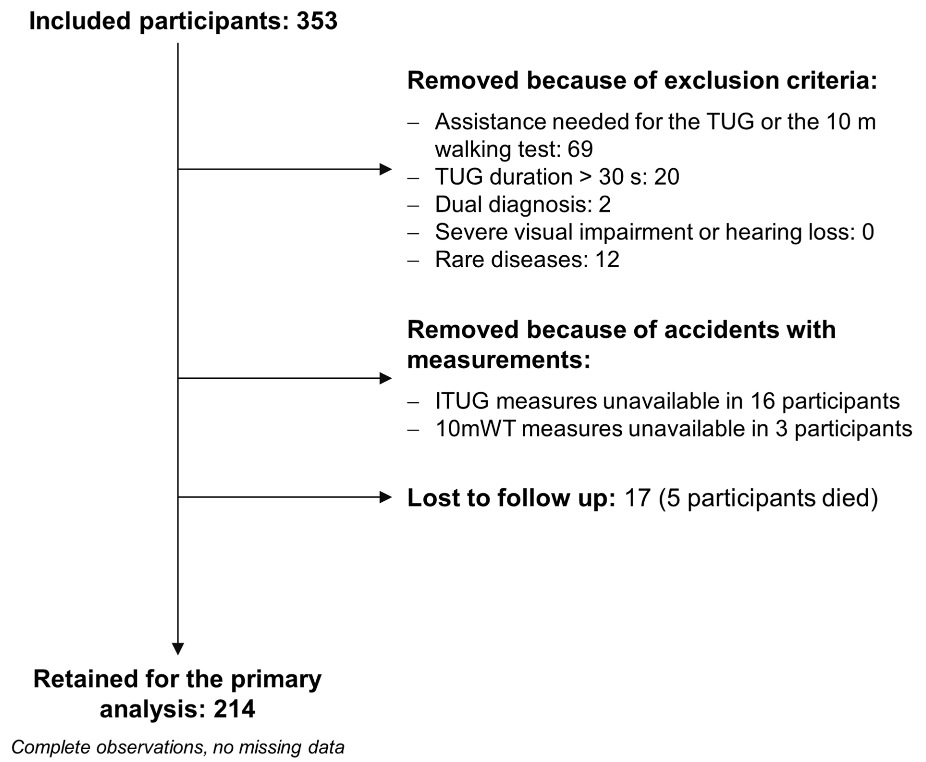

FIGURE 1
Study flow diagram. Regarding the two patients with a dual diagnosis, one had undefined peripheral neuropathy plus myopathy, and the second suffered hemiparesis due to a stroke and Parkinson's disease. Eleven patients were affected by an uncommon polyneuropathy (e.g., chronic inflammatory demyelinating polyneuropathy, genetic demyelinating neuropathies), and one patient had a rare stroke (stroke in Behcet's disease). Due to unexpected problems with the inertial sensors (e.g., the sensors were not fully charged), instrumented TUG (ITUG) measures were unavailable for 16 patients. Three patients were excluded because of an operator error during the 10 m walking test (10 mWT). The primary analysis consisted of logistic regression modeling with faller vs. non-faller as the response variable.

probability of being a faller was used to split the Mini-BESTest measures into four ranges, defining four levels of balance deficit.

Figure 4C shows the relationship between the (back-transformed) duration of the TUG turning phase and the probability of being a faller. Again, four levels of balance impairment were distinguished from faller probability.

The Mini-BESTest cut-off separating mild and moderate balance deficit (i.e., 2.94 logits; the test is positive if the Mini-BESTest measure is below this threshold) had a sensitivity of 0.92 (specificity: 0.20; Table 3) for faller identification, thus identifying with a good approximation those subjects less at risk of falling due to a balance disorder. The 0.06 logits cut-off, which marks the limit between a moderate and severe balance deficit, had a specificity of 0.86 (sensitivity: 0.29).

For the turning duration, the cut-off between a mild and moderate balance impairment (1.91 s, back-transformed; the test is positive if the turning duration is above this threshold) had a sensitivity of 0.96 (specificity: 0.16). The 3.80 s cut-off had a specificity of 0.87 (sensitivity: 0.24; Table 3).

4. Discussion

The current study shows that the Mini-BESTest scale and the duration of the turning phase of the TUG test measured with an inertial measurement unit have substantial criterion validity as balance measures.

Both these measures predict the patient's probability of being a faller within 9 months. In addition, the Mini-BESTest (but not the turn duration) is also valid for predicting the chance of being a recurrent faller.

Assessing criterion validity involves assessing the degree to which the measures adequately reflect those from a criterion standard (43). In the current study, fall risk is supposed to be the criterion standard for balance.

Relating balance directly to falls is well-aligned with the balance construct definition and with previous studies evaluating the criterion validity of balance measures.

Balance has been defined as a person's ability not to fall (3). Therefore, a fall indicates, by definition, that a person has a decreased "ability not to fall" and hence a poor balance. Furthermore, when a person is about to fall during a motor task, it indicates that the "ability not to fall" is reduced. In this regard, the lowest balance level is indicated in some items of the Performance Oriented Mobility Assessment – Balance (POMAB), the Berg balance scale, and the Mini-BESTest (likely the most used balance scales) by a fall or a near-fall (7).

Finally, the current work aligns with studies in which the criterion validity of other balance tests has been evaluated by testing their ability to predict falls [e.g., (33, 44)]. Some authors have stated that a measure of balance that identifies individuals prone to falling has predictive (i.e., criterion) validity (45).

TABLE 1 Participants' clinical characteristics.

Age, years, median (1st–3rd Q)		76.2 (66.7–81.2)	
Gender, *N* (%)	Males	124 (57.9)	
	Females	90 (42.1)	
Condition, *N* (%)	Acute	102 (47.7)	
	Chronic	112 (52.3)	
Diagnosis, *N* (%)	Hemiparesis	122 (57.0)	
	PNLL	52 (24.3)	
	PD	21 (9.8)	
	VP	19 (8.9)	
Cognitive impairment, *N* (%)	Present	80 (37.4)	
	Absent	134 (62.6)	
Assistive device, *N* (%)	Yes	101 (47.2)	
	No	113 (52.8)	
Urinary incontinence, *N* (%)	Present	33 (15.4)	
	Absent	181 (84.6)	
Motor FIM, score, median (1st–3rd Q)	Admission	67 (51–75)	$p < 0.001$
	Discharge	81 (75–86)	
Mini-BESTest, logits, median (1st–3rd Q)	Admission	0.17 (−0.53–1.32)	$p < 0.001$
	Discharge	1.32 (0.17–2.31)	
Gait speed, m/s, median (1st–3rd Q)	Admission	0.76 (0.58–1.02)	$p < 0.001$
	Discharge	0.96 (0.74–1.17)	
Step length, m, median (1st–3rd Q)	Admission	0.46 (0.38–0.55)	$p < 0.001$
	Discharge	0.50 (0.43–0.60)	
Cadence, steps/s, median (1st–3rd Q)	Admission	1.73 (1.52–1.93)	$p < 0.001$
	Discharge	1.90 (1.70–2.06)	
Walk ratio, cm/steps/min, median (1st–3rd Q)	Admission	0.46 (0.38–0.52)	$p = 0.136$
	Discharge	0.45 (0.39–0.52)	
Total TUG duration, s, median (1st–3rd Q)	Admission	17.3 (12.7–23.0)	$p < 0.001$
	Discharge	13.7 (10.9–17.9)	
Sit-to-Walk duration, s, median (1st–3rd Q)	Admission	1.32 (1.18–1.58)	$p < 0.001$
	Discharge	1.27 (1.13–1.48)	
Turn duration, s, median (1st–3rd Q)	Admission	3.12 (2.26–3.98)	$p < 0.001$
	Discharge	2.76 (2.16–3.34)	
Turn peak angular velocity, °/s, median (1st–3rd Q)	Admission	89.5 (71.6–114.5)	$p < 0.001$
	Discharge	104.6 (83.6–127.7)	

The FIM motor score and the mobility measures were collected on admission and discharge from inpatient rehabilitation. The presence of cognitive impairment, using an assistive device for independent walking, and urinary incontinence are from the evaluation at discharge. 1st–3rd Q: first to third quartile; N: number of *p*-values from the Wilcoxon signed rank test with continuity correction are in the rightmost column. The Wilcoxon test was used to assess a change in the mobility and disability measures between admission and discharge. Mini-BESTest measures are expressed in logits. As a total raw score, the median value of the Mini-BESTest measures corresponded to 14 (0.17 logits) at admission and 19 (1.32 logits) at discharge.

Supplementary appendix 3 reports an excursus on the validity of mobility measures when used as balance measures.

4.1. Balance measures in the clinic: predicting the risk of falling

The ability to predict falls of some of the mobility measures evaluated here has already been studied (21), meaning it seems essential to clarify what our work adds to the present state of knowledge.

First, only neurological patients with mobility impairment have been recruited here. While deeply investigated in community-dwelling (including independent) participants of older age, falls are less studied in more severely impaired patients (5).

Moreover, unsurprisingly, a test that works well in community-dwelling, independent persons may not work well when applied to disabled individuals. For example, the TUG test does not discriminate

TABLE 2 Validity analysis of the gait and mobility measures: multiple logistic regression.

Model	b	e^b	p-values	AUC (95% CI)	AIC
h				0.66 (0.59–0.74)	281.7
Age, years	0.00	1.00			
Gender, male	−0.57	0.56			
Condition, chronic	0.76	2.15			
Cognitive impairment, yes	0.31	1.36			
Urinary incontinence, yes	0.65	1.92			
h + GS				0.67 (0.60–0.74)	280.2
Gait speed, m/s	−0.98	0.37	0.063		
h + WR				0.67 (0.59–0.74)	283.3
Walk ratio, cm/steps/min	0.97	2.64	0.565		
h + MB				0.69 (0.62–0.76)	276.1
Mini-BESTest, logits	−0.29	0.75	0.006		
h + TUG				0.68 (0.61–0.75)	279.4
TUG duration, s	0.06	1.06	0.040		
h + STW				0.67 (0.60–0.74)	280.4
STW duration, s	1.31	3.72	0.069		
h + Turn				0.69 (0.62–0.76)	274.0
Turn duration, s	1.45	4.24	0.002		
h + ω				0.68 (0.60–0.75)	278.5
Peak angular velocity, °/s	−0.01	0.99	0.023		

Coefficients (b) and exponentiated coefficients (e^b) from the multiple logistic regression models. h: model h, the model only includes fall risk factors from the medical history. h+: models including the fall risk factors from the medical history (i.e., the same variables included in model h) plus a single gait or mobility measure. For example, in h + GS the gait speed (GS) is added to the risk factors from model h. WR, walk ratio; MB, Mini-BESTest; TUG, total duration of the TUG test; STW, sit-to-walk duration; Turn, TUG turning duration; ω, peak of the vertical angular velocity during turning. Only the estimate of the mobility measure is reported for the h + models. p-value: type 1 error probability of the likelihood ratio test comparing model h with one of the seven h + models. p-values < 0.05 indicate that adding the mobility measure to the fall risk factors from the history increases the model's predictive accuracy. Therefore, the added mobility measure is a significant faller predictor. The area under the curve (AUC) and the Akaike information criterion (AIC) of the h and h + models are also reported. 95% CI: 95% confidence intervals of the AUC.

fallers from non-fallers in high-functioning elderly. On the contrary, it is more valuable in lower-functioning older people (21).

Patients suffering from a neurological disorder, like those studied here, are "by definition" at an increased risk of falling (2). However, in the clinic, it is crucial to discriminate the patients at a very high risk of falling from those at a relatively lower risk. This practical question prompted the current study.

The definition of the four levels of balance impairment (Figure 4) and the sensitivity and specificity analysis of meaningful cut-offs for the Mini-BESTest and the turning duration try to answer this question.

For both the Mini-BESTest and the turn duration, the cut-off that demarcates a mild from a moderate balance impairment has a high sensitivity (>0.90) and poor specificity for identifying a faller. In contrast, the cut-off between moderate and severe balance deficit has high specificity (>0.85) but low sensitivity. Therefore, these cut-offs could work as "SnOUT" and "SpIN" tests, respectively (46).

In addition, these cut-offs could be of great interest for setting therapeutic goals. For example, improving the patients' balance above 2.94 Mini-BESTest logits through rehabilitation could be considered a clinically important goal since falling is substantially less probable beyond this threshold.

The same reasoning applies to the 1.91 s turning duration threshold.

The current study is not the first to evaluate the Mini-BESTest ability to predict falls. However, in several studies, falls have been collected retrospectively [e.g., (47–50)]. The results of our study align well with other studies in which the Mini-BESTest was anchored to prospective falls, confirming this scale has a sensible capacity in fall risk assessment [e.g., (51)].

A novelty of our work is that the ability in fall risk evaluation of measurements from inertial sensors, like the Turning duration, has also been considered. Research that assesses the risk of falling from movement measures obtained with these devices is still a young field. For example, a recent meta-analysis showed that using sensor measures during walking and sit-to-stand actions can discriminate between fallers and non-fallers but the same meta-analysis concluded that their discrimination accuracy remains undetermined (52).

In addition, it should be stressed that similar to the Mini-BESTest, retrospective (i.e., history of falls) rather than prospective falls (as done here) are often used as the criterion standard (53). In this regard, it is noteworthy that using fall history as the standard for classification has been criticized by some scholars in fall risk assessment studies (54).

Finally, the findings concerning the walk ratio are noteworthy as among the seven gait and mobility measures, the walk ratio performed worse in terms of faller risk assessment. As with any negative result,

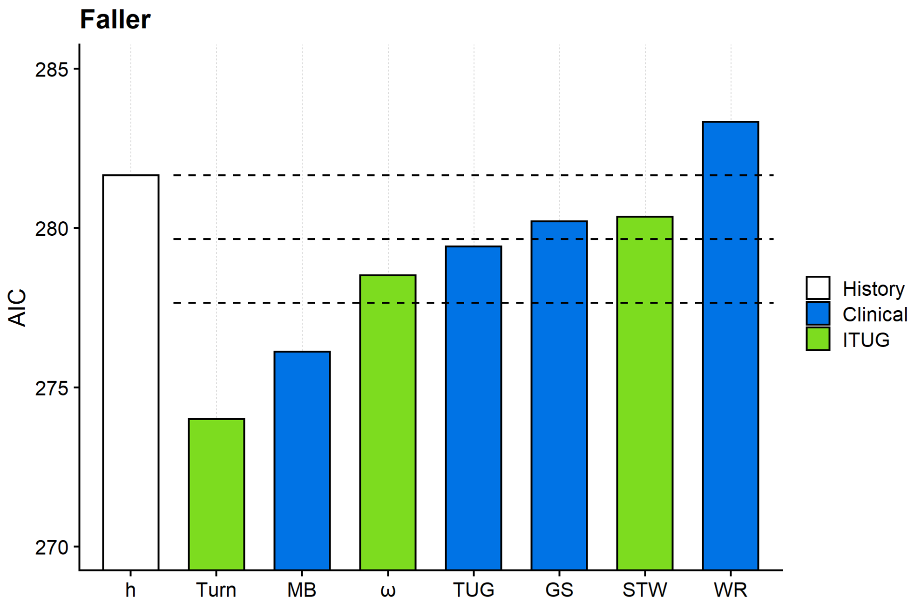

FIGURE 2
Comparing the criterion validity of the gait and mobility measures. The figure shows the Akaike information criterion (AIC) of model h and the seven h + models. Model h (white column) includes only fall risk factors from the medical history. For graphical reasons, Turn abbreviates model "h + Turn," MB model "h + MB" and so on. Turn: duration of the TUG turning phase; MB: Mini-BESTest; ω: peak angular velocity along the vertical axis during the TUG turning phase; TUG: total TUG duration; GS: gait speed; STW: sit-to-walk duration; WR: walk ratio. Mobility measures from clinical tests and ITUG are given in blue and green, respectively. The uppermost horizontal dashed line marks the AIC of model h. The second and the third horizontal dashed lines mark −2 and −4 from the model h's AIC. The response variable was the faller status (faller vs. non-faller) in all models.

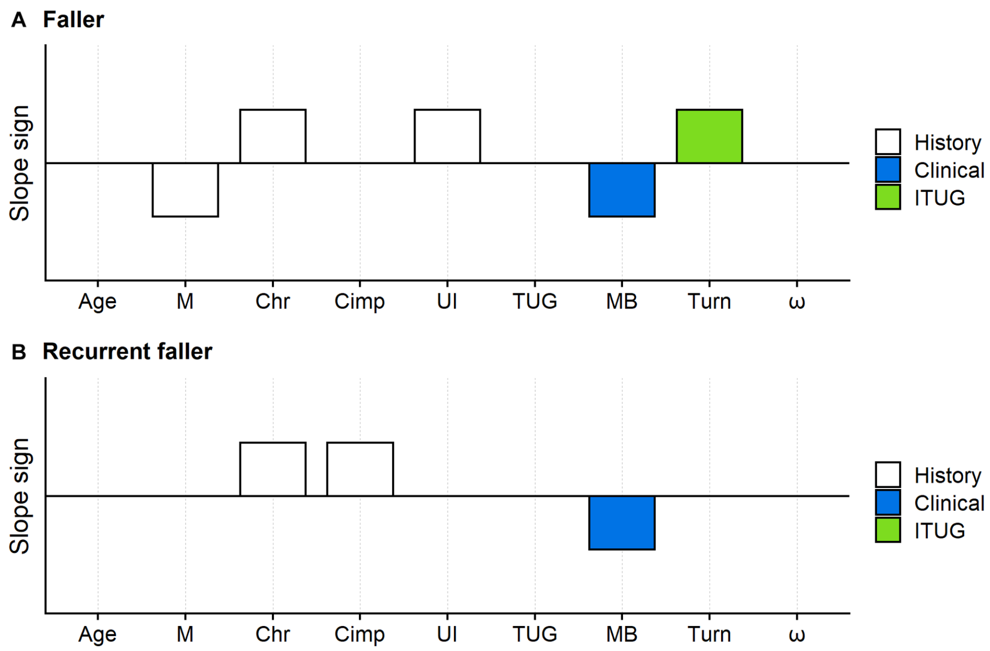

FIGURE 3
Faller and recurrent faller optimal predictors: results of the LASSO logistic regression. The variables simultaneously tested in the LASSO logistic regression models were: age, gender (M: male), condition (Chr: chronic disease), cognitive impairment (Cimp), urinary incontinence (UI), the TUG test total duration (TUG), the Mini-BESTest (MB) and the turn duration of the TUG test (Turn). White bars: fall risk factors from the medical history; blue bars: mobility measures from clinical tests; green bars: ITUG measures. The bars mark the predictors selected by the LASSO procedure, while variables without bars are those whose coefficients were shrunk to zero by the LASSO. Upward bars indicate positive predictors' coefficients (i.e., variables positively associated with the faller or recurrent faller risk). Downward bars indicate otherwise. For example, M decreased the risk of being a faller, while Chr increased this risk. According to the LASSO logistic regression, the predictors of the optimal model for faller risk assessment **(A)** were: male gender, chronicity, urinary incontinence, the Mini-BESTest logit measure, and the turn duration. Optimal predictors for recurrent faller **(B)** were chronicity, cognitive impairment, and the Mini-BESTest.

