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Cognition and mobility with aging or neurological conditions: Assessment and intervention strategies

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Cognition and mobility with aging or neurological conditions: Assessment and intervention strategies

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Editorial: Cognition and mobility with aging or neurological conditions: Assessment and interventions strategies

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Editorial on the Research Topic
Cognition and mobility with aging or neurological conditions: Assessment and interventions strategies

Introduction

Aging and neurological conditions may impact everyday mobility activities. Age-related cognitive decline may be associated with difficulties with mobility is essential to avoid social isolation and negative consequences on quality of life. Different types of interventions (cognitive training, aerobic exercise training, and educational programs) may maintain or improve cognition and mobility in older individuals or individuals with neurological conditions.

Therefore, we host this special Research Topic for Frontiers in Neurology and Frontiers in Neurorehabilitation that focuses on cognition and mobility with aging and neurological conditions. The aim of this Research Topic is to share and discuss recent advances to better assess and potentially improve cognition and/or mobility in older adults or adults with neurological disorders.

This Research Topic includes 15 manuscripts: 11 original research articles, two systematic reviews, one perspective paper, and one study protocol. The papers cover three main domains: (1) cognition; (2) mobility; and (3) interactions between cognition and mobility.

Cognition

Establishing reliable tests to measure different cognitive functions following a stroke is essential for clinicians' practices and for improving scientific knowledge. The Oxford

Cognitive Screen (OCS) is a screening tool that provides a "snapshot" of a patient's cognitive profile. To foster the usability of OCS for both clinicians and researchers, Iosa et al. proposed a new visual snapshot that expresses OCS sub-tests as a function of the six cognitive domains: language and arithmetic, memory, visuomotor control, orientation, spatial exploration, and executive functions.

Functional cognitive assessments may be complementary to neuropsychological tests to assess cognition in stroke patients. As an example, Jaywant et al. assessed a 10-item, short-form Weekly Calendar Planning Activity (WCPA-10) as a cognitive instrumental activity of daily living, in patients who had a stroke and were undergoing acute rehabilitation. This tool involves entering a list of simulated, fictional appointments into a weekly schedule while keeping track of, and adhering to multiple task rules and ignoring built-in obstacles and distractions. The results showed that WCPA-10 captures functional performance deficits in stroke patients. This study highlights the need to use performance based, functional cognitive assessments, even for those who perform well on cognitive screening tools.

In the study by Park et al., machine learning models were used to evaluate whether a comprehensive visual rating scale, based on magnetic resonance imaging, can predict progression to dementia. The authors found that tree-based machine learning algorithms outperformed logistic regression in predicting conversion from mild cognitive impairment to dementia, based on features of the comprehensive visual rating scale and clinical data.

Mobility

Four papers evaluated the effects of aging and neurological conditions on the spectrum of mobility, including gait, driving, and autonomous transportation. Two studies proposed new interventions to promote mobility in patients with neurological conditions.

Jiang et al. presented the Composite Activity-related Risk of Falls Scale (CARFS). This scale is designed to measure the risk of falls in relation to the activity-specific fear of falling and physical behavior. The paper attests to the reliability and validity of the CARFS in older people with various medical conditions and persons who had a stroke or spinal cord injury.

In a perspective paper, Dale et al. described the feasibility of standardized objective balance assessments in individuals with progressive supranuclear palsy (PSP). The authors encourage safe practices to facilitate more objective balance testing in individuals with PSP.

In a systematic review and meta-analysis, Karpodini et al. evaluated the pooled evidence from 18 randomized controlled trials, comparing the effect of rhythmic auditory stimulation to a control intervention on gait in individuals with Parkinson's disease. The results showed a beneficial effect of rhythmic auditory stimulation on gait, mobility, and quality of life.

Classen et al. investigated the readiness of older adults to accept autonomous shuttles as a mode of transportation. A total of 104 older drivers completed an Automated Vehicle User Perception Survey before and after journeying in an automated shuttle. Technology readiness and barriers to autonomous vehicles were the main predictors of the intention to use the automated shuttle.

Older drivers with cognitive disorders may benefit from interventions to improve their on-road driving safety. As an example, George et al. evaluated the effect of a group-based support and education program (the CarFreeMe TI program) on community mobility (e.g., the use of public transportation) for 20 individuals with traumatic brain or spinal cord injuries who cannot fully return to driving. Although this program did not increase the number of outings away from home, the individuals who received the intervention were more likely to use public transport and transport services, and had an improved quality of life when compared with individuals who received information related to transport options (control group).

In a study protocol, Delphin-Combe et al. proposed an innovative therapeutic educational program (the ACCOMPAGNE program) for patient/natural caregiver dyads who wish to implement self-regulation strategies in driving activity and to improve self-awareness of a patient's driving ability. Awareness has been suggested as a key motivator in compensatory behavior regarding modifications to driving performance.