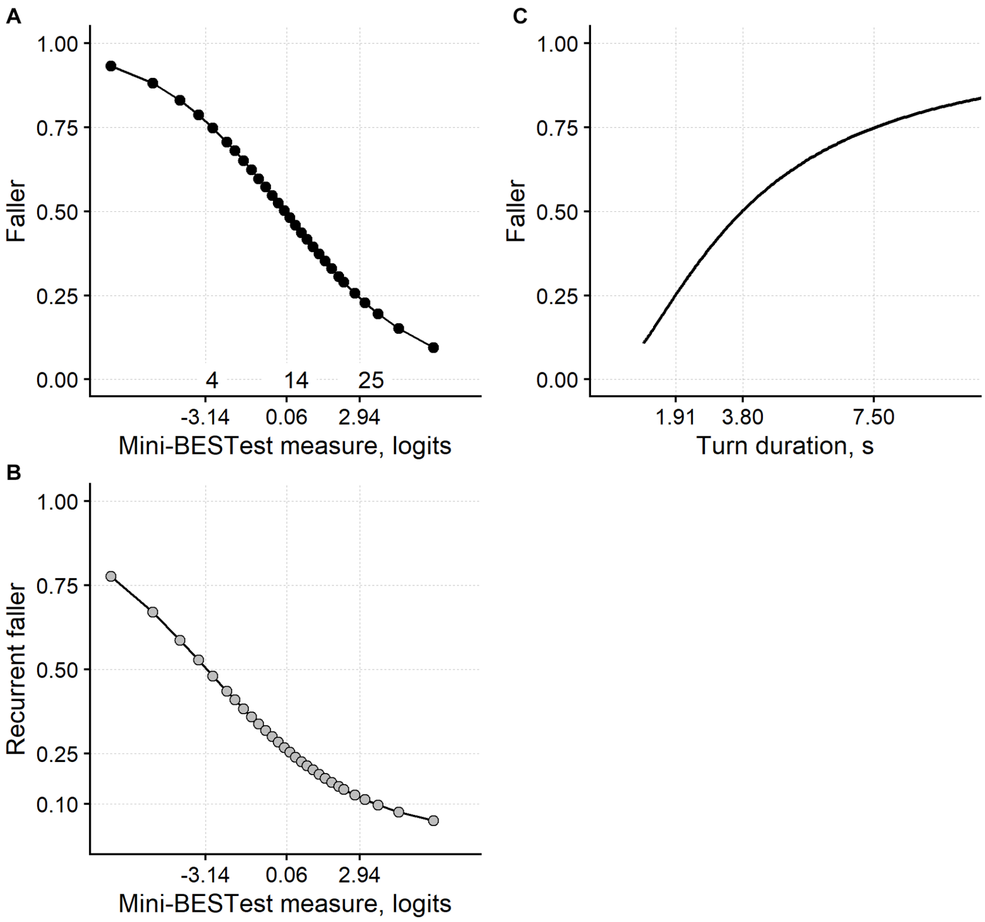

FIGURE 4
Fall risk assessment from the Mini-BESTest and the turn duration. **(A)** The relationship between the Mini-BESTest logit measure and the probability of being a faller within 9 months. **(B)** The relationship between the Mini-BESTest and the probability of being a recurrent faller. **(C)** The relationship between the turn duration and the faller probability. The curves are derived from simple logistic regression models. As expected from the main analyses, the Mini-BESTest has been confirmed as a significant predictor of the chance of being a faller (likelihood ratio test, $p < 0.001$) and a recurrent faller ($p = 0.003$). Turning duration significantly predicted the chance of being a faller ($p < 0.001$). Turn duration was ln-transformed for modeling and is plotted here back-transformed. Faller probability (0.25, 0.50, and 0.75) can be used to define four ranges of balance impairment delimited in the three plots by the vertical dashed lines. For example, it is proposed that a person measuring more than 2.94 logits on the Mini-BESTest (i.e., scoring ≥25) suffers a mild balance impairment since their risk of falling is <0.25. A person measuring between 0.06 and 2.94 logits suffers a moderate balance impairment and so on for a severe and very severe balance deficit. The same reasoning applies to the turn duration. The numerals "4," "14," and "25" in panel **(A)** correspond to the Mini-BESTest total ordinal score immediately above the logit thresholds.

we feel that more research is needed before concluding that the walk ratio has no criterion validity for balance assessment.

The walk ratio could work in fall risk assessments when other versions of the walking test are administered [e.g., fast walking (55)]. Interestingly, and potentially in line with the current findings, it has been shown that a reduced walk ratio is associated with fall risk in people with high gait speed (>1.0 m/s) but not in impaired persons walking at a lower speed (<1.0 m/s) (56).

A peculiar feature of the walk ratio is that it is constant at different walking speeds, indicating that gait speed is increased by raising both step length and cadence. Therefore, when the walk ratio decreases, which is generally the case here, an actual motor control law is violated.

Although disappointing, that a parameter with strong physiological and pathophysiological validity, such as the walk ratio, does not work well in the clinic is not an unusual finding. Regarding the fall risk assessment, this seems to be the case with dynamic posturography. In dynamic posturography, patients stand on moving platforms: the face validity of this task for assessing balance is unquestionable. However, surprisingly enough, dynamic posturography could not predict falls (57).

Not only the walk ratio but also gait speed performed poorly in the current study. This is an unexpected finding (58), given the recommendations of some authoritative studies (1, 2). In summary, gait parameters seemed to perform less well than other mobility measures in fall risk assessment.

4.2. Study's limitations and future developments

First, the diagnostic accuracy of the models tested here is limited. Even if the AUCs of the ROC curves are significantly larger than 0.5,

TABLE 3 Sensitivity and specificity analysis of the cut-offs proposed for fall risk assessment.

MB			Turning duration		
Cut-off: 0.06 logits (14)			*Cut-off: 3.80 s*		
	Fallers	**Non-fallers**		**Fallers**	**Non-fallers**
Positives	24	18	Positives	20	17
Negatives	58	114	Negatives	62	115
Sn: 0.29; Sp: 0.86			Sn: 0.24; Sp: 0.87		
Cut-off: 2.94 logits (25)			*Cut-off: 1.91 s*		
	Fallers	**Non-fallers**		**Fallers**	**Non-fallers**
Positives	75	106	Positives	79	111
Negatives	7	26	Negatives	3	21
Sn: 0.92; Sp: 0.20			Sn: 0.96; Sp: 0.16		

MB, Mini-BESTest scale; Sn, sensitivity; Sp, specificity. For the MB scale, the cut-offs are provided as interval measures expressed in logits and total ordinal scores (in brackets). Turning duration cut-offs are provided back-transformed as in Figure 4. Participants are classified as fallers or non-fallers and as positive or negative to tests. Hence, fallers testing positive are true positives, non-fallers testing negative are true negatives, fallers testing negative are false negatives, and non-fallers testing positive are false positives. The MB scale and the Turning duration are used as tests to detect the patient who will fall, i.e., the test is considered positive when the measure flags a person as a future faller. Therefore, the MB is positive if its measure (or ordinal score) is below the cut-off value. The turning duration is positive if above the cut-off.

these are 0.7 at most. However, these AUC values align with previous reports on fall risk assessment [e.g., (21, 33, 59)].

Caveats should be put forward regarding the sensitivity and specificity analysis of the Mini-BESTest and turn duration cut-offs. Tests with high sensitivity but insufficient specificity could work suboptimally to "rule out" a condition. The same applies when tests with high specificity, but reduced sensitivity, are used to "rule in" a condition (46). Altogether, these facts strengthen the idea that the current work should be considered a metrology study about validity rather than a diagnostic one.

As reported in the Methods section, the diseases included in the sample represented three primary motor syndromes: hemiparesis, parkinsonism, and sensory ataxia. This classification is reasonable for syndrome-level disciplines such as Physical and Rehabilitation Medicine in the first place. However, we have to admit that it could be limited for the neurologist.

Future development of this line of research could consider the patients' neurological profiling in greater detail. In this context, it is also noteworthy that disease-specific scales such as the National Institutes of Health Stroke Scale (NIHSS) or the Unified Parkinson's Disease Rating Scale (UPDRS) could have a fall risk prediction value that has not been considered here.

We also feel it important to stress that while we generally refer here to fall risk assessment in "neurological patients," our findings apply only to the three motor syndromes studied here. Future works are needed to assess the falling risk in rare and selected neurological diseases (e.g., demyelinating polyneuropathies, atypical parkinsonisms, neuromuscular disorders).

Regarding the patients recruited, we excluded those needing more than 30 s to complete the TUG test. However, in some patients, the TUG test duration can be longer, with studies reporting TUG test durations of two or more minutes [e.g., (60)]. Taking this into account, the current work did not consider those persons with a motor impairment of extreme severity, which could be those with the highest falling risk.

Clinical and methodological reasons prompted the approach used in this study. First, it is obvious that a TUG test duration >30 s already flags a clinically severe mobility impairment. In this regard, it should be stressed that 30 s is approximately three times the upper limit of the "healthy" 3 m TUG test duration (60). As rehabilitation clinicians, we believe that when the gait and balance impairment is so severe, there is likely little added value from a timed or even instrumented test. In these cases, scales, even relatively simple and classical ones such as the Performance Oriented Mobility Assessment's balance domain (61), can fruitfully serve the job.

From a methodological point of view, software algorithms have been used here to automatically split the TUG test into different phases and obtain measures from them. While the dependability of these algorithms has been demonstrated (15), it should also be noted that automatic algorithms can fail, for example, in selected populations such as frail individuals (62). In this regard, it seems reasonable that the more gait and mobility are pathological (e.g., the slower the patient), the more challenging it will be for the algorithms to recognize mobility patterns and thresholds for TUG test segmentation.

As another methodological point, defining no upper limitation to the TUG test duration would allow the inclusion of persons with a TUG test duration of 60 s or even longer. Even when participants suffering from a severe mobility impairment can be found (60), they are likely a minority. In addition, people who can walk without physical assistance (see the second exclusion criterion) with such a long TUG test duration would be even rarer. Including these persons would increase the chance of including far-outs in the dataset, a statistical issue carefully considered in the primary analysis (see the Methods section).

As reported above, the fact that gait speed does not predict falls is an unexpected finding given its importance in the patients' assessment (13). In a sense, gait speed is an omnibus measure since it is the product of step length and step cadence (i.e., step frequency). It can be hypothesized that if even just one of these two component measures is corrupted by a significant measurement error (63), gait speed accuracy in fall risk evaluation would also be compromised. Based on this consideration and the results reported here, assessing the criterion validity in fall prediction and balance assessment of step length and step cadence separately is a reasonable continuation of the current line of research.

4.3. Conclusion

The conclusions of this study are as follows: (i) the Mini-BESTest scale and the turn duration of the TUG test predict the probability of a neurological patient falling at least once in 9 months; (ii) the Mini-BESTest, but not the turn duration, also predicts the patient's probability of becoming a recurrent faller (i.e., falling two or more times); and (iii) the criterion validity of the TUG turning duration as a balance measure is high, and that of the Mini-BESTest is even higher.

Adopting the "seeing to foresee, foreseeing to provide" motto, correctly predicting the risk of falling allows adequate fall prevention through information on behaviour and pharmacological and non-pharmacological interventions. In this line of reasoning, an obvious next step in the current line of research is developing algorithms simultaneously including all the relevant variables for fall risk assessment to obtain an instrument to accurately define the risk of falling at a single-person level.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Comitato Etico Milano Area 2, Milan, Italy. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AC and MC: study conception. MP, EA, GP, VR, and PA: data collection. MP, GG, PA, and CM: database organization. AC: statistical analysis, figures' preparation, writing the first draft of the manuscript, and manuscript review according to the co-author modifications. MP, SS, CM, PT, GG, EA, GP, VR, PA, and MC: manuscript commenting. All authors contributed to the article and approved the submitted version.

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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.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1228302/full#supplementary-material

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Change in sensory integration and regularity of postural sway with the suspensory strategy during static standing balance

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Background and aim: The suspensory strategy, a method for controlling postural balance in the vertical direction of the center of mass (COM), is considered by the elderly as a means of balance control. The vertical COM control might alter the sensory integration and regularity of postural sway, which in turn impacts balance. However, to date, this was not confirmed. Thus, this study aimed at investigating the influence of the suspensory strategy achieved through knee flexion on the static standing balance.

Methods: Nineteen participants were monitored at knee flexion angles of 0°, 15°, and 65°. Time-frequency analysis and sample entropy were employed to analyze the COM data. Time-frequency analysis was utilized to assess the energy content across various frequency bands and corresponding percentage of energy within each frequency band. The outcomes of time-frequency are hypothesized to reflect the balance-related sensory input and sensory weights. Sample entropy was applied to evaluate the regularity of the COM displacement patterns.

Results: Knee flexion led to a decreased COM height. The highest energy content was observed at 65° knee flexion, in contrast with the lowest energy observed at 0° in both the anterior–posterior (AP) and medial-lateral (ML) directions. Additionally, the ultra-low-frequency band was more pronounced at 65° than that at 0° or 15° in the ML direction. Furthermore, the COM amplitudes were notably higher at 65° than those at 0° and 15° in the AP and ML directions, respectively. The sample entropy values were lower at 65° and 15° than those at 0° in the ML direction, with the lowest value observed at 65° in the vertical direction.

Conclusion: The suspensory strategy could enhance the sensory input and cause sensory reweighting, culminating in a more regular balance control. Such suspensory strategy-induced postural control modifications may potentially provide balance benefits for people with declining balance-related sensory, central processing, and musculoskeletal system functions.

KEYWORDS

sensory integration, sensory input, sensory weights, time-frequency analysis, postural regularity, sample entropy, suspensory strategy, knee flexion

1. Introduction

Maintaining upright balance depends on the capacity to maintain the center of pressure (COP) and/or center of mass (COM) within or anticipated to stay within the base of support (BOS) (1, 2). In this context, ankle and hip strategies established in the postural control during the standing posture effectively drive the COP and COM within the BOS, particularly in the anterior–posterior (AP) and medial-lateral (ML) directions (3). However, the COM control during fall prevention is not limited to the two-dimensional control on the horizontal plane but also involves COM vertical control (3, 4). In addition to the ankle and hip strategies, the suspensory strategy is the third postural strategy which employs flexing of the knee joints to lower the COM toward the base of support and achieve COM vertical control (3, 4). However, this suspensory strategy contributes to balance control by lowering COM, which remains a controversial topic (4–6).

The rationale of the suspensory strategy is that a flexed knee combined with flexion of the ankle and hip joints can lower the COM height and absorb internal and external perturbations; thus, effectively increasing stability and reducing the likelihood of falling (3–5). Previous studies also suggested that elderly people might be more inclined to use the suspensory strategy, such as bending the knees or lowering the COM to increase posterior stability (3, 4). However, a study has reported that different depths of squatting (i.e., different knee flexion angles) decrease the functional stability limits by inducing changes in joint mobility and muscle activation patterns (6). These divergent findings may be partially attributed to variations in the employed resources, such as COM, joint angle, and muscle activation, and assessment method. For instance, a change in COP or COM sway indicates balance ability in most studies (1, 2, 7). However, the appellate approach tends to ignore the sensory inputs and central processes in postural control. Moreover, the COP or COM sway has recently been utilized to evaluate the engagement of sensory integration, such as vision, vestibular, and proprioception, and estimate the regularity of posture sway (8–11). This represents an assessment of the potential factors that influence the postural balance. Therefore, by building upon the analysis of amplitude magnitude and integrating the sensory system and regularity of postural sway, a suspensory strategy examination could potentially offer further insights into its role in postural balance within the existing framework of postural control strategy.

Time-frequency analysis and nonlinear analysis of COP or COM data have been demonstrated as crucial tools for evaluating the overall posture system to estimate the sensory component and regularity of postural sway (10–14). Time-frequency analysis of COP and COM is recommended for studying human posture control, as it is believed to offer a better understanding of the underlying mechanisms, such as sensory input or sensory weighting in the static balance, than the traditional measures, such as amplitude, average velocity, or area (10, 13, 15). By calculating the local energy content within different frequency bands using time-frequency analysis, the sensory weightings of various sensory inputs can be assessed, and the overall energy content in the range of 0–6.25 Hz can reflect the collective balance-related sensory input, providing balance-related sensory integration insights during static standing (10, 15, 16). Sample entropy, which is a widely-used nonlinear evaluation method, has been employed for the assessment of postural regularity (14, 17, 18). It provides valuable means of quantifying the regularity and variability present in postural control, which is crucial for understanding the underlying neuromuscular mechanisms governing balance (14). Prior studies have suggested that the increase in the sample entropy of postural sway could be explained by the low level of postural sway regularity and having less attention dedicated to balance control (11, 18, 19). In conjunction with the notion that healthier balance control involves reduced attentional engagement in postural sway, which in turn leads to a greater degree of central control becoming automated (20), an elevation in postural sway entropy typically signifies enhanced balance control.

In addition, a review has reported that the COM vertical control is crucial for the standing balance and requires integration of multisensory cues that are critical for balance in vertical direct estimation, vertical perception, and stability (21). However, to date, no studies have directly addressed the sensory integration and regularity of suspensory strategy for static standing. Therefore, it is important to clarify the differences in the vertical postural control, such as the suspensory strategy, with sensory integration and regularity of postural sway from other postural controls, such as the hip and ankle postural control, for planning rehabilitation of older adults and patients with motor disorders and the design of exoskeletons considering the sensory integration and motor control of the user. Previous studies have reported that knee flexion modifies the passive stabilization achieved through ligaments and bone shape during standing and replaces it with active stabilization from muscle engagement (22). Thus, we hypothesized that suspensory strategy with knee flexion could change the sensory integration which in turn could lead to an increase in attention demand owing to the active involvement of the muscles. Accordingly, this study aimed at exploring the effect of knee joint flexion as a suspensory strategy to maintain static standing balance.

2. Methods

2.1. Participants and equipment

Based on the preliminary data, most of the parameters showed large effect sizes. Thus, the G*Power (3.1.9.7) was used with an F test. The sample size calculation revealed that a minimum of 12 samples were necessary for the experiment, with an effect size of $f = 0.4$, alpha = 0.05, and power = 0.8 (23). Nineteen healthy young adults (11 males and 8 females; mean age ± SD, 24.3 ± 2.2 years; age range, 21–30 years; weight, 62.7 ± 13.8 kg; and height, 169.5 ± 5.9 cm) were enrolled in this study. The participants with any current or past orthopedic or neurological illnesses were excluded from the study. Prior to inclusion, the participants were informed about the study and they signed a consent form for participation in this study. Consequently, all the participants were enrolled in this study. This study was approved by the review board of our institution (22–66) and was conducted in accordance with the ethical guidelines set forth by the 1964 Declaration of Helsinki.

Three-dimensional motion capture kinematic data were acquired using seven high-speed cameras (Hawk cameras, Motion Analysis

Abbreviations: ANOVA, Analysis of variance (ANOVA); AP, Anterior–posterior; BOS, Base of support; COM, Center of mass; COP, Center of pressure; ML, Medial-lateral.

Corp., Santa Rosa, CA, United States). The collected data were then analyzed using a motion analysis system (Cortex, version 5.0.1, Motion Analysis Corp.). Thirty-five retroreflective markers were placed at the specific anatomical points (24, 25). Markers were placed on the front and back of the head, shoulders, elbows, and wrists. Markers were also placed on the seven cervical vertebrae, sternum, scapula, anterior and posterior iliac spines (ASIS and PSIS, respectively), lateral thigh, medial and lateral femoral epicondyle, lateral shank, medial and lateral malleolus, second metatarsal head, fifth metatarsal head, and heel. The marker coordinate data were collected at a sampling rate of 200 Hz.

2.2. Procedures

To manipulate the suspensory strategy, participants were instructed to adopt three different postures with 0° (knee is locked by screw home mechanism) (22, 26), 15° (provide active stabilization and enable elastic absorption) (5, 22), and 65° (with lower stiffness, which may lead to separation of the head from the whole-body movement) (27) of knee flexion (Figure 1). The feet were positioned at the same place with the interval as the hip width, and had the same orientation in all postures. No specific instructions were provided regarding the other joints. No specific instructions were provided regarding the other joints. To stabilize their gaze and avoid exceeding the bending posture, participants were asked to gaze at the fixation point with a 9-cm diameter circle at approximately 5 m in front of them across all tasks. The participants practiced the postures beforehand and received feedback from examiners to correct any errors during the trials. Knee joint angles and COM heights were verified to ensure compliance with the experimental design every trial. The experimental procedure involved asking the participants to stand in each of the three positions for at least 35 s, with the order of the positions randomized. The participants were instructed to maintain each posture with different knee flexion angles for at least 35 s, and the order of the postures was randomized. After recording the data in one posture, the participants returned to a relaxed standing posture and rested for 10 s until the next posture. Ideally, there were no rest periods between each two postures, but if the participants experienced fatigue during the experiment, a 5-min break was provided.

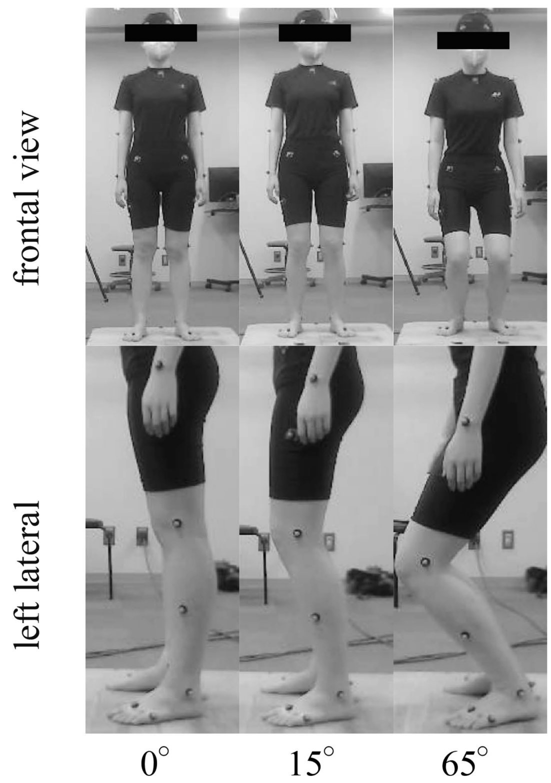

FIGURE 1
Representative pictures of a participant standing at three knee flexion angles (0°, 15°, and 65°).

2.3. Data collection and processing

Kinematic data, including knee joint angles and COM position, were analyzed using Visual3D software (version 6, C-Motion, Inc., Germantown, MD, United States) and processed with MATLAB (MATLAB 2022b, The MathWorks, Inc., Natick, MA, United States). A fourth-order, zero-lag Butterworth filter with a 10-Hz cutoff frequency was applied to the kinematic data to obtain a low-pass filtered signal (4). For the next data processing session, 30 s of kinematic data were extracted from the recorded data 35 s after visually confirming the knee angle and postural stability. In concrete terms, the knee angle was measured using a goniometer before recording the data, and then the knee angle was confirmed using Visual3D software offline data processing after recording. If the knee angle was incorrect, participants were asked to hold their posture again. The COM sway amplitudes in the AP, ML, and vertical directions were calculated at the selected analysis intervals and normalized according to the height of each participant. The COM height was calculated as the average COM height at the selected analysis intervals and normalized to the height of each participant (4).

In accordance with prior studies (10, 13), a time-frequency analysis was conducted on the AP and ML directions of the COM to explore the sensory energy input in the current study. Specifically, the COM signal was processed using Gabor transform, which is a time-frequency analysis technique used to extract the energy content during different frequency band of the signals. The Gabor transform is shown in Eq. (1).

$$G(t,f) = \int_{-\infty}^{+\infty} x(\tau) e^{-\sigma\pi(t-\tau)^2} e^{-j2\pi f\tau} d\tau \quad (1)$$

The Gaussian window with a width controlled by parameter σ in Equation (1) is represented by output G(t, f), which displays the central oscillator location at various frequencies. The integral of G(t, f) along the frequency axis represents the accumulation of information from different frequency bands.

The total energy content was determined by adding the energy in the frequency range of 0–6.25 Hz (10). To assess alterations in the proportion of energy content from different sensory systems, the frequency range was divided into four bands: (1) ultra-low-frequency band (below 0.1 Hz); (2) very-low-frequency band (0.10–0.39 Hz); (3) low-frequency band (0.39–1.56 Hz), and (4) moderate-frequency band (1.56–6.25 Hz), which correspond to the visual system, vestibular system, cerebellar system, and proprioception, respectively (10, 15, 27–30). The local energy content of each frequency band was calculated as a percentage of the total energy by referring to the sensory weights (10, 31, 32). Sample entropy was previously used to analyze the regularity of postural sway data during static standing (11, 33). Thus, it was calculated for the AP, ML, and vertical COM displacements. The computation method for sample entropy was implemented using an approach developed by Richman and Moorman, which was translated into MATLAB functions and utilized for further calculations (33–35). The sample entropy is shown in Equations (2–4).

$$\text{Sample entropy }(\text{m,r,N}) = -\ln\left(\frac{A}{B}\right) \quad (2)$$

$$A = \left(\frac{(N-m-1)(N-m)}{2}\right) \quad A^m(r) \quad (3)$$

$$B = \left(\frac{(N-m-1)(N-m)}{2}\right) \quad B^m(r) \quad (4)$$

The length of the sequences to be compared is denoted by m, the tolerance value for accepting matches is denoted by r, the length of the data is denoted by N, the probability that sequences match for m + 1 point is denoted by $A^m(r)$, and the probability that sequences match for m point is denoted by $B^m(r)$. However, there is no consensus on the parameter selection, but for balance control studies, the parameter settings are commonly set to m = 2 or 3 and r between 0.1 and 0.25 standard deviation (SD) (33). For this study, the parameters were set as m = 2 and r = 0.2 multiplied by the SD (33–35). Generally, the sample entropy value approaches zero for a perfect regularity pattern. Conversely, if the signal has more irregularity, the sample entropy value tends to be higher (35, 36).

2.4. Statistical analyses

All statistical analyses were performed using SPSS Statistics (version 18.0; IBM Corp., Armonk, NY, United States). The Shapiro–Wilk test was conducted to test normality. One-way repeated-measures analysis of variance (ANOVA) or Friedman's test was used to examine the effects of posture (three different degrees of knee flexion) on the outcome measure. *Post hoc* analyses between the two postures with different knee flexions were conducted using the Bonferroni paired comparison method or pairwise comparisons. For one-way repeated-measures ANOVA, Cohen suggested that small, medium, and large effects would be reflected in the partial eta squared values (η^2) to 0.01, 0.06, and 0.14 (23). According to Cohen's guidelines, Kendall's W value was used for Friedman's test, with values in the range of 0.1–0.3 indicating a small effect, values in the range of 0.3–0.5 indicating a moderate effect, and values ≥ 0.5 indicating a large effect (23). The significance level was set at a p-value < 0.05.

3. Results

Friedman's test indicated a significant effect of the knee flexion angle on the COM height [$\chi^2(2) = 38.00$, $p < 0.001$, Kendall's W = 1.00]. *Post hoc* analyses revealed a significant difference in the COM height among the three knee flexion angles (all $p < 0.001$). Specifically, the median (Q1–Q3) of the COM height were 51.62% (50.47–52.68), 50.65% (49.33–51.35), and 41.47% (39.03–43.22) at 0°, 15°, and 65° knee flexion, respectively.

Friedman's test revealed significant differences in the AP [$\chi^2(2) = 8.84$, $p < 0.05$, Kendall's W = 0.23], ML [$\chi^2(2) = 17.16$, $p < 0.001$, Kendall's W = 0.45], and vertical [$\chi^2(2) = 34.11$, $p < 0.001$, Kendall's W = 0.90] direction in the COM sway among the three knee flexion angles. *Post hoc* analyses were performed to further investigate specific pairwise differences. COM sway amplitude at 0° knee flexion in the AP direction was significantly smaller than that at 65° ($p < 0.05$), and the sway amplitude at the 0° knee flexion in the ML direction angle was significantly smaller than that at both 15° and 65° (both $p < 0.05$; Table 1). The COM sway amplitude at 65° knee flexion in the vertical direction exhibited the largest amplitude, whereas the COM sway amplitude at the knee flexion angle 0° had the smallest amplitude (both $p < 0.05$; Table 1).

Significant differences in the total energy content of all frequency bands in the COM AP direction among the three different angles of knee flexion [$\chi^2(2) = 14.632$, $p < 0.001$, Kendall's W = 0.39] were revealed. *Post hoc* analyses indicated that the total energy content at 65° knee flexion was significantly lower than that at 0° and 15° (both $p < 0.05$; Figure 2A). For the percentage of energy content of each frequency band in the COM AP direction, Friedman's test revealed no significant differences among the three

TABLE 1 The median (Q1, Q3) deviation for each COM amplitude and sample entropy of the AP and ML directions and the mean (standard deviation) for sample entropy vertical direction.

		Knee flexion angle		
	COM direction	0°	15°	65°
COM sway amplitude (%)	AP	1.09 (0.70, 1.31)	1.20 (0.84, 1.52)	1.61 (1.24, 2.41)*
	ML	0.48 (0.35, 0.82)	0.80 (0.61, 1.02)*	0.97 (0.82, 1.12)*
	Vertical	0.15 (0.10, 0.24)	0.34 (0.17, 0.44)*	1.06 (0.75, 1.25)*#
Sample entropy	AP	0.33 (0.27, 0.43)	0.35 (0.32, 0.41)	0.31 (0.26, 0.39)
	ML	0.41 (0.37, 0.53)	0.34 (0.30, 0.35)*	0.26 (0.21, 0.33)*
	Vertical	0.55 (0.20)	0.55 (0.20)	0.29 (0.09)*#

COM AP, COM anterior–posterior direction; COM ML, COM medial-lateral direction; Q1, first quartile; Q3, third quartile. *$P < 0.05$, compared with 0° knee flexion; #$p < 0.05$, compared with 15° knee flexion.

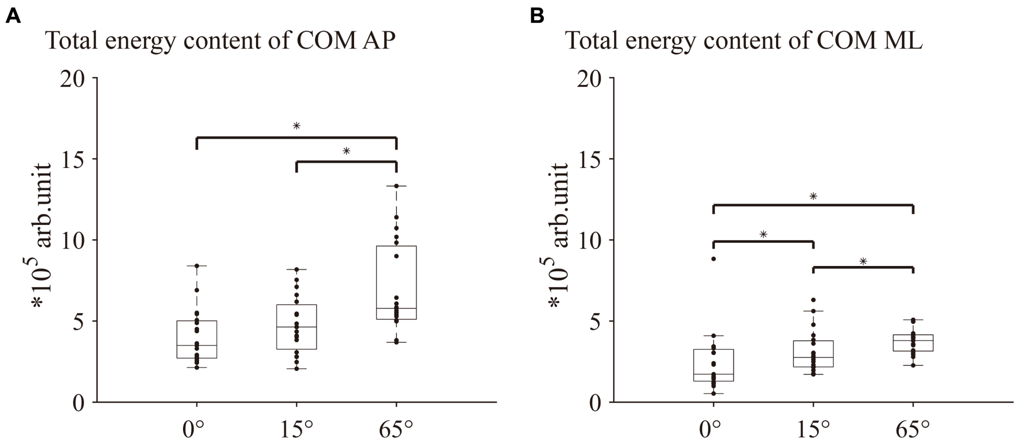

FIGURE 2
Comparison of the total energy content of COM AP and ML between 0°, 15°, and 65° knee flexion. **(A)** Total energy content of COM AP. **(B)** Total energy content of COM ML. COM AP, COM anterior–posterior direction; COM ML, COM medial-lateral direction. * indicates $p < 0.05$.

knee flexion angles in the ultralow-, low-, and moderate-frequency bands (Figures 3A,E,G). One-way repeated-measures ANOVA revealed a significant difference in the percentage of the very-low-frequency band among the three knee flexion angles [$F(2, 36) = 5.71$, $p < 0.05$, $\eta^2 = 0.24$]. *Post hoc* analysis showed that the energy percentage of the very-low-frequency band was significantly lower at the 65° knee flexion angle than those at 0° and 15° knee flexion angles (all $p < 0.05$; Figure 3C).

Friedman's test revealed a significant difference in the total energy content in the COM ML direction among the three knee flexion angles [$\chi^2(2) = 20.632$, $p < 0.001$, Kendall's W = 0.543]. *Post hoc* analyses indicated that the total energy content at the 65° knee flexion was significantly lower than those at 0° and 15°(both $p < 0.05$; Figure 2B). For the percentage of energy content of each frequency band in the COM ML direction, no significant differences were observed in the low-and moderate-frequency bands among the three knee flexion angles (Figures 3F,H). Friedman's test and one-way repeated measures ANOVA revealed a significant difference in the ultra-low-frequency band [$\chi^2(2) = 9.58$, $p < 0.05$, Kendall's W = 0.25] and very-low-frequency band [$F(2, 36) = 13.36$, $p < 0.001$, $\eta^2 = 0.43$] among the three knee flexion angles. *Post hoc* analysis showed that the energy percentage of the ultra-low-frequency band was significantly lower at a 65° knee flexion angle than those at 0° and 15° (both $p < 0.05$; Figure 3B), and the energy percentage of the very-low-frequency band was significantly lower at the 0° and 15° knee flexion angles than that at 65°(both $p < 0.05$; Figure 3D).

Friedman's test was conducted to compare the sample entropy of the COM among the three knee flexion angles. There was no significant difference in the sample entropy of the COM AP direction among the three knee flexion angles [$\chi^2(2) = 4.11$, $p = 0.13$, Kendall's W = 0.23]. A significant difference was observed in the COM ML direction [$\chi^2(2) = 15.47$, $p < 0.001$, Kendall's W = 0.45], with the 0° knee flexion angle exhibiting a significantly higher sample entropy than those at 15° and 65° (both $p < 0.05$; Table 1). Furthermore, a significant difference was observed in the sample entropy in the vertical direction [$\chi^2(2) = 21.72$, $p < 0.001$, Kendall's W = 0.87]. *Post hoc* analysis revealed that the 65° knee flexion angle displayed a significantly lower sample entropy than those at 0° and 15° (both $p < 0.001$; Table 1).

4. Discussion

This study analyzed COM sway using classical parameters (amplitude), time-frequency analysis, and non-linear analysis to investigate the effect of the suspensory strategy on the static standing balance by knee flexion. In the classical parameter analysis, the COM sway amplitude in the AP, ML, and vertical directions showed an increase during knee flexion. In terms of the time-frequency analysis, the results showed that the full-band energy content increased and the sensory weights changed while the knee was flexed. Thus, this work demonstrated that knee flexion alters the postural control in the vertical direction and this suspensory strategy alters the balance-related sensory integration and postural sway regularity.

4.1. Postural sway amplitude

During static standing, the COM sway amplitude is typically inversely related to the balance ability; thus, smaller amplitudes indicate better balance (12, 37). However, some studies have shown that postural sway amplitude can decrease during heightened tension (17), postural stiffness (37), or less attention (8), which does not necessarily indicate an improvement in the posture. Our study revealed that the COM sway amplitude in the AP and ML directions was slightly increased, and this level of increase did not seem to threaten the balance. However, there were noticeable alterations in the vertical direction by knee flexion with a substantial magnitude of change. Based on previous studies (8, 17, 37) suggesting that potential sway serves as an exploratory mechanism which ensures that multiple sensory systems provide continuous dynamic input (16, 38, 39), the small increase in COM sway amplitude in the horizontal plane in this study may imply functionality rather than improvement in or worsening of balance. The change in COM sway amplitude in the vertical direction may occur in the knee flexion state with the increased freedom of the lower limb (e.g., more freedom of movement in the knee joint in a knee flexion stance relative to a straight knee stance); thus, allowing for balance control to potentially employ more control strategies in the vertical direction of the COM, also known as

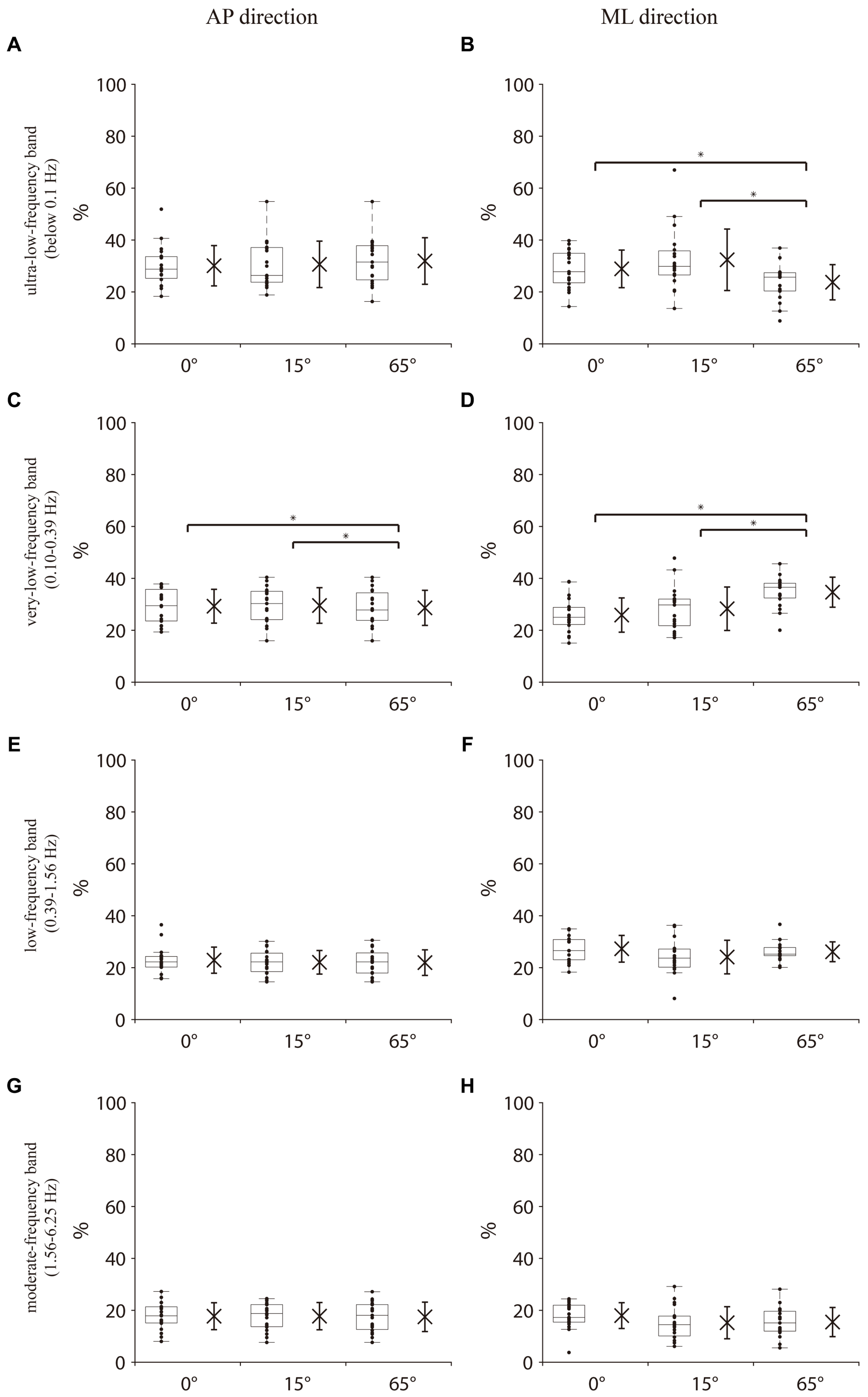

FIGURE 3
Percentage of energy content in each frequency band in the COM AP and COM ML directions. **(A,B)** Ultralow-frequency band (<0.1 Hz, visual system). **(C,D)** Very low-frequency band (0.1–0.39 Hz, vestibular system). **(E,F)** Low-frequency band (0.39–1.56 Hz, cerebellar system). **(G,H)** Moderate-frequency band (1.56–6.25 Hz, proprioception and spinal reflexive loop). The box plot represents the median values and interquartile range of the entire sample for each measurement and displays the maximum and minimum values through the upper and lower whiskers. Data for each participant are represented by dots. The x on the left side of the box plot indicates the mean of all the data and the whiskers on x indicate the standard deviation. COM AP, COM anterior–posterior direction; COM ML, COM medial-lateral direction. * indicates $p < 0.05$.

suspensory strategies (3, 4). However, there is a TRADE-OFF phenomenon in postural control, implying that better stabilization and the benefit from larger postural sway may not coexist. Further studies are needed to clarify the suspensory strategy effects during perturbation and explain whether the suspensory strategy of knee flexion can lead to better stabilization in multiple environments.