Interactions between cognition and mobility

Four papers investigated the associations between cognitive performance and mobility measures. Locomotor adaptation, i.e., the ability to adjust stepping movements to changing environmental demands, is essential to walk safely in constantly changing environments.

Pottorf et al. revealed that older individuals with mild cognitive impairment and Alzheimer's Disease showed a reduced magnitude of locomotor adaptation, particularly during the early adaptation phase of split-belt walking. Interestingly, the authors found associations between reduced locomotor adaptation and cognitive impairments, suggesting that individuals who have cognitive impairments may also demonstrate impairments in locomotor adaptation.

Another study examined the associations between turning mobility and cognitive functions in patients with chronic post-stroke symptoms (Kuan et al.). The authors found that turning mobility was significantly associated with global cognitive function and distinct cognitive domains, such as visuospatial ability and language. The authors concluded that stroke patients,

with poorer cognition, impairments in language, or visuospatial ability, may be more prone to instability when performing walking turns or turning to the paretic side.

Lee et al. evaluated changes in dual-task performance after robotic upper extremity rehabilitation in individuals who had a hemiplegic stroke. After 4 weeks of robotic rehabilitation, participants improved more in single motor tasks than in single cognitive tasks. The benefits of robotic rehabilitation on motor outcomes were even more evident in the dual-task conditions. After a mild traumatic brain injury (mTBI), patients may report imbalance during walking, with head movements caused by injury to the vestibular system. D'Silva et al. showed that after a mTBI, people may exhibit a slower usual gait speed compared with age-matched controls. In particular, with head turns and an added cognitive task, their gait speed decreased and continued to be significantly slower than the healthy controls. The authors highlight the important implications for people with mTBI as they return to work, leisure, and community activities.

Conclusion

Assessing cognitive functions, especially executive functions, in a real-life context in different populations of people with neurological conditions should be further explored, as they play a major role in everyday mobility activities. Furthermore, there is now a large body of evidence indicating that interventions (e.g., educational intervention or training programs) may help older drivers and those with cognitive impairments to maintain their mobility and quality of life. Finally, with health and environmental issues, changes in daily mobility are observed, especially in urban areas. A better understanding of the associations between cognitive functions and different modes of mobilities (walking, cycling, or riding a personal mobility device) could help to design new interventions to promote active mobility in older adults and those with neurological impairments.

Author contributions

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

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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Impaired Performance on a Cognitively-Based Instrumental Activities of Daily Living Task, the 10-Item Weekly Calendar Planning Activity, in Individuals With Stroke Undergoing Acute Inpatient Rehabilitation

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Performance-based, functionally relevant, and standardized measures of cognitive-instrumental activities of daily living (C-IADL) can complement neuropsychological tests of cognitive impairment and provide valuable clinical information to inform rehabilitation planning. Existing measures have been validated in the outpatient setting. Here, we sought to evaluate a 10-item, short-form of a C-IADL measure, Weekly Calendar Planning Activity (WCPA-10), in inpatients with stroke undergoing acute rehabilitation. The specific goal was to determine if the WCPA-10 could differentiate between stroke patients undergoing acute inpatient rehabilitation and healthy control individuals. We also explored whether the WCPA-10 would identify C-IADL limitations in stroke patients screened as having intact cognition. Seventy-seven stroke inpatients undergoing rehabilitation and 77 healthy control participants completed the WCPA-10, which involves entering a list of simulated, fictional appointments into a weekly schedule while keeping track of and adhering to multiple task rules and ignoring built-in obstacles and distractions. Compared to the control group, stroke patients had significantly worse accuracy, made more errors, used fewer cognitive strategies, followed fewer rules, took more time to complete the task, and were less efficient. 83% of stroke patients were less accurate than predicted by their age, and 64% used less strategies than their age prediction. Among 28 participants who screened as having "normal" cognitive function on the Montreal Cognitive Assessment, the majority had deficits on the WCPA-10. Our results provide initial support for use of a brief C-IADL assessment, WCPA-10, for individuals with stroke undergoing inpatient rehabilitation. They indicate that stroke patients have deficits in C-IADL accuracy, efficiency, and strategy use at this stage of stroke recovery. Results highlight the need to use performance based, functional cognitive assessments, even for those who perform well on cognitive screening tools.

Keywords: neurorehabilitation, executive functioning, activities of daily living, cerebrovascular disease, neuropsychology

INTRODUCTION

Cognitive impairments are common and persistent following stroke and contribute to limitations in daily activities and poor functional outcomes (1). Neuropsychological testing is the gold standard for assessing cognition in stroke patients at the impairment level. Functional cognitive assessments that objectively assess performance in complex or cognitively-based instrumental activities of daily (C-IADL)— such as organizing a schedule, paying bills, or managing medications—can serve as a valuable complement when assessing cognition in stroke patients. C-IADL measures reflect the integration of multiple cognitive skills, predominantly executive functions, applied to functionally relevant activities (2). An individual with stroke may perform well on structured neuropsychological measures, but have considerable difficulty in everyday unstructured activities that require the ability to initiate, plan, multitask or cope with unexpected obstacles. Although performance on C-IADL tasks is associated with standardized neuropsychological tests, the correlations only range between 0.27 and 0.60, suggesting that each provides unique contributions to characterizing the person's overall cognitive profile (3).