4.2. Sensory integration

One of the aims of this study was to examine the effects of suspensory strategy of bending the knee on sensory integration. Time-frequency analysis of the COM or COP is a frequently employed method to explore sensory input and measure sensory reweighting (10, 15, 16, 31). In terms of energy content, prior studies have suggested that an increase in sensory energy within the 0–6.25 Hz frequency range correlates with an increase in the balance-related sensory input (10, 13). This study findings indicated that balance-related sensory input showed an increase during knee flexion in both AP and ML directions. These findings may further explain the fact that older people prefer to choose the suspensory strategy of knee flexion with a lowered COM for balance control when performing internal perturbations (4) as balance-related sensory functions diminish with age (7, 20, 39), and the increased sensory input from knee flexion may compensate for this sensory deficit. According to the descriptions of the balance-related sensory reweights in each frequency band from previous studies (10, 15, 31), in terms of the sensory weights in the AP direction, the results of the present study only showed a decrease in the vestibular sensory-related weights when the knee flexion was 65 °. Interestingly, in the ML direction, the present study showed that in the 65° knee flexion, the visual-related weights decreased, but the vestibular-related sensory weights increased (10, 15, 31). This suggests that the suspensory strategy by knee flexion increases the balance-related sensory input simultaneous with the changes in the balance-related sensory weights, and that this change is inconsistent in the AP and ML directions of balance. Therefore, a suspensory strategy of knee flexion may compensate for some deficits in the balance-related sensory acquisition to increase postural control and alter the balance-related sensory weights in the standing balance.

4.3. Regularity of postural sway

Typically, a decrease in sample entropy increases the regularity of postural sway, reflecting a shift toward more attention and less automatic control required to control balance. However, an increase in sample entropy decreases the regularity of postural sway, which in turn corresponds to less attention and more automatic control required for balance (11, 17, 19). According to this interpretation of sample entropy, the findings of this study support the fact that in the static standing position, knee flexion decreases the passive stability and increases the active stability, thereby requiring muscle activity and increased attention to postural stability (22, 27, 40). This phenomenon was only observed in the ML and vertical directions. This may not be a good indication of healthier balance control because most conceptualizations of static balance suggest that better static balance corresponds to more automatic control and less attentional involvement (20, 41). However, in daily life, it is not only important to automatically maintain static balance but also cope with unexpected perturbations. More attention to postural control may allow for quicker balance response and recovery when subjected to external perturbations. Moreover, some studies suggest that directing additional attention to balance might offer a more advantageous strategy, particularly for aging individuals or those grappling with compromised balance-related capacities (39). Additionally, this may aid in elucidating the findings of our previous study which showed that older adults are more inclined to adopt a suspensory strategy for postural sway (4). Declines in balance-related sensory functions and central motor abilities are common with age (12, 42). Consequently, it may be rational to intensify attentional allocation to maintain balance. Thus, adopting a suspensory strategy with knee flexion could serve as an effective means of directing more attention toward balance in the elderly. This study elucidated the nuanced relationship between knee flexion, postural sway regularity, and attentional demand.

4.4. Limitations

This study has several limitations. First, the study sample consisted of only young individuals, limiting the generalizability of the findings to other older age groups. Future research should include participants across a wider age range to examine the potential age-related differences in balance control during squatting. Second, this study focused solely on sensory input and sample entropy under open-eye conditions. Future investigations could consider incorporating other sensory conditions, such as eyes closed or altered visual feedback, to provide a more comprehensive understanding of the sensory contributions to balance control during squatting. This study examined three specific knee flexion angles (0°, 15°, and 65°) but did not include intermediate angles between 15° and 65°. Investigating a broader range of knee flexion angles would provide a more detailed understanding of how different angles affect balance control and the associated sensory input. Finally, this study did not collect electromyograms, and a more detailed analysis of the conclusions or muscle contributions may require support from these data. Addressing these limitations in future studies will enhance our knowledge of balance control during squatting and provide a more comprehensive understanding of the underlying mechanisms.

In conclusion, this study revealed that suspensory strategy by knee flexion led to an increased COM amplitude in healthy adults, and the suspensory strategy may be able to increase the functionality and attentional control of postural sway to some extent. Balance gains from suspensory strategy may be more appropriate for older adults with declining balance-related sensory, central processing, and musculoskeletal system function. However, it should be noted that this study population did not include older adults and more complex dynamic balances. Further research should be conducted to fully analyze the suspensory strategy. From a clinical perspective, this study provides new insights into a rehabilitative approach to balance control in older adults using a suspensory strategy. This work could also offer pertinent insights for the design of knee joint exoskeletons, particularly concerning the interplay between the use of knee joint exoskeletons, overall postural sway control, the potential effects of exoskeleton movement on the integration of sensory functions, and the attention of the user toward postural control.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Faculty of Health Sciences at Hokkaido University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

LJ: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing, Funding acquisition. SK: Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing, Funding acquisition. TI: Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing. YK: Conceptualization, Methodology, Supervision, Writing – review & editing. AC: Data curation, Supervision, Validation, Writing – review & editing. KY: Data curation, Supervision, Writing – review & editing. YW: Supervision, Writing – review & editing. MS: Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing. HT: Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing.

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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.

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A non-expensive bidimensional kinematic balance assessment can detect early postural instability in people with Parkinson's disease

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Background: Postural instability is a debilitating cardinal symptom of Parkinson's disease (PD). Its onset marks a pivotal milestone in PD when balance impairment results in disability in many activities of daily living. Early detection of postural instability by non-expensive tools that can be widely used in clinical practice is a key factor in the prevention of falls in widespread population and their negative consequences.

Objective: This study aimed to investigate the effectiveness of a two-dimensional balance assessment to identify the decline in postural control associated with PD progression.

Methods: This study recruited 55 people with PD, of which 37 were men. Eleven participants were in stage I, twenty-three in stage II, and twenty-one in stage III. According to the Hoehn and Yahr (H&Y) rating scale, three clinical balance tests (Timed Up and Go test, Balance Evaluation Systems Test, and Push and Release test) were carried out in addition to a static stance test recorded by a two-dimensional movement analysis software. Based on kinematic variables generated by the software, a Postural Instability Index (PII) was created, allowing a comparison between its results and those obtained by clinical tests.

Results: There were differences between sociodemographic variables directly related to PD evolution. Although all tests were correlated with H&Y stages, only the PII was able to differentiate the first three stages of disease evolution (H&Y I and II: $p = 0.03$; H&Y I and III: $p = 0.00001$; H&Y II and III: $p = 0.02$). Other clinical tests were able to differentiate only people in the moderate PD stage (H&Y III).

Conclusion: Based on the PII index, it was possible to differentiate the postural control decline among the first three stages of PD evolution. This study offers a promising possibility of a low-cost, early identification of subtle changes in postural control in people with PD in clinical practice.

KEYWORDS

Parkinson's disease, balance, postural instability, cinematic assessment, early Parkinson

1 Introduction

Balance impairment (BI), i.e., deficiency to control the body's center of mass over its support's base to achieve postural stability, is a common and debilitating motor alteration of Parkinson's disease (PD), causing high disability levels (1–3). BI is a remarkable signal of postural instability, a complex and poorly understood motor symptom identified as a feature of PD in its late stages (4). Postural instability occurs 10–15 years after first diagnosis (5) and can be clinically detected from moderate disease stages, being the cardinal signal for progression from stage II to stage III according to Hoehn and Yahr (H&Y) rating scale, the most commonly used scale to control PD evolution (6). Despite the severe consequences involving BI, imposing an increased fall risk as the disease progresses, only 2% of newly diagnosed people with PD (PwPD) were classified as fallers and 15% as rare fallers (7), pointing to a necessary more attentive view of the issue.

BI is an independent risk factor for falls, injury, and significant mobility restriction, with a high negative impact on functionality. Unfortunately, the responsiveness of postural instability to current treatment strategies is limited (2, 3). Regarding medication treatment, although some significant positive effects are reported, there is no consensus regarding the effects of Levodopa on balance (8). Regarding surgical treatment, according to the target neural structure, deep brain stimulation may decrease or improve the balance in PwPD (9). Regarding non-medication treatment, a compelling review (10) demonstrates that exercise intervention reduces the rate of falls on PwPD, albeit with a modest effect.

Changes in BI are deeply related to PD. In healthy people, postural responses to perturbations are generated and controlled by automatic mechanisms that maintain standing posture and prevent falls (11). The sequence of events is automatically triggered in response to postural perturbations: (1) activation of sensory systems; (2) integration of sensory information; and (3) planning an adequate motor response to maintain the body's center of gravity within the base of support (12). Nigrostriatal dopaminergic denervation and white matter alterations (13) may affect this ability in at least three distinct ways: (1) by impairing proper sensory integration involving the basal ganglia; (2) by perturbing the adjustment process for an appropriate escalating neuromuscular response; and (3) by perturbing the adjustment of muscle tone (14). Furthermore, non-motor aspects, mainly cognitive impairment in PD, such as altered attention, narrow cognitive focus, comorbid dementia, and fear of falls, could also affect balance control (15).

Early postural instability detection is an important challenge in PD since it can be used to diagnose and categorize PwPD in severity stages and subtypes based on phenotypes, i.e., tremor and axial (16). Furthermore, early postural instability detection is essential to identify people with increased fall risk. It must include accurate, time- and cost-effective assessments to identify patients at high risk of falling to allow timely preventive intervention (17). Adequate and timely recognition of balance disorders is critical to avoid injuries associated with falls, worsening quality of life, reduced mobility, and social isolation. In addition, quantifying balance deficits is relevant for monitoring patients over time (18).

It is widely recognized that PD includes BI and a consequent increased risk of falls as the disease progresses. However, there is a trend toward underreporting of BI (7). Given these concerns, clinical and laboratory instruments are developed to assess the postural instability associated with PD. These assessments can play a crucial role in objectively measuring and monitoring balance problems faced by individuals with PD in a controlled environment.

The efficient clinical evaluation of postural control and balance is crucial to guide the intervention to preserve functionality and decrease the fall risk in PwPD. Several clinical tests, such as the Berg Balance Scale (BBS), Tinetti, Mini-Balance Evaluation Systems Test (Mini-BESTest), Timed Up and Go (TUG) test, and Pull-test (PT), have been used to evaluate the balance and the postural control in PwPD (18). Scales based on the self-perception of BI have also been used to identify the fall risk in PwPD (19). The main advantages of this kind of test and scale are the short time and ease of application, no demand for sophisticated equipment, and, consequently, the low cost. On the other hand, results obtained by self-perception are subjective and may be biased by cognitive and mood alterations, which are common in PwPD. Clinical tests depend on the personal and subjective interpretation of the examiner and cannot offer a detailed and precise quantification and qualification of balance alterations (20).

A review of the psychometric properties of balance and fall risk prediction measures in PD showed that only 6 of the 68 outcome measures have strong psychometric properties. Among them, the Mini-BESTest and Push and Release test are best at body level (21). Furthermore, a critical review by the International Parkinson and Movement Disorders Society Task Force assessed the clinometric properties of existing rating scales, questionnaires, and timed tests that assess gait, balance, and posture alterations in PD. They found no scale suitable for evaluating gait, balance, and posture, as none of the instruments investigated adequately or separately assessed all constructs (18).

Besides the clinical tests, several measures to assess balance and fall risk prediction that require the use of laboratories or sophisticated instruments have been developed. These instruments assessed the ability to shift the mass and gravity center, spatiotemporal gait parameters, and sensory integration to quantify balance and/or fall risk (21). "Posturography," "wearable devices," "gait analysis," and "center of pressure" (COP) have been used to track the postural control and gait of PwPD. Studies using posturography showed that people in the early stages of PD have a decrease in the limit of stability area and an increase in postural sway, and these conditions gradually deteriorate as the disease progresses (22, 23). Early abnormalities of anticipatory postural adjustments during turning in individuals in H&Y stage II (24) and abnormal standing sway in newly diagnosed individuals have also been demonstrated (25). However, a recent study showed that static posturography could detect significant balance decline only between very early and intermediate stages of disease progression, i.e., between H&Y stages I and III (16). Wearable devices installed in the neck, waist, back, lower limbs, and other body parts can also detect subtle changes in postural instability and the fall risk of PwPD (26).

Although these laboratory-based instruments may be used as an objective complementary tool to clinical balance tests to assess balance performance in PwPD, sophisticated tools to evaluate balance and fall risk have limited clinical utility because they are expensive. Such instrumentation is only commonly available in some clinics. Thus, clinic-based or bedside assessments using this equipment on a routine basis are only eventually possible.

Postural sway is a sensitive measure of the complex sensorimotor control loop responsible for controlling standing balance; it has been considered an excellent measure of postural instability (27). Traditionally, postural sway has been measured with a force plate under the feet. However, Ciria et al. (28) recently demonstrated that results obtained by two-dimensional kinematic evaluation of the head movements during stance posture were strongly correlated and coherent with COP sway registered by the force platform. Therefore, measuring head movements can be an alternative for studying human postural changes.

Recently, a new approach to movement analysis based on movement decomposing has been proposed by Miranda et al. (29) This method allows for a more detailed analysis of movement kinematics, providing a nonlinear approach to motor control characteristics. Considering the complex changes in movement in PwPD, this approach may be helpful. In fact, using this new approach, D'Alencar et al. (30) showed that the index provided by a two-dimensional movement analysis that uses kinematic gait variables was more sensitive to detect subtle gait alterations in early PD stages than clinical tests. Therefore, a similar method based on two-dimensional kinematic analysis of head movements during stance posture may also offer a non-expensive clinic-based evaluation that is more objective when compared to current recommended clinical tests to identify changes in postural control in PwPD. This method could be used isolated or combined with clinical tests to identify the progression of postural instability in PwPD. Recent studies have shown that models combining clinical and inertial sensor outcomes showed higher discriminative ability in classifying fallers and non-fallers among PwPD than clinical-only or mobility-only models (31, 32).

While new methods can provide a more objective evaluation of balance disruption and fall risks, their clinical utility could be limited due to costs, team, and equipment requirements. Recognizing this limitation, the primary objective of this study was to explore a straightforward and cost-effective approach that holds potential for clinical application in identifying the progression of postural instability in individuals with PD. By developing a more accessible method, the study aimed to enhance the practicality and feasibility of assessing postural instability in a clinical setting based on a two-dimensional kinematic evaluation of the balance performance in PwPD.

2 Materials and methods

2.1 Participants

A convenient sample of 55 people with PD (above 50 to allow for high-quality estimates according to COSMIN standards), 37 men, 11 participants in stage I, 23 in stage II, and 21 in stage III according to the H&Y rating scale were recruited from Brazil's AMPARO Network.[1] The study included individuals who met the following criteria: (1) They had idiopathic PD (stages I–III according to the H&Y rating scale) diagnosed by an experienced specialist in movement disorders using the UK Brain Bank criteria (33), and they were taking antiparkinsonian medications; (2) They were capable of independent ambulation; and (3) They showed no signs of dementia (determined by a Montreal Cognitive Assessment [MoCA] score above 21) or major depression (determined by a Geriatric Depression Scale score below 6). Additionally, participants were excluded if respiratory or cardiovascular diseases, clinically significant musculoskeletal alterations, other neurological disorders, or uncorrected visual/auditory impairments were present.

1 www.amparo.numec.prp.usp.br

2.2 Design and procedures

The present study obtained approval from a local ethics committee (#CAAE 67388816.2.0000.0065) and adhered to the principles outlined in the Declaration of Helsinki. Prior to the commencement of the study, each participant provided written informed consent. A cross-sectional design was employed, wherein participants underwent both motor and cognitive evaluations within a single session. These assessments were carried out by a physiotherapist with specialized expertise in movement disorders. All individuals diagnosed with PD were tested during their ON period, which occurred 40 to 120 min after their L-dopa dose. A detailed overview of the study's stages and procedures is presented in Figure 1.

2.2.1 TUG test

The TUG test is an easy, inexpensive, and efficient clinical application to assess mobility and functional balance. Participants were instructed to get up from a chair and walk in a straight line at their normal speed for 3 m, walk around a marked area, and then go back to the chair and sit down. The procedure was timed in seconds, starting with the command to do the test and the moment when the participant gets up from the chair until the participant returns to the chair and sits. The use of supports, crutches, and canes to help them was not allowed.

This measurement is useful in an outpatient setting because it only requires a few minutes and easy-to-handle equipment. The TUG test is shown to be highly correlated with functional mobility and gait speed in PD (34) and has also been proven to have high test–retest reliability and inter-rater reliability in PD (35).

2.2.2 Pull test: unified Parkinson disease rating scale – Section III

The 30-item Push and Release test of Section III of the Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale (MDS-UPDRS) was administered to assess BI. A satisfactory response to the pull test requires the ability to mount an adequately sized backward step to compensate for the rapid backward displacement in the center of gravity initiated by pulling backward on a patient's shoulders (36).

This test was treated as a continuous variable scored on an ordinal severity scale from low (0) to high (4). Excellent factor validity, test–retest reliability (ICC ¼ 0.93), high internal consistency, and responsiveness have been demonstrated (37). We proceeded according to the recommendation by Visser et al., i.e., a sudden, firm, rapid shoulder jerk without warning but with prior explanation and performed only once. Participants remained in a comfortable position with their eyes open, and the examiners stood behind the subjects,

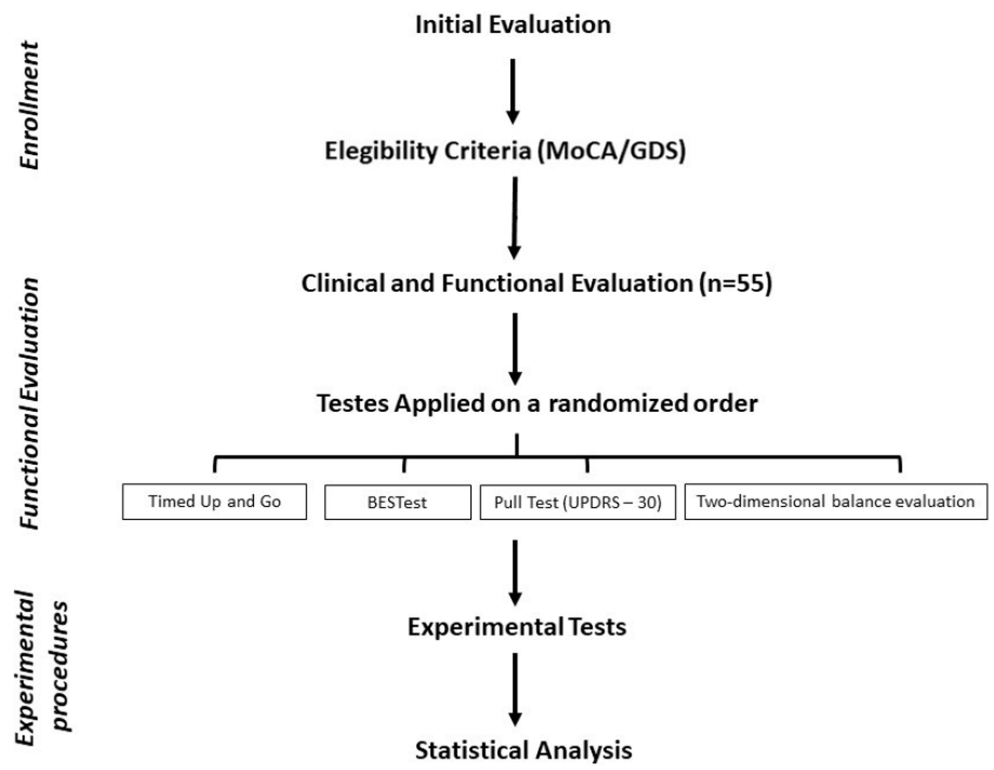

FIGURE 1
Flowchart of the study steps and procedures.

who were instructed to push back against the examiners' palms placed on their shoulder blades while the examiners flexed the curves to allow for backward movement of the trunk while supporting the participants' weight with their hands.

The examiners suddenly removed their hands when the subjects' shoulders and hips moved into a stable position just behind their heels, allowing them to step back to regain balance.

2.2.3 Balance evaluation systems test

The balanced performance of the participants in the groups was evaluated using the BESTest. The assessment process consists of six domains: biomechanical constraints, stability limits, anticipatory postural adjustments, postural response to the induced loss of balance, sensory orientation, and stability in gait (38). To use the BESTest to differentiate balance deficits, the examiner scores each item from 0 (worst) to 3 (best). The sum of all scores is the total result. Each category establishes its own result, making it very useful to know which postural control disorders are compromised. All evaluators were previously trained to apply the test.

2.2.4 Two-dimensional balance analysis

The two-dimensional balance assessment was performed using the following instruments:

- A GoPro™ Hero Silver camera
- A headband
- Yellow stickers measuring 19 mm in diameter
- Calibration paper featuring two reference points placed 20 cm apart
- Camera tripods with height adjustment (quantity: 01)
- The GoPro™ Hero 7 Black application
- CvMob™ software, version 3.6 (accessible at http://cvmob.ufba.br).

The participants were instructed to maintain a bipedal posture for 30 s from an auditory signal (GO), with their feet parallel (20 cm between them), on yellow dots marked on the floor. Their visual focus had to be held at a point located on the front wall. The height of the point in relation to the floor was adjusted according to the participant's height. The camera was inserted in its silicone shield and fitted to a fixed adjustable tripod, being lowered and positioned at a distance of 20 cm from the reference point (yellow stickers) so that it recorded the top of the head (Figure 2).

The video parameters used for filming had the following configuration: (1) wireless control (connected to a Motorola™ Moto X Style smartphone); (2) narrow field of view; (3) 30 frames per second; (4) 720 bpi resolution; and (5) low light option turned off.

The kinematic balance variables were measured with the CvMob™ movement analysis system (39). From the trajectory and velocity data of the selected marker (sticker), the movement element decomposition method (29) was used to segment the movement into elements, defined by start and end at zero velocity. For each element, the method estimates the average velocity and displacement, and for the overall movement, it calculates the average displacement and the average of the average velocities of the elements, as well as the total quantity of elements found. These indices are estimated for each coordinate axis (anteroposterior and mediolateral). Only variables related to anteroposterior oscillation motion were used.

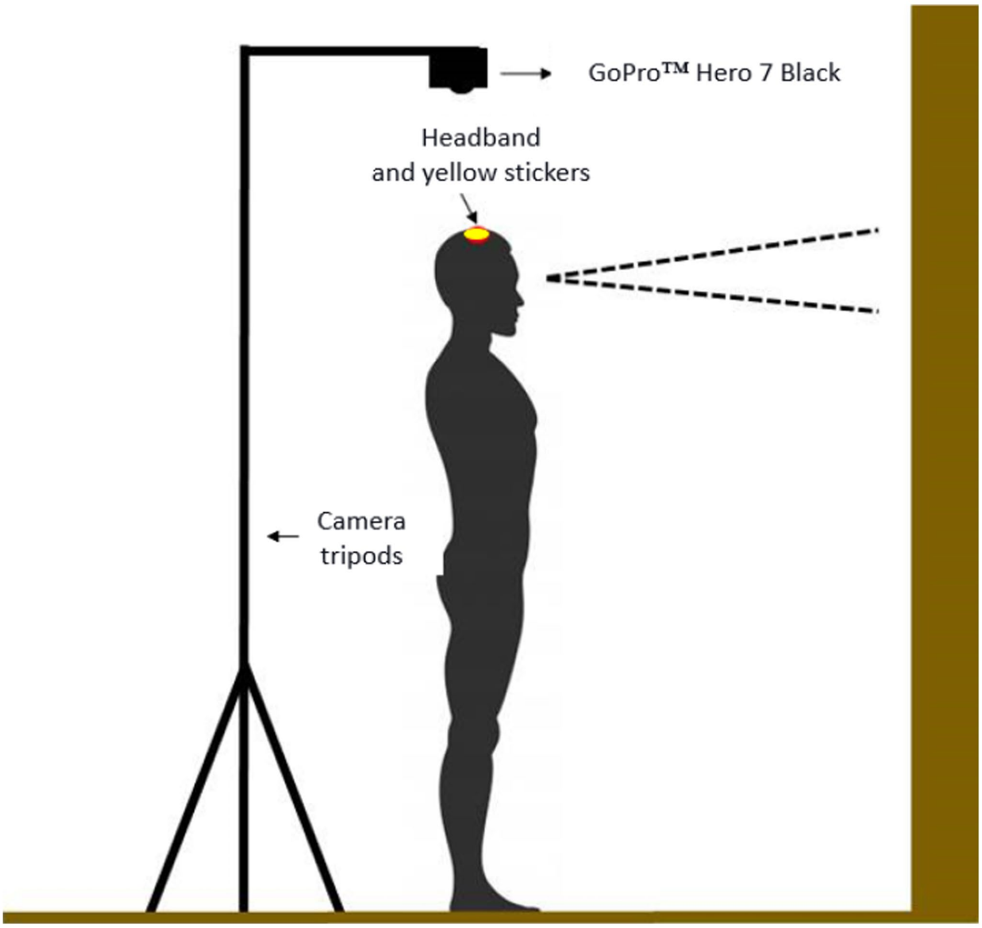

FIGURE 2
The representation of two-dimensional balance assessment procedures.

For constructing the Postural Instability Index (PII), three physiotherapists specialized in PD and a physicist specialized in movement analysis analyzed the behavior of all variables acquired by the CvMob™ system and their relationship with the evolution of PD. The behavior of the balance variables was analyzed to form an estimated value that directly correlates with postural stability, as inferred from the variability of oscillations in trajectory and velocity indicators. This estimated value has the potential to accurately reflect the progressive clinical evolution of the disease while considering the varying severity degrees. Based on the results of this exploratory analysis, we decided to include in the formula to calculate the PII only the three more powerful variables to detect the progression in postural instability in order to facilitate the implementation and interpretation in clinical practice.

The variables used in the formula were as follows: $\overline{V_y}$: average velocity of the element size in the anteroposterior direction, which indicates the oscillation's speed, which has been strongly associated with postural instability (40) and fall risk (21) in PD; N_y: number of elements on the y-axis (antero-posterior), which indicates the number of inversions made in the oscillation's trajectory; and $\overline{Dm_y}$: average displacement size of the movement element in the y-direction (antero-posterior), which indicates the oscillation's amplitude. Using these variables, the *PII* was defined according to Eq. (1):

$$PII = \frac{\overline{V_y} \cdot \boldsymbol{N_y}}{\overline{Dm_y}} \quad (1)$$

Thus, the frequency and magnitude of oscillations play a central role in determining one's postural stability, with a higher frequency of small oscillations in the anteroposterior direction resulting in decreased stability.

2.3 Analysis

Normal distribution of the samples was assessed using the Kolmogorov-Shapiro test, and for variables that demonstrated a normal distribution, such as age and MDS-UPDRS-III, the distribution homogeneity was tested using Levene's test.

Variables did exhibit a normal distribution, including age, schooling, MoCA, UPDRS II, UPDRS III, TUG and BESTest, which were tested using one-way ANOVA, with the H&Y stages being considered as factors. The effect size was tested for each factor that reached a statistically significant level. In cases where statistically significant differences were detected, Tukey's post-test was applied for pairwise comparisons between the groups.

Variables that did not exhibit a normal distribution, including GDS, MDS-UPDRS-30, and PII, were tested using Kruskal-Wallis ANOVA (KW-ANOVA), with the H&Y stages being considered as factors. When statistically significant differences were observed, multiple comparisons of the average ranks for each pair of groups were applied; normal *z*-values were computed for each comparison, as well as *post-hoc* probabilities (corrected for the number of comparisons) for a two-sided test of significance.

Additionally, Spearman's rank-order correlation was used to test correlations between the balance measures and H&Y and MDS-UPDRS-III scores. Finally, the same test was used to test the correlation between PII and the other balance tests.

A significance level of $p < 0.05$ was used to determine the statistical significance of the findings. All statistical analyses were performed using Statistica version 13 (TIBCO Software Inc., United States).

3 Results

No significant differences were found among the groups in terms of age, gender, schooling, and GDS scores. However, as expected due to disease progression, significant differences were observed in MoCA, MDS-UPDRS-II, and MDS-UPDRS-III scores (Table 1). All balance measures showed significant correlations with H&Y stages and MDS-UPDRS-III (Table 2).

3.1 Pull-test and balance performance

The KW-ANOVA for test 30 of the MDS-UPDRS revealed a statistically significant effect of disease stages according to H&Y (Table 3). Subsequent multiple comparison tests indicated significant differences between stages I and III and stages II and III (Table 3), but no significant difference between stages I and II (Figure 3).

3.2 TUG and balance

The one-way ANOVA for the time taken to complete the TUG test demonstrated a statistically significant effect of disease stages according to H&Y (Table 3). Tukey's *post-hoc* test revealed significant differences between stages I and III and stages II and III (Table 3), but no significant difference between stages I and II (Figure 4).

3.3 BESTest and balance performance

The one-way ANOVA for DGI scores showed a statistically significant effect of disease stages according to H&Y (Table 3). Tukey's *post-hoc* test indicated significant differences between stages I and III and stages II and III (Table 3), but no significant difference between stages I and II (Figure 5).

3.4 Two-dimensional balance evaluation

The KW-ANOVA for the PII revealed a statistically significant effect of disease stages according to H&Y (Table 3). Multiple comparisons indicated significant differences between stages I and II ($p < 0.006$), stages I and III, and stages II and III (Table 3; Figure 6).

Furthermore, the PII was statistically significantly correlated with all clinical balance tests, as can be observed in Table 4.

4 Discussion

Several laboratory-based instruments have been used to evaluate the postural instability associated with PD. Although they may offer a more objective evaluation than clinical tests, the use of sophisticated equipment to identify balance disruption and fall risks has limited clinical utility because they are expensive and demand a highly trained team. This study aimed to investigate a straightforward and non-expensive approach with potential clinical application to identify the progression of postural instability in PwPD.

Our results show that the PII, obtained through the proposed bidimensional kinematic evaluation of head movements during quiet posture, was effective in identifying the progressive increase in postural instability between H&Y stages I, II, and III of PD, while currently recommended clinical tests were able to show significant differences only between the initial and intermediate stages of the

TABLE 1 Clinical and demographic characteristics of participants ($n = 55$).

Variable	H&Y1 ($n = 11$)	H&Y2 ($n = 23$)	H&Y3 ($n = 21$)	H/F	p-value	ES	H&Y1 vs. H&Y2	H&Y1 vs. H&Y3	H&Y2 vs. H&Y3
Age (Years)	65.4 (8.09)	66.3 (8.3)	68.5 (7.6)	0.64	>0.05[a]	–	–	–	–
Gender (Male)	7	16	13	–	>0.05[b]	–	–	–	–
Schooling (Years)	13.8 (4.4)	11.6 (4.02)	12.8 (5.7)	0.47	>0.05[a]	–	–	–	
MDS-UPDRS II (Score)	8.18 (3.7)	12.6 (3.7)	14.4 (7.2)	5.1	0.0003[a]	0.79	0.013[c]	0.003[c]	>0.05[c]
MDS-UPDRS III (score)	10.1 (4.5)	22 (7.3)	27.2 (12)	12.76	0.0001[a]	0.99	0.001[c]	0.001[c]	>0.05[c]
MoCA	26 (2.9)	25.2 (3.7)	23.7 (2.2)	4.18	0.0128[a]	0.71	>0.05[c]	0.015[c]	>0.05[c]
GDS	2.3 (1.5)	3.3 (2.2)	4.3 (3.1)	4.14	>0.05[b]	–	–	–	–

For continuous variables, mean values are presented together with standard deviation values, in parentheses. H&Y, Hoehn and Yahr scale; UPDRS-III, Section 3 of the unified Parkinson's disease rating scale; MoCA, montreal cognitive assessment; GDS, geriatric depression scale; ES, effect size.
[a]ANOVA one-way.
[b]Kruskal-Wallis ANOVA.
[c]Tukey post-test.

disease (I and III; II and III). In other words, the PII could identify subtle balance alterations between two early stages of disease progression.

In the past decade, the number of articles published on postural control in PwPD has increased annually in the scientific literature. This upward trend in article production over time suggests that postural control in PwPD has gradually gained importance as a research topic (20). Currently, the most common way to assess postural control in clinical practice is to use rating scales and motor tests. These tools are susceptible to clinician bias, are insensitive to mild impairments (ceiling effects), and have low reliability (41, 42). Our findings made a significant contribution by demonstrating that the low-cost and user-friendly kinematic assessment we proposed exhibited greater sensitivity in detecting early signs of postural control decline compared to other commonly used clinical tests. This suggests that our assessment has the potential to be readily employed in clinical practice.

Postural instability in PwPD is correlated with the disease severity, being more pronounced in people in the more advanced stages of the disease (43). The progression from H&Y stage II to III marks a critical milestone in PD when gait and BI result in increased motor disability, reducing independence in daily living activities (44). In fact, in the present study, all adopted clinical tests were correlated with H&Y stages and could detect progression in the postural instability from I or II to III H&Y stages. A longitudinal study with PwPD showed that a balance deficit is observed in up to 70% of people in the advanced stages of the disease, being one of the main risk factors for falls (45). Other studies using clinical tests (37) or several different technologies, such as force platforms to measure the COP displacement during quiet posture (46, 47), posturography to evaluate postural sway (48), and accelerometry (25) to measure the range of motion variability, average movement velocity, and movement asymmetry (49, 50), have shown increased postural instability from moderate to advanced PD stages.

Current understanding of postural control changes in early to moderate PD is limited and requires further clarification. Few studies have compared or correlated the balance changes between disease stages and progression, especially the early ones (51). Duncan et al. (52) showed that balance performance measured by the BESTest declined over 6 to 12 months in PwPD. However, only four participants in this study were in H&Y stage I, and the BESTest score was only weakly correlated with the H&Y stages at the study beginning. A review of TUG's psychometric and clinical properties indicated that the H&Y stage must be consistently recorded in the different studies. The authors recommended that further studies divide the sample into stages when performing balance analyses rather than just providing descriptive population data (53). One of the few studies that compared TUG performance in early PD stages (H&Y I and II) and controls found no difference, suggesting no balance decline in early disease stages (54). Finally, the PD severity could be tracked objectively by the quantifiable responses of the pull-test parameters (36), the more relevant alteration can be observed in people in H&Y stage III who had a significantly impaired compensatory response to backward pull (55). Then, it is not a surprise that in the present study, all tests mentioned above, despite being correlated with the H&Y stage, could distinguish only between stages III and I–II.

The studies using laboratory-based instruments have shown better sensitivity to detect postural instability in the early PD stage than clinical tests. Among the 32 studies included in a review on posturography to assess postural control in PD, only half of them included PwPD in H&Y stage I, and only some took into account the stage of the disease's evolution in the analysis of results (56). Studies using this method showed that PwPD in the early stage had a larger sway area (57) and a larger anteroposterior and mediolateral sway range (58) than the control subjects. This previous study also showed that PwPD in H&Y stage II–III presented higher postural control asymmetry than in H&Y stage I. Mild baseline subclinical changes in postural sway were found in PwPD in H&Y stage I (only two participants) and II (59). Studies found a significant correlation between sway indices (22) and anteroposterior and mediolateral sway ranges recorded with eyes closed (60) and H&Y stages (I–III) but did not investigate differences among each H&Y stage. Low-frequency modulation of the center of the pressure may differentiate PwPD in H&Y stage II from those in stage III (56). Small perturbations can more easily destabilize PwPD in H&Y stage III than those in stages I–II, showing larger CoP displacements (61).

TABLE 2 Correlation between balance tests and H&Y stages.