C-IADL measures can be particularly valuable for stroke patients in the acute inpatient rehabilitation setting, because they can identify functional cognitive weaknesses and inform early cognitive rehabilitation intervention. This is important because early post-stroke executive dysfunction is associated with long-term disability and limitations in activities of daily living (4–6). Cognitive difficulties in the early post-stroke period are also independently associated with functional mobility in the chronic phase (7), possibly because impaired cognition interferes with attention to and control of motor movements (8), particularly when the difficulty of walking is high (9). Early, tailored cognitive interventions can alter the trajectory of recovery post-stroke (10). C-IADL measures may also be optimal for administration during acute inpatient rehabilitation because they are within the scope of practice of occupational therapists, and do not require specialty consultation with a neuropsychologist.

There are few performance-based C-IADL assessments that have been described specifically for the inpatient rehabilitation of stroke patients. Exceptions include the Executive Function Performance Test, which incorporates bill paying, medication management, using the telephone, and cooking (11); and the Kettle Test, which involves preparing beverages according to specific criteria (12). Both measure the level of verbal assistance needed to complete the task; however, feasibility can be constrained by the kitchen and cooking equipment needed for the Kettle Test and the cooking subtests of the Executive Function Performance Test. The Multiple Errands Test (13) is another real-world measure of executive function, for which an inpatient, hospital-based version has been developed (14). It requires multitasking and suppression of habitual responses, similar to ecologically-valid measures of executive functions that were previously developed for adults with brain injuries such as the Six Elements Test (15) and the Hotel task (16). A limitation of the hospital-based Multiple Errands Test is that it is site-specific and requires patients to be moved off unit to the hospital lobby, which can reduce feasibility given the time constraints of the inpatient setting.

The Weekly Calendar Activity (WCPA) (17, 18) is a complex C-IADL measure, similar to the MET, that can be implemented on a desktop or table using only paper and pencil. It involves entering a list of simulated, fictional appointments into a weekly schedule while keeping track of and adhering to multiple rules. Some appointments have set days and times ("fixed") while others include choices of days or times ("flexible") so the person has to make decisions, plan ahead and problem-solve to manage potential conflicts. The task of entering appointments into a weekly schedule is easily recognized as relevant to functional abilities in everyday life and appears easy on the surface; however, appointment conflicts, rule constraints and unexpected obstacles create significant cognitive challenges that require a strategic approach. The standard 17-item version of the WCPA differentiates between healthy controls and a wide range of populations with executive dysfunction including those with multiple sclerosis (19), mild cognitive impairment (20), attention-deficit hyperactivity disorder (21), pediatric acquired brain injury (22), and epilepsy (23). Accuracy on the WCPA correlates with inhibitory control and set-shifting as assessed by the Delis-Kaplan Executive Functioning System (19).

A shorter 10 item version of the WCPA (WCPA-10) was created to decrease the time needed for administration and to be more feasible for the inpatient setting. Seven of the easiest items from the WCPA-17 item appointment list were removed. All other components remained exactly the same. Whether the WCPA-10 can differentiate between healthy adults and individuals with stroke in evaluating C-IADL ability after stroke, and specifically in the inpatient rehabilitation setting with the shorter 10-item version, has to date not been established. Given that the WCPA-10 relies on planning, working memory shifting, and inhibition—abilities that are frequently impaired post-stroke (24, 25)—the WCPA may be sensitive to C-IADL deficits and differentiate patients from age-matched healthy adults in the acute inpatient rehabilitation setting.

The goal of this study was to compare individuals with stroke to healthy age-matched adults in performance on the 10-item short-form/inpatient version of the WCPA. We hypothesized that relative to the healthy control group, individuals with stroke would have lower percentage accuracy of appointments entered, and a lower number of strategies used, which are the primary outcomes of C-IADL and cognitive strategy use, respectively, on the WCPA-10. We also hypothesized that compared to healthy participants, stroke patients would spend less time planning, take longer to complete the task, follow fewer rules correctly, and use fewer cognitive strategies. We predicted that WCPA-10 performance would be correlated only modestly with an impairment-level screening measure of cognition, given that there is only partial overlap between impairment-based and C-IADL measures of cognition (26). Finally, we explored whether the WCPA-10 would be sensitive to C-IADL dysfunction in individuals who screened as having normal cognitive functioning.

METHODS AND MATERIALS

Participants

$N = 77$ individuals with stroke and $N = 77$ healthy age matched controls from a larger existing normative database were included in this study. Stroke patients were all undergoing acute inpatient rehabilitation on a 22-bed general rehabilitation unit at a large, urban academic medical center. Inclusion criteria were the same as for admission