H&Y stage	Spearman R	*p*-value
Pull-test	0.83	0.000001
BESTest	−0.61	0.000001
TUG	0.53	0.000029
PII	0.80	0.000001

H&Y, Hoen & Yarh scale; Pull test, unified Parkinson disease rating scale– Section III; BESTest, balance evaluation systems test; TUG, timed up & go test; PII, postural instability index.

TABLE 3 Balance measures of participants ($n = 55$).

Variable	H&Y1 ($n = 11$)	H&Y2 ($n = 23$)	H&Y3 ($n = 21$)	H/F	*p*-value	ES	H&Y1 vs. H&Y2	H&Y1 vs. H&Y3	H&Y2 vs. H&Y3
Pull-test	0.00 (0.0)	0.43 (0.72)	1.95 (0.22)	36.37	0.00001[b]	–	>0.05[d]	0.00003[d]	0.00001[d]
BESTest	89.72 (4.96)	82.69 (7.35)	73.85 (9.89)	15.12	0.00001[a]	0.99	>0.05[c]	0.001[c]	0.001[c]
TUG	7.58 (1.61)	9.06 (1.59)	11.20 (2.71)	11.93	0.000[a]	0.99	>0.05[c]	0.001[c]	0.004[c]
PII	0.46 (0.06)	0.69 (0.56)	1.27 (0.62)	33.21	0.00001[b]	–	0.0006[d]	0.0002[d]	0.000001[d]

For continuous variables, mean values are presented together with standard deviation values, in parentheses. H&Y, Hoen & Yarh scale; Pull test, unified Parkinson disease rating scale– Section III; BESTest, balance evaluation systems test; TUG, timed up & go test; PII, postural instability index; ES, effect size.
[a]ANOVA one-way.
[b]Kruskal-Wallis ANOVA.
[c]Tukey post-test.
[d]Kruskal-Wallis multiple comparisons.

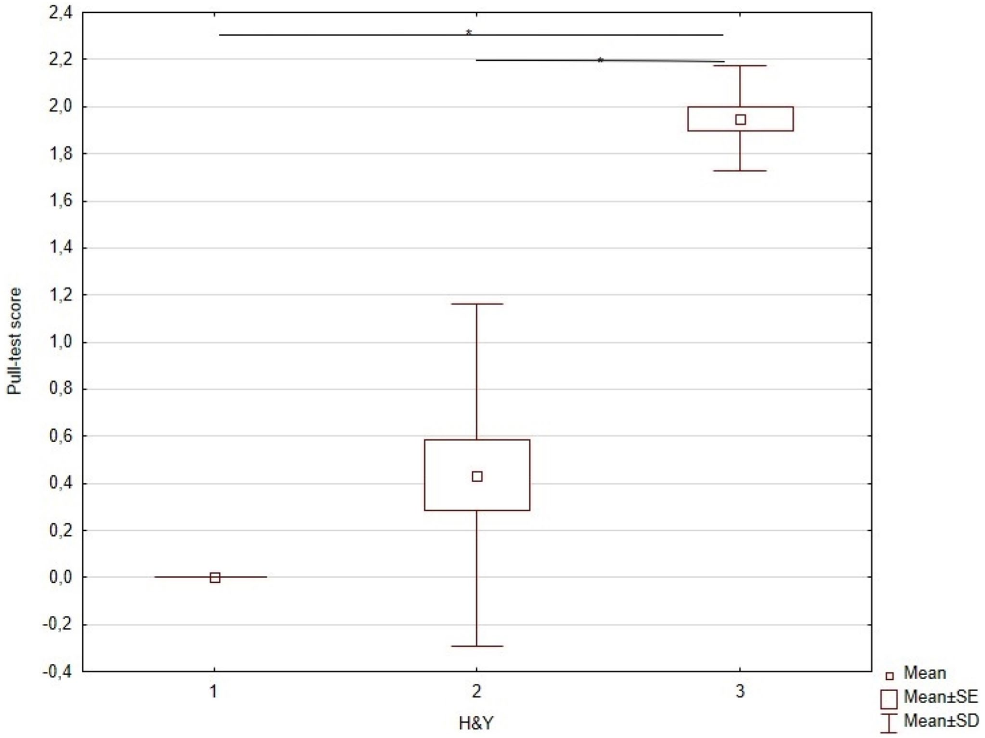

FIGURE 3
KW-ANOVA demonstrating the pull-test differences between H&Y stages I and III, and II and III.

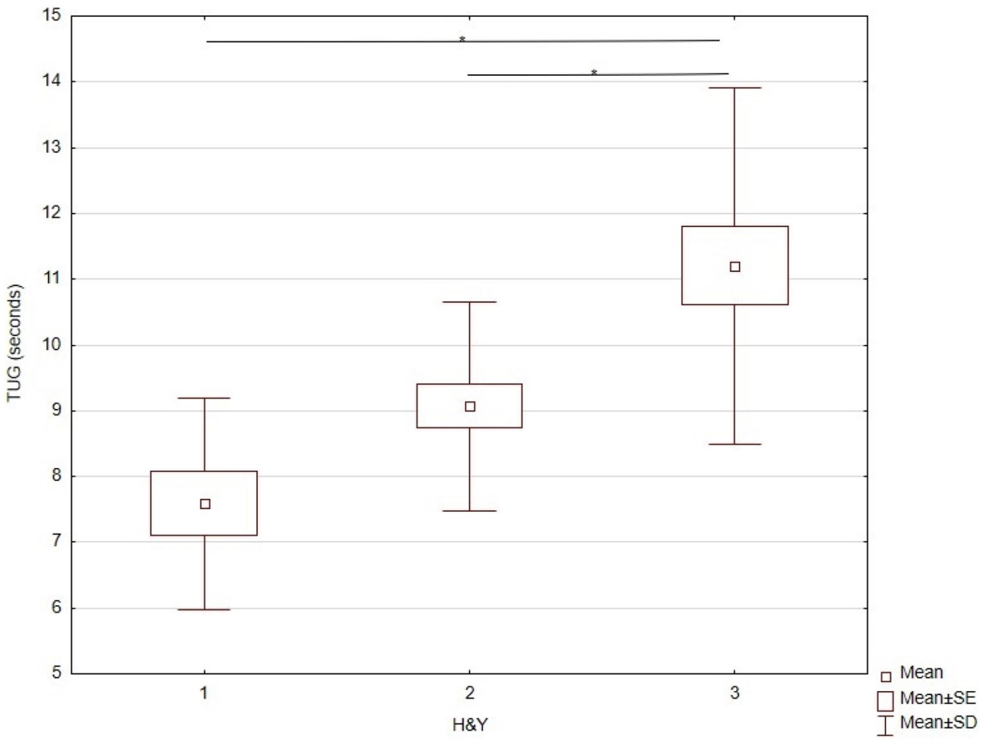

FIGURE 4
KW-ANOVA demonstrating TUG differences in H&Y stages between I and III, and II and III.

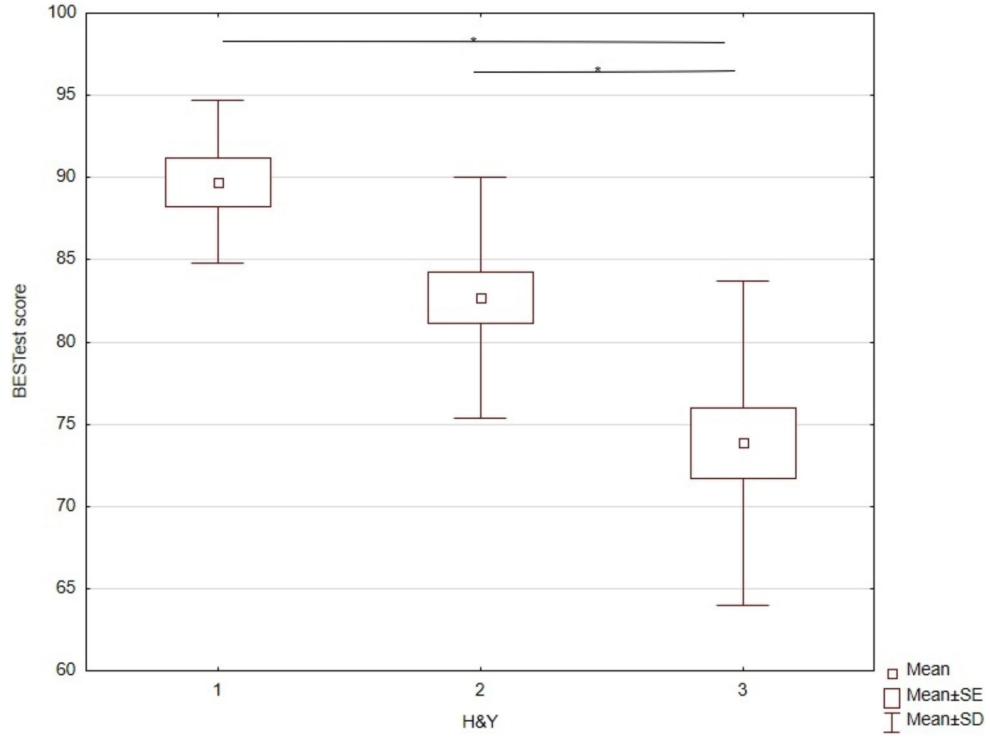

FIGURE 5
KW-ANOVA demonstrating the BESTest differences Between H&Y stages I and III, and II and III.

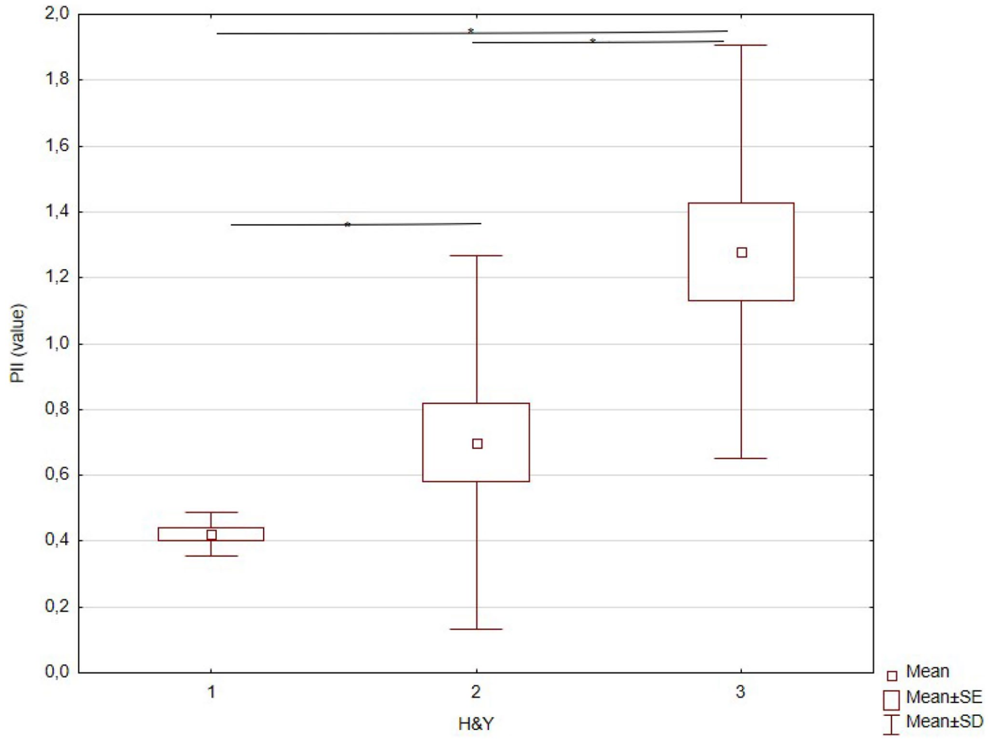

FIGURE 6
KW-ANOVA demonstrating the PII differences between H&Y stages I and II, II and III, and I and III.

TABLE 4 Correlation between PII and balance tests.

PII	Speaman R	p-value
Pull-test	0.70	0.000001
BESTest	−0.53	0.000001
TUG	0.54	0.00001

Pull test, unified Parkinson disease rating scale– Section III; BESTest, balance evaluation systems test; TUG, timed up & go test; PII, postural instability index.

Furthermore, PwPD in H&Y stages II–III presented higher postural control asymmetry than those in stage I (62). In contrast, when comparing postural instability among the three early PD stages, a recent study using static posturography could detect a significant balance decline only between H&Y stages I and III (16). The PII detected significant differences among the three H&Y stages in the present study.

The PII building from the kinematic variable obtained by head movement during quiet posture was based on the relationship between speed, range, and the number of moving elements in the anteroposterior direction. In fact, previous studies showed that increased oscillation of the COP in the anteroposterior direction is a remarkable alteration in PwPD, associated with postural instability (40, 63, 64). Furthermore, the mean root square of anterior–posterior trunk acceleration while standing on foam with eyes open was included in the top 10 ranked models to identify PwPD fallers (32). Most importantly, the stability threshold in anterior and posterior directions may have already decreased in H&Y stage II (65), and the relationship between anteroposterior and lateral stability (larger anteroposterior than lateral oscillations) has been observed since H&Y stages I and II (66). The early alterations in anteroposterior stability, marked by a higher frequency of small movements in the anteroposterior direction, may explain why the frequency, speed, and size of this head movement element in this direction used to calculate PII were able to differentiate the first three PD stages. Notably, individuals in moderate stages of PD face difficulties in scaling their postural responses effectively (67) and exhibit shorter steps, requiring more steps to respond to pulls in the anteroposterior direction (68). The decline in the ability to select and execute appropriate reactive movements regarding direction, amplitude, and speed could lead to postural instability in PD. This decline may be explained by the overlap of several alterations associated with PD, such as axial rigidity, bradykinesia of postural responses, impaired sensory integration, and less automaticity of postural responses (15). Although PII was strongly correlated with recommended clinical tests, it was able to show subtle alterations in anteroposterior stability between very early and early stages (H&Y I and II) that were not detected by clinical tests.

The reproducibility of the variables derived from the two-dimensional software employed in creating the PII must be more explored, highlighting the need for further research utilizing similar or more sophisticated resources. Continuing this effort, our study has the potential to introduce a novel perspective for assessing subtle postural instability in the early stages of PD, facilitating early therapeutic interventions. Moreover, the PII assessment holds promise for detecting balance alterations both pre- and post-intervention, offering valuable, innovative, and non-expensive interventions.

A recent study has shown that the age of PwPD instead of disease duration defines the onset of postural instability, i.e., the older the PwPD at disease onset, the sooner the postural instability onset (69). The present study showed no significant difference between PwPD in H&Y stages I, II, and III. Then, the age differences cannot explain the current results.

Although the results of this study are reliable and significant, we should highlight some limitations. The foremost is the small number of participants, especially regarding PwPD early PD stage (H&Y stage I). More participants in this stage of PD should be analyzed in further studies to confirm our findings. However, considering that participants were strictly selected and the clinical and postural evaluations were performed according to gold-standard scientific procedures, including the randomization of the order of the tests' application, the relevance of the study's contribution is still maintained. Additionally, the PII was built based on head oscillations only. Although a previous study using an identical method with healthy people showed a high correlation between COP measurements obtained by the force platform and head movement obtained by CvMob (28), further studies should conduct a direct comparison with other state-of-the-art methods in PwPD.

By utilizing two-dimensional movement analysis software that incorporates kinematic postural variables, we successfully distinguished variations in BI across the initial three stages of PD progression. This study presents a hopeful prospect of employing a clinical tool to detect subtle alterations in the postural control of individuals with PD.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The present study obtained approval from a Local Ethical Committee (#CAAE 67388816.2.0000.0065) and adhered to the principles outlined in the Helsinki Declaration. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

GS: research project (organization and execution), statistical analysis (design), and manuscript (writing of the first draft). Md'A: research project (organization and execution) and manuscript (writing of the first draft). AH and AR: manuscript (review and critique) and statistical analysis (review and critique). JM: research project (conception), statistical analysis (review and critique), and manuscript (writing of the first draft, review, and critique). MP: research project (conception, organization, and supervision), statistical analysis (design, execution, review, and critique), and manuscript (writing of the first draft, review, and critique). All authors contributed to the article and approved the submitted version.

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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.

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Effectiveness and cost of integrated cognitive and balance training for balance and falls in cerebellar ataxia: a blinded two-arm parallel group RCT

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Background: In patients with cerebellar ataxia (CA), dual-tasking deteriorates the performance of one or both tasks.

Objective: Evaluate the effects of 4 weeks of cognitive-coupled intensive balance training (CIBT) on dual-task cost, dynamic balance, disease severity, number of falls, quality of life, cognition and cost among patients with CA.

Methods: This RCT compared CIBT (Group 1) to single-task training (Group 2) among 32 patients with CA. The intervention included either dual-task (CIBT) or single-task training for 4 weeks followed by 6 months of unsupervised home exercises. Dual-task timed up-and-go test (D-TUG) assessed dual-task cost of the physical and cognitive tasks. Assessment time points included baseline 1 (Week 0:T1), baseline 2 (Week 6:T2), post-intervention (Week 10:T3), and follow-up (Week 34:T4).

Results: Compared to single-task training CIBT improved the dual-task cost of physical task [MD −8.36 95% CI (−14.47 to −2.36, $p < 0.01$), dual-tasking ability [−6.93 (−13.16 to −0.70); $p = 0.03$] assessed using D-TUG, balance assessed using the scale for the assessment and rating of ataxia (SARAbal) [−2.03 (−4.04 to −0.19); $p = 0.04$], visual scores of the SOT (SOT-VIS) [−18.53 (−25.81 to −11.24, $p \leq 0.01$] and maximal excursion [13.84 (4.65 to 23.03; $p \leq 0.01$] of the Limits of Stability (LOS) in the forward direction and reaction time in both forward [−1.11 (−1.42 to −0.78); $p < 0.01$] and right [−0.18 (0.05 to 0.31); $p < 0.01$] directions following 4 weeks of training. CIBT did not have any additional benefits in reducing the number of falls, or improving disease severity, quality of life and cognition. The mean cost of intervention and healthcare costs for 7 months was HKD 33,380 for CIBT group and HKD 38,571 for single-task training group.

Conclusion: We found some evidence to support the use of CIBT for improving the dual-tasking ability, dual-task cost of physical task and dynamic balance in CA. Future large fully-powered studies are needed to confirm this claim.

Clinical trial registration: https://clinicaltrials.gov/study/NCT04648501, identifier [Ref: NCT04648501].

KEYWORDS

cerebellar ataxia, dual-task, dynamic balance, postural stability, cost, falls

Introduction

Cerebellar ataxia (CA) is not a disease but instead describes a collection of symptoms associated with both genetic and acquired diseases that affect the cerebellum or its connections. CA is characterized by postural and gait instability, a lack of coordination of the extremities and trunk, and cognitive impairment (1). The overall prevalence of the diseases associated with CA is 8.22 per 100,000 population (2). Spinocerebellar ataxia has a prevalence ranging from 0.9 to 3.0 per 100,000 population (3). The overall burden of CA is high, with an annual mean cost of EUR 18,776 per patient in Spain (4) and a 6-month mean cost of HKD 146,832 in Hong Kong (HK) (5).

Poor balance and walking difficulties are common symptoms of diseases associated with CA (6), and frequent falls among individuals with CA result in significant burdens for both the individual and the healthcare system (5). The fall rate, defined as at least one accidental fall within the past 12-month period, is estimated at 93% among individuals diagnosed with CA (7). Rehabilitation exercises are considered the first-line treatment for patients with CA (8), and evidence supports the ability of rehabilitation exercises to improve balance and reduce disease severity (9). However, the limited number of high-quality studies, combined with heterogeneity among the diseases resulting in CA, have prevented the development of evidence-based guidelines for rehabilitative interventions (6). Although patients with CA show limited motor re-learning (10), some evidence supports the occurrence of motor re-learning when individuals with CA engage in repeated practice (11, 12). Understanding the potential for motor re-learning among individuals with CA is critical for designing appropriate therapeutic interventions for this population.

Dual-tasking describes the simultaneous performance of two tasks (13). The cerebellum is found to play a significant role in controlling such neural networks during the task (14). Dual-tasking deteriorates the performance of either or both tasks, which is referred to as the dual-task cost (15) among patients with neurological disorders (16, 17). In individuals with CA, dual-tasking is associated with an increased risk for falls (18) and worsen gait disturbances (19). Clinical studies of patients with CA have found that adding cognitive demands to a physical task increases the dual-task cost (19, 20). Balance training that involves dual-tasking reduces the dual-task cost among patients with stroke (21), Parkinson's disease (22), and traumatic brain injury (23).

Currently available interventions for improving balance and gait among individuals with CA do not address the potential benefits of combined intensive balance training and cognitive training in this population. Dual-task training improves dual-tasking in patients with neurological disorders other than CA (22, 23), and dual-task training in patients with CA has been suggested based on these prior findings (18, 19). Studies in the past have examined the influence of dual-tasking on balance and gait variables in this population (18, 24, 25). Studies evaluating the effectiveness of dual-task training in patients with CA are limited (19). The work by Selim et al. on the effectiveness of dual-task training on stability and function is restricted to children aged 5 to 10 years (26). Therefore there is a need for conducting an experiment that tests the benefits of dual-task training among adult patients with CA. We designed a cognitive-coupled intensive balance training (CIBT), an intervention that couples intensive balance with cognitive training, and previously found that CIBT is feasible and safe for patients with CA (27). In the current study, we conducted a randomized controlled trial (RCT) to evaluate the effectiveness and cost of CIBT training in a population with CA when compared with conventional single-task training, consisting of intensive balance training, coordination training, and cognitive exercise training, delivered separately. We assessed dual tasking, dynamic balance, disease severity, quality of life, cognition, and cost.

Materials and methods

An assessor- and statistician-blinded, two-arm, parallel-group RCT comparing dual-task training (CIBT) with single-task training (conventional balance, coordination, and cognitive training delivered separately) was conducted between January 2020 and June 2021 among 32 patients with CA. Eligible participants were randomized into one of two groups: Group 1: dual-task training (CIBT, experimental group); Group 2: single-task training (conventional balance, coordination, and cognition training delivered separately; active control group). Study groups and allocation were concealed. Potential patients with CA were recruited from the Hong Kong Spinocerebellar Ataxia Association (HKSCAA). Ethics approval was obtained from the Human Subjects Ethics Sub-committee of HK (Ref: HSEARS20190322001). The trial was registered with clinicaltrials.gov before the onset of data collection (Ref: NCT04648501).

Study participants were randomized into one of the two intervention groups before the first baseline assessment using permuted blocks determined using computer-generated random numbers. Allocation was performed by a researcher who was blinded to recruitment, assessment of study variables, or intervention delivery. One HK-registered physiotherapist delivered the intervention for both groups. All assessments were performed by individuals blinded to group allocation. We conducted two baseline assessments (T1 and T2) to allow for the prospective evaluation of the number of falls and disease severity progression during a 6-week period. The first baseline assessment (T1) was completed after obtaining written informed consent and demographic data. Participants were then requested to return after 6 weeks for the second baseline assessment (T2), at which point all assessment variables were evaluated, including fall history over the past 6 weeks. The post-intervention assessment was performed after 4 weeks of supervised intervention exercises (T3), and a follow-up assessment was performed after 6 months of unsupervised home practice of intervention exercises (T4).

The following inclusion criteria were applied: (1) individuals of both genders aged 18–60 years; (2) individuals with a confirmed diagnosis of CA (of any type); and (3) individuals able to walk independently with or without assistive walking aids. The following exclusion criteria were applied: (1) any previous history of other neurological diseases (such as Parkinson's disease, stroke, or polyneuropathies) or musculoskeletal problems severely impairing balance, gait, or motor performance; (2) wheel-chair or bed-bound patients who can walk only with handheld support; (3) severe visual impairment preventing exercise participation; or (4) severe cognitive impairment, defined as a score <16 on the Montreal Cognitive Assessment (MoCA) scale (28).

Treatment was initiated for both groups after T2 and continued for 7 months, including 4 weeks of supervised training at HK Polytechnic University (PolyU) and 6 months of unsupervised home training. For the first 4 weeks, both groups attended 60-min training sessions at PolyU, 3 times a week for 4 weeks. After the initial 4-week training phase, participants were asked to complete unsupervised home exercise programmes consistent with their intervention group assignments for the next 6 months.

Training sessions for the experimental, dual-task CIBT group (Group 1) consisted of 10 min of warm-up, 40 min of CIBT training, and 10 min of cool-down. The CIBT programme involves the performance of four types of cognitive tasks during the following physical tasks: sit-to-stand; standing with feet apart; one leg, tandem standing; multidirectional reaching; stair climbing; and walking 10 m. The details of the cognitive tasks are reported elsewhere (27). Motor–cognitive interactions occur when highly challenging cognitive tasks are performed simultaneously with physical tasks, increasing the risk of falls among individuals with CA (19). A careful calibration of the cognitive task difficulty level is necessary to ensure the safety of participants. Each participant's tolerance for motor–cognitive interactions was assessed individually, and the initial difficulty level and progression of both cognitive and physical tasks were determined for each individual to ensure safety.

Treatment sessions for the single-task training group (active control, with conventional balance training, coordination training, and cognitive training were delivered separately; Group 2) consisted of 10 min of warm-up, 20 min of conventional balance and coordination exercises in line with previously published literature (29), 20 min of single-task cognitive training (using the same four tasks used during CIBT), and 10 min of cool-down. In addition, fall prevention strategies were also taught for both the groups. In summary, the CIBT group had 40 min of dual-task training and the control group had the same 40 min of similar exercises included in the CIBT but were delivered as single-task training. For the 6-months follow-up period, the home-based exercises were similar to the exercises delivered during the 4-week intervention phase. The participants were handed pamphlets summarizing the exercises. The dosage of exercises during the follow-up period for both groups was similar however, they were unsupervised.

The progression of treatment for both groups was determined by the Physiotherapist delivering the intervention. The type of physical task and the cognitive task were tailor-made that suit the capacity of the participants. Treatment progression was done once every week. The physical task progression principles included reducing the base of support, physical support, verbal cues, altering the support surface, and changes in the speed of the activity such as walking slower or faster. The progression for cognitive tasks included changes in the difficulty of arithmetic calculation, difficulty of memory tasks and complexity of cognitive tasks such as recollecting rare vegetables or seasonal fruits.

Primary outcome measure

The dual-task costs of physical and cognitive tasks were assessed using the timed up-and-go test (TUG). The standard, single-task TUG (30); the dual-task TUG (D-TUG); and counting backwards were assessed consecutively. During the D-TUG, participants were instructed to count backwards by four from a random starting number while performing the standard TUG. The time to complete the task (in seconds) was recorded. The time required (in seconds) to count backwards by fours from the same starting number without performing a physical task was also recorded. The dual-task cost of physical tasks was estimated using the following formula: [(D-TUG − Standard TUG) ÷ Standard TUG] × 100 (31). The dual-task cost of cognitive tasks was assessed using the following formula: [(D-TUG − Standard backward counting backwards) ÷ Standard counting backwards] × 100. The scores of the DTUG was used to assess dual-tasking ability.

Secondary outcome measures

We included standardized and validated measures for assessing functional balance [Berg Balance Scale (BBS) (30) and Scale for the Assessment and Rating of Ataxia (SARA) balance component (SARAbal) (30)], dynamic stability (LOS) (32, 33), sensory interaction (SOT) (33, 34), number of falls, cognitive function (MoCA) (35), ataxia severity (SARA) (30, 36), and number of falls and quality of life (EuroQol-5 dimension-5 level [EQ-5D-5L]) (37). A summary of the proposed outcome measures, the domains tested, interpretations, and the assessment timeline are reported elsewhere (27). To ensure the rigor of the balance assessment we have used the International Classification of Function (ICF) model in choosing the assessents (38). Body structure and function level assessment of balance identifying the underlying impairment is reported using the DTUG, SOT, and LOS. Activity level assessment of balance is reported using the BBS and TUG. The SARA and SARA-bal are disease-specific measures appropriate for patients with CA (32).

Adherence

Adherence to the intervention protocol was monitored using electronic diaries to reduce missing values and recall errors. At the end of the 4-week supervised training session, participants were provided information on how to access and complete the electronic diaries.

Cost estimation

Cost was assessed using digital or manual self-reported questionnaires. Each participant's digital diary interface was encoded with a unique identification number to ensure privacy. Participants were instructed to complete the digital diary once per month. The researcher interface of the digital diary provided a summary of completed items for all participants. The research assistant followed up with non-responders every

TABLE 1 Cost sheet.

Direct cost	Unsubsidized price per unit
Cost of intervention	HKD 250
Consultation with GP	HKD 445
Visit to specialist (Geriatric day hospital)	HKD 1,960
Specialist outpatient	HKD 1,190
Consultation with TCM	HKD 445
Accident and emergency department contact following falls	HKD 1,230
Hospitalization charge per day (admission plus fees)	HKD 5,100/day
Intensive care ward/unit	HKD 24,400/day
Surgical intervention following falls	Variable
Drugs	Variable
Dressing or injection	HKD 100
Professional home care	HKD 535
Community allied health service	HKD 1,730
Aids and appliances	Variable

Source for cost sheet: 1. Hospital Authority. Fees and charges. Available online at: http://www.ha.org.hk/visitor/ha_visitor_index.asp?Parent_ID=10044&Content_ID$=$10045&Ver$=$HTML (accessed February 9, 2018). 2. Localiiz. Public or Private? A Guide to Healthcare in Hong Kong. Localiiz the Site with Insight (2017). Available online at: http://hk.localiiz.com/public-or-private-a-comprehensive-guide-to-healthcare-in-hong-kong/#.WmkrfYVOJR (accessed January 25, 2018).

month by phone. A printed version of the cost and fall (manual) diary was provided to participants with limited access to the internet. Postage-paid envelopes were included with each printed cost diary to obtain a better response rate, and participants were instructed to post the completed forms once per month. Table 1 lists the direct medical costs. The derived costs of items relevant to the healthcare perspective are reported as the unsubsidised rate for medical care for 2018 (in HKD).

Statistical analyses

The analysis was performed according to the intention-to-treat principle. Maximum likelihood imputation was used to generate data for missing items. Demographic data are reported as the mean and standard deviation (SD) for continuous variables and as the number and percentage for categorical variables. To establish baseline differences between groups, we applied the independent *t*-test for continuous variables and the Chi-square test for categorical variables. Variables without a normal distribution were log-transformed prior to analyses. The mean attendance percentage for the treatment sessions was calculated as the percentage of training sessions attended by the participants against the total number of planned treatment sessions for both supervised (institution-based) and unsupervised (home-based) training sessions. Changes in primary and secondary outcome measures (evaluated at T2, T3, and T4) across the intervention groups were evaluated using an analysis of covariance (ANCOVA) at a 95% confidence interval (CI). Baseline scores were adjusted for disease duration, ataxia severity, and assistive walking device use (co-variates). T2 and T3 were compared to establish immediate treatment effects, whereas T3 and T4 were compared to evaluate the long-term effects of the intervention. Considering the large number of comparisons, to minimize the likelihood of type 1 error Bonferroni correction was included in the analysis. Effect sizes (Cohen's F) were computed using the formula $[\sqrt{ή p^2}/(1 - ή p^2)]$, where $ή p^2$ is the partial eta-squared value obtained from the analysis of covariance. The effect size was interpreted as small if the value of Cohen's F was 0.10 or below, moderate at 0.25, and large at 0.40 or above (39). The mediation effects of dual-task cost of the physical and cognitive task on reducing the number of falls were assessed using the Sobel test. The mean cost of the intervention and health care costs through the follow-up period are reported as the mean and SD. The EQ-5D-5L response was converted into a utility score used to estimate the gain or loss in quality-adjusted life-years during the follow-up period. The cost-effectiveness of the intervention will be reported in a subsequent paper.

Results

Sixty potential participants were approached through the HKSCAA between January 2019 and December 2021. Of these, 32 participants were deemed eligible and consented to participate. Enrolled participants were randomized into the experimental (Group 1, $n = 16$) and control groups (Group 2, $n = 16$) after the first baseline assessment (T1). At the end of the 4-week intervention phase (T3), one participant from Group 1 was lost to follow-up. One additional participant from the Group 1 and one participant from the Group 2 withdrew from the study during the 6-month follow-up assessment (T4). The withdrawal was not related to the study intervention. Figure 1 illustrates the flow of this study.

The baseline characteristics of study participants are presented in Table 2. The mean age of study participants was 48 years (SD: 10.2 years), and 60% of enrolled participants had a subtype of spinocerebellar ataxia, whereas the remaining participants had either degenerative or idiopathic ataxia. The demographic characteristics were insignificant between the groups at baseline. We found insignificant differences in ataxia severity scores (SARA) and ataxia-specific balance scores (SARAbal) between the two baseline assessments (T1 and T2), indicating that participants remained stable in terms of disease severity. The mean attendance percentage for institution-based intervention sessions across both groups was 85%, but it dropped to 62% during the 6-month follow-up period. No adverse events, such as falls, were encountered during the intervention phase. Less than 25% (7 of 32) of participants reported mild muscle pain following the first two intervention sessions, and the pain subsided completely within a few days. The intervention was well-tolerated by all participants across both groups. The mean scores of all outcome measures at all four assessment time points can be found in Appendix 1.

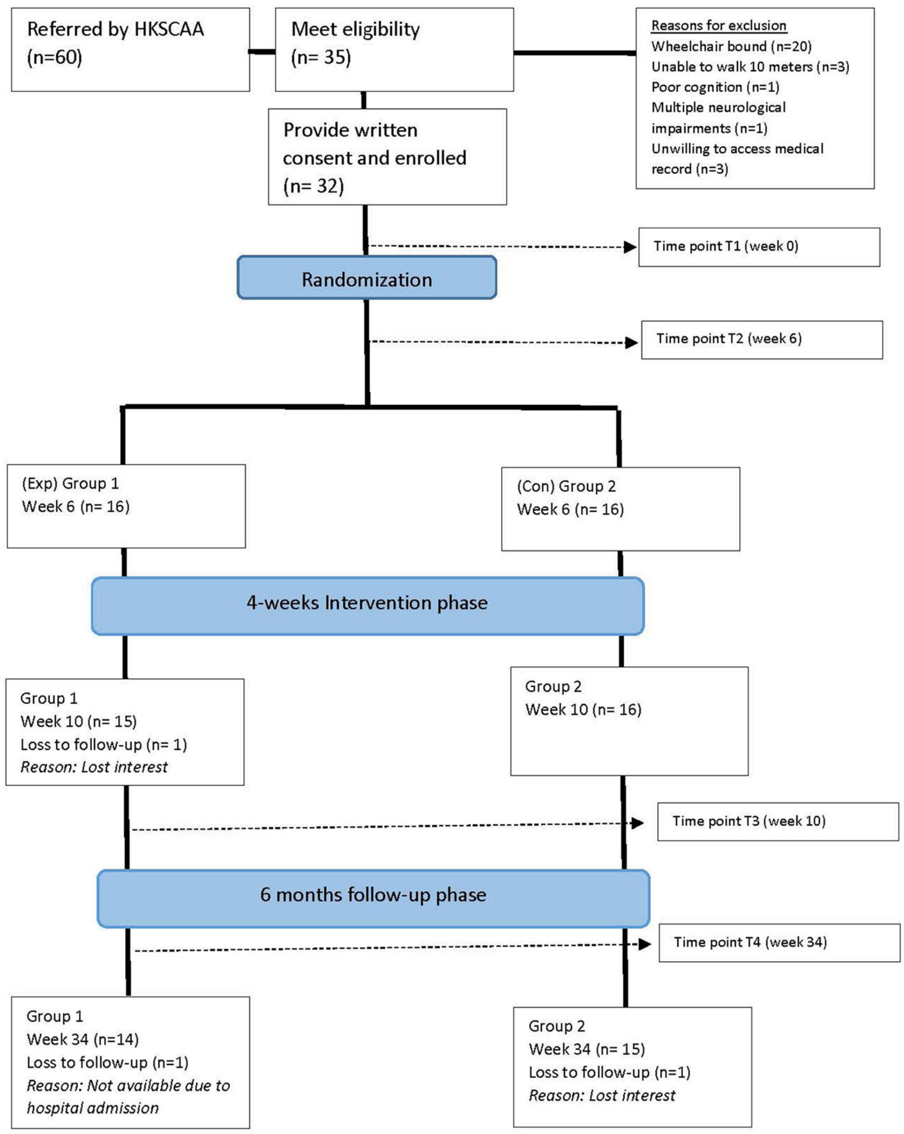

FIGURE 1
Flow of the study. HKSCAA, Hong Kong Spinocerebellar Ataxia Association.

Effect of exercise on dual tasking

Compared to single-task training the CIBT resulted in a significant improvement in dual-tasking ability [MD −6.18, 95% CI (−10.93 to −1.45; $p = 0.01$] and dual-task cost of physical task [MD −8.36 95% CI (−14.47 to −2.36, $p < 0.01$) assessed using the DTUG immediately following the intervention. The effect size of these changes ranged from small to moderate. A summary of between-group differences with 95% confidence interval of all outcome measures is reported in Table 3. A summary of within-group differences at post-intervention and follow-up assessment for all the outcome measures is reported in Appendix 2.

Effect of exercise on dynamic balance

Compared to single-task training the CIBT significantly improved dynamic balance assessed using SARAbal [−2.03 (−4.04 to −0.19); $p = 0.04$], dynamic stability assessed using maximal excursion [13.84 (4.65 to 23.03); $p \leq 0.01$] and reaction time [−1.11; (−1.42 to −0.78); $p < 0.01$] of the LOS test in the forward direction and reaction time [−0.18 (0.05 to 0.31); $p < 0.01$] in the right direction of the LOS. We found a significant reduction in visual scores of the SOT (SOT-VIS) [−18.53 (−25.81 to −11.24), $p \leq 0.01$] among the CIBT group suggestive of a reduction in visual reliance following 4 weeks of CIBT. The effect size of these changes ranged from moderate to large. Benefits attained were not retained for any of these balance measures during the follow-up assessment.

TABLE 2 Demographics of the participants ($n = 32$).

Total no. of participants			Group 1 ($n = 16$) (CIBT)	Group 2 ($n = 16$) (Control)	p
Age Mean (SD)	Mean (SD)		50.20 (14.41)	46.00 (14.05)	0.75
	Range		32–75	26–75	
Gender	Male		8 (50%)	10 (56%)	0.87
	Female		8 (50%)	8 (54%)	
Ethnicity	Chinese		16 (100%)	16 (100%)	1
Occupation	Employed		8 (50%)	9 (56%)	0.52
	Unemployed		4 (25%)	3 (19%)	
	Retired		4 (25%)	4 (25%)	
Diagnosis	Spinocerebellar ataxia	SCA-1	2 (12%)	0 (0%)	0.91
		SCA-3	8 (50%)	7 (44%)	
		SCA-11	0 (0%)	2 (12%)	
	Post-infectious cerebellar degeneration		1 (6%)	1 (6%)	
	Unknown cause for ataxia		5 (31%)	6 (38%)	
Age at disease onset	Mean (SD)		37.70 (14.31)	30.67 (8.29)	0.24
	Range		19–56	17–40	
Disease duration	Mean (SD) in years		12.50 (10.73)	15.33 (11.11)	0.35
	Range		3–36	2–38	
Use of assistive walking device	Yes		14 (88%)	13 (81%)	0.92
	No		2 (12%)	3 (19%)	

SCA, Spinocerebellar ataxia.

Effect of intervention on falls

We did not find significant differences between the two groups for the percentage of fallers, the number of falls per person per month, or the number of near falls per person per month at both post-intervention (T3; Table 4) and at the end of the 6-month follow-up phase. The relative effects of the intervention on falls, measured as the ratio between incidence rates between groups, was 0.83 (95% CI: 021–1.96; $p = 0.21$) for the number of falls in the past month and 0.95 (95% CI: 0.12–4.01; $p = 0.32$) for near falls, indicating no significant differences between groups. Considering the insignificance of the findings the mediation effect was not further explored.

Effect of exercise on disease severity

No between or within-group differences were identified in disease severity assessed using SARA among the CIBT group suggestive of no additional effect of the intervention on disease severity.

Effect of exercise on health-related quality of life and cognitive function

ANCOVA demonstrated no beneficial effect of the intervention on the health-related quality of life assessed using the EQ-5D-5L and cognitive function assessed using the MoCA at the end of 4 weeks of intervention as well as during the follow-up assessment.

Cost

The mean cost of the intervention and the healthcare cost across 7 months is reported in Table 5. The mean cost for delivering the intervention, including the cost of hiring a registered physiotherapist, the cost of the intervention site, and the administrative costs, associated with an average of 12 sessions over 4 weeks for each group, were HKD 4,200. The total mean cost of the intervention plus the healthcare costs for 7 months was HKD 33,380 for Group 1 and HKD 38,571 for Group 2.

Discussion

This study compared CIBT, consisting of intensive dual-task training, with conventional single-task training among patients with CA. Both groups were delivered 4 weeks of supervised exercises, followed by 6 months of unsupervised home exercises. Assessed outcomes included dual-task cost, dual-tasing ability, dynamic balance, fall rate, disease severity, health-related quality of life, and cognition. Some immediate beneficial effects were

TABLE 3 Between-group mean difference and 95% confidence interval across assessment time points T3 (post-intervention) and T4 (follow-up).

Outcome measure		Time points	MD (95% CI)	*P* value	Partial eta squared	Effect size (Cohen's F)
Measures of dual–tasking and balance						
Dual-task-cost (Physical task)		T3	−8.36 (−14.47 to −2.26)	<0.01*	0.09	0.30
		T4	−6.99 (−13.26 to −0.73);	0.03*		
Dual-task-cost (Cognitive task)		T3	−14.80 (−33.94 to 4.33)	0.12	0.005	0.07
		T4	−11.95 (−27.41 to 3.52)	0.12		
Dual-task TUG		T3	−6.93 (−13.16 to −0.70)	0.03*	0.09	0.30
		T4	−7.99 (−0.08 to 16.07)	0.06		
SARA-Bal		T3	−2.03 (−4.04 to −0.19)	0.04*	0.12	0.36
		T4	−0.74 (−3.99 to 2.51)	0.64		
BBS		T3	1.75 (−4.48 to 7.96)	0.57	0.01	0.10
		T4	4.16 (−3.80 to 11.94)	0.28		
SOT	SOT-SOM	T3	−4.42 (−10.90 to 2.06)	0.17	0.09	0.30
		T4	1.49 (−1.58 to 4.54)	0.32		
	SOT-VIS	T3	−18.53 (−25.81 to −11.24)	<0.01*	0.64	1.3
		T4	−16.94 (−23.44 to −10.44)	<0.01*		
	SOT-VEST	T3	−0.89 (−6.53 to 4.75)	0.74	0.05	0.22
		T4	−2.54 (−11.01 to 5.91)	0.54		
	SOT-COMP	T3	9.03 (−1.32 to 19.39)	0.8	0.09	0.30
		T4	0.06 (−9.61 to 9.73)	0.99		
LOS	LOS-F-RT	T3	−1.11 (−1.42 TO −0.78)	<0.01*	0.50	1
		T4	−0.69 (−0.94 TO −0.44)	<0.01*		
	LOS-F-MXE	T3	13.84 (4.65 to 23.03)	<0.01*	0.32	0.68
		T4	21.01 (9.07 to 32.95)	<0.01*		
	LOS-R-RT	T3	−0.18 (0.05 to 0.31)	<0.01*	0.01	0.10
		T4	−0.05 (−0.41 to 0.29)	0.73		
	LOS-R-MXE	T3	−0.17 (−25.56 to 22.12)	0.88	0.01	0.10
		T4	−2.70 (−11.65 to 6.24)	0.54		
	LOS-B-RT	T3	−0.51 (0.22 to 0.78)	<0.01	0.05	0.22
		T4	−0.03 (−0.35 to 0.42)	0.19		
	LOS-B-MXE	T3	−8.35 (−28.42 to 11.72)	0.40	0.01	0.10
		T4	4.41 (−6.13 to 14.92)	0.39		
	LOS-L-RT	T3	0.14 (−0.79 to 0.35)	0.20	0.01	0.10
		T4	0.03 (−0.30 to 0.36)	0.84		
	LOS-L-MXE	T3	2.27 (−17.41 to 21.95)	0.81	0.01	0.10
		T4	9.41 (0.34 to 18.49)	0.04*		
Measures of disease severity, quality of life and cognition, mean (SD)						
SARA		T3	−3.41 (−7.01 to 0.18)	0.17	0.08	0.29
		T4	−2.87 (−7.09 to 1.34)	0.47		
HK-MOCA		T3	−0.61 (−3.65 to 2.43)	0.68	0.01	0.10
		T4	0.80 (−2.09 to 3.70)	0.57		

(Continued)

TABLE 3 (Continued)

Outcome measure		Time points	MD(95% CI)	*P* value	Partial eta squared	Effect size (Cohen's F)
EQ-5D-5-L	EQ-VAS	T3	−5.43 (−13.40 to 2.53)	0.17	0.10	0.33
		T4	−5.32 (−10.88 to 0.25)	0.06		
	QALY	T3	0.04 (−0.07 to 0.16)	0.49	0.01	0.10
		T4	−0.02 (−0.13 to 0.09)	0.71		

The mean difference is expressed as group 1 (CIBT)- group 2 (Control). T3, assessment timeline 3; T4, assessment timeline 4; RT, reaction time; MXE, Maximal excursion; SOT, Senosry Organization Tesst; Som, somatosensory; Vis, visual; Vest, vestibular; Comp, composite; BBS, Berg balance scale; SARA-bal, Balance sub-component of the scale for the assessment and rating of ataxia; R, right; F, front; L, left; B, back; RT, Reaction time; MXE, Maximal excursion; LOS, Limits of stability; EQ-5D-5L, Euro-qol 5 dimension, 5 level; EQ-VAS, visual analog scale of the Euro Qol questionnaire; QOL, Quality-adjusted life year; SARA, scale for the assessment and rating of ataxia; TUG, Timed up and go test; HK-MOCA, Montreal Cognitive Assessment Scaale; Hong Kong version.

TABLE 4 Comparison of 1 month falls reporting at the end of intervention phase (T3).

Category	Falls rate (falls/person-1 month)		IRR experimental-control (95% CI)	*p*
	Group 1	Group 2		
Number of falls	0.31	0.37	0.83 (0.21–1.96)	0.21
Number of near falls	2.68	2.81	0.95 (0.12–4.01)	0.32

IRR, Incidence ratio rate; p, level of significance.

TABLE 5 Mean cost of the intervention and the healthcare cost of 7 months across the intervention groups.

Cost items	Group 1		Group 2	
	Mean units	Mean cost	Mean units	Mean cost
Cost of intervention	12	$4,200	12	$4,200
Visit to GP	4.75	$2,114	4.06	$1,808
Visit to specialist	2.13	$4,165	3.75	$7,350
Chinese medicine	2.63	$1,168	6.38	$2,837
Acupuncture	4.69	$2,086	6.5	$2,893
Hospitalization	0.94	$4,781	1.56	$5,969
Surgical expense	0	0	0	0
Medical supplies	NA	$2,633	NA	$3,220
Medical investigation	1.63	$9,962	0.25	$1,232
AHS	0	0	0	0
Rehab service	NA	$914	NA	$3,586
Transport	NA	$1,096	NA	$4,203
Home modification	NA	$261	NA	$1,273
Total cost	$33,380		$38,571	

GP, General practioner; AHS, Allied Health services; $, Hong Kong Dollars.

observed following the intervention on the dual-task cost of physical tasks and dual-tasking ability assessed using the DTUG. This improvement can be accounted to the contribution of the cerebellum in shifting an additionally demanding task such as dual-tasking to an automatic task with repeated practice (40, 41). The attention theory helps understand this concept where repeated practice results in an improved capacity to shift attention to the secondary task during dual-tasking (42, 43). We found some immediate effects of the intervention on the dynamic balance assessed using the SARAbal. The scale assesses the ability to walk, stand and sit unsupported. A reduction in the postural sway during sitting and standing increased the SARAbal score post-intervention. These changes are in line with previous literature (29). The positive changes captured using the SOT are suggestive of an improvement in the sensory interaction of balance following the intervention. The long-term benefits of CIBT were limited in that we found insignificant differences between groups after 6 months of home-based unsupervised exercises. CIBT did not have any additional benefits in reducing the number of falls or improving disease severity, quality of life and cognition compared to conventional single-task training. The mean cost of intervention and healthcare costs for 7 months was HKD 33,380 for group 1 and HKD 38,571 for group 2.

The dual-task cost of both physical and cognitive tasks during dual-tasking is high among individuals with CA (18, 20, 44). Evidence indicates that repeated practice of dual-tasking results in reductions in dual-task costs, resulting in improved dual-tasking ability (15). Our study also provided some evidence for the reduction in dual-task cost of physical tasks and an improvement in dual-tasking ability following CIBT. A reduction in reaction time, task automatization and optimization of attention allocation during dual-task (45) explains the reduction in dual-task cost (15). We hypothesized dual-task training (CIBT) will have an advantage over single-task training in reducing the number of falls. However, the findings of this study did not support our hypothesis in that, there were no significant between-group differences in the number of falls. We also did not find beneficial effects of CIBT compared with conventional training on quality of life. The inability to identify any significant effects of CIBT may be due to the short intervention period. An extended intervention period, such as 8 or 12 weeks, may be necessary to observe significant changes in the number of falls, quality of life and cognition. Secondly, our falls assessment captured the number of falls in the past 1 month. An ongoing falls assessment throughout the trial period may have better captured the number of falls. Lastly, the follow-up period of 6 months for the fall assessment may have been too short to capture the difference in the number of falls between the groups. Furture studies need to consider ongoing assessments for capturing fall history and longer follow-up periods to see the benefits of dual-task training on falls in this population.

Physical exercises, including sit-to-stand; standing with feet apart; one leg, tandem standing; multidirectional reaching; stair climbing; and walking, are beneficial for improving dynamic balance among individuals with CA (9, 29). The physical training tasks included for both groups included these types of exercises; therefore, we anticipated balance improvements would occur in both groups. Our findings revealed balance improvement assessed using the SARAbal and not in BBS following the intervention. SARAbal is a disease-specific measure of balance and is arguably more sensitive to changes in balance in this population when compared to the BBS. The other interesting finding in terms of dynamic balance was revealed in the laboratory-based assessment tools (SOT and LOS). We found significant between-group differences among the visual scores of SOT (SOT-VIS) and maximal excursion in the forward (MXE-F-LOS) direction and reaction time in the forward (RT-F-LOS) and right (RT-R-LOS) directions of the LOS test. These differences could be argued due to the nature of the assessment. Both these assessments require participants to follow the visual cues on the screen which mimic dual-tasking. Group A demonstrated superior dual-tasking ability during the assessment which may have resulted in better performance. In addition, the sensitivity of the LOS to identify subtle changes in dual-tasking may have been superior when compared to the BBS. Lastly, previous studies report the impairment in vestibular-ocular reflex (46), visual influence and dependence (47, 48) during dynamic tasks in this population. The findings of our study demonstrate a decrease in visual scores of the SOT post-intervention suggestive of a reduction in visual dependence during the dynamic balance task. Future studies are warranted to further examine the relationship between dual-tasking and its effects on visual dependence and vestibulo-ocular reflex in this population. The gains achieved in dynamic balance were not sustained during the follow-up assessment. Within-group differences of these outcome measures between time points T3 and T4 revealed an insignificant difference suggestive of a lack of retention of training effects following 6 months of unsupervised home exercise. The mode of exercise may have influenced the results. The participants were asked to perform unsupervised exercises for 6 months. Though measures were taken to ensure an adequate number of treatment sessions per week, the lack of direct supervision limited researchers from ensuring the adequacy of the exercise dosage. Future studies need to consider measures to ensure adequacy of treatment dosage during the follow-up period.

The CIBT exercise did not have additional benefits in improving the disease severity compared to the control. SARA is a composite score of both motor and non-motor symptoms including impairments in balance, speech, incoordination of limb, and eyeball movement. Our balance training exercises had a positive effect on gait, sitting and standing balance and dysmetria (finger-chase, dysdiadokokinesia and heel-shin slide test) of the SARA among both the groups. A mean reduction of 4 points in the SARA scale among group 1 met the minimal detectable change for intraindividual score differences of <3.5 (49). Yet additional benefits of CIBT over the control intervention on disease severity and the influence of the intervention on non-motor symptoms are still uncertain. For the cognitive assessment, our participants' average score of the MOCA is indicative of mild cognitive impairment (50). The MOCA assesses short-term memory, visuospatial abilities, executive function, attention, language, and orientation. Insignificant within and between-group differences in the scores are suggestive that dual-task training alone is not sufficient to improve for aforementioned cognitive function among patients with CA.

In contrast to our hypothesis, the cost findings across the groups were comparable. We hypothesized a greater reduction of falls rate among group 1 that will yield higher healthcare cost savings. Our follow-up of 6 months may not have been sufficient to capture the healthcare cost difference between the two groups. Our previous study reported the mean 6 monthly costs of CA among the HK population as HKD 146,832 (5). In contrast, the current study reports an average mean healthcare cost of HKD 35,975 per 7 months. The difference in the estimation is due to the difference in the cost estimation perspective. The former study was done from a societal perspective that included non-medical expenses such as loss of productivity while the present study focuses only on the healthcare perspective. Secondly, the participants included in this study are ambulant and arguably have lesser healthcare expenses when compared to the former cohort.

Strengths and limitations of the study

Our study has several strengths. (1) We implemented multiple strategies (digital diary, follow-up phone call reminders, and routine encouragement to continue exercise) to minimize missing data, (2) rigorous methodological procedures were adopted to ensure the quality of this study, (3) the use of a standardized set of outcome measures with sound psychometric properties were used for assessing the study variables, (4) the use of ICF classification for choosing the outcome measures increased the rigor of balance assessment, and (5) additional measures were taken to ensure adequate home-based practice, including tracking the participants' attendance through the digital diary and phone calls to remind participants with poor attendance.

The findings of this study have to be interpreted with caution due to the following limitations (1) we targeted recruiting 44 participants however 12 months of data collection yielded only 32 participants making the study findings underpowered. Future studies need to consider including more public hospitals in HK and Mainland China to increase the sample size, (2) our sample did not include any acquired causes of CA and therefore generalizing the finding to all types of CA is limited, (3) our sample is restricted to ambulant patients with CA and therefore the benefits of dual-tasks training among patients with poor balance and the non-ambulant is unknown, (4) we used the past 1-month fall history to record the number of falls and we likely missed falls during the period beyond the assessment window, (5) our measures for tracking the adherence to home-exercise including digital diary and phone call reminder limited the researchers from ensuring adequate treatment dosage during the follow-up period. More objective tracking measures such as fitit, applewatch or other similar trackers need to be considered in the future, and (6) finally, our cost estimation was self-reported, though the self-reporting was completed every month the change for recall bias cannot be eliminated.

Conclusion

This study demonstrates some evidence to support the benefits of 4 weeks of intense dual-task training on the dual-task cost of physical task, dual-tasking ability and dynamic balance. The long-term benefits of CIBT are found to be limited. CIBT did not improve falls, quality of life and cognition in this population.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethics approval was obtained from the Human Subjects Ethics Sub-committee of HK (Ref: HSEARS20190322001). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

SJW: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing. AC: Conceptualization, Funding acquisition, Validation, Writing—original draft. SLW: Conceptualization, Funding acquisition, Methodology, Validation, Writing—original draft. CC: Conceptualization, Formal analysis, Funding acquisition, Writing—original draft. MP: Conceptualization, Funding acquisition, Methodology, Validation, Writing—original draft.

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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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1267099/full#supplementary-material

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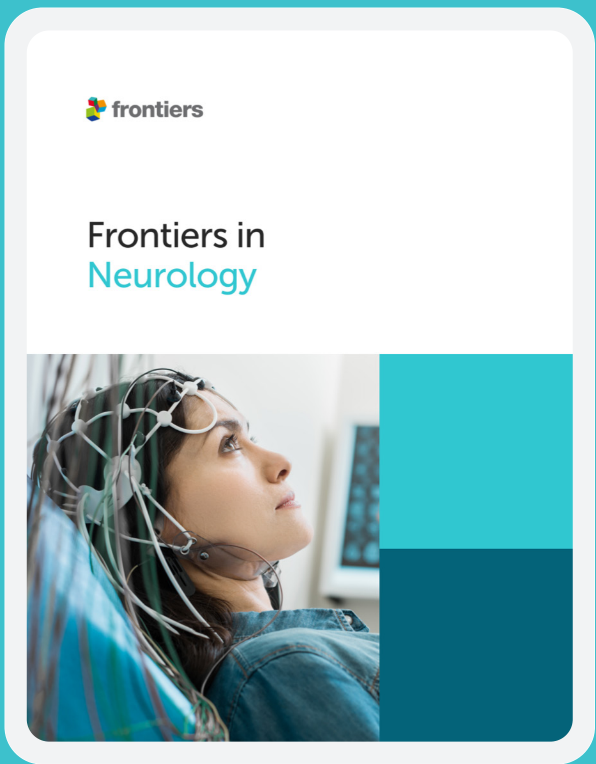

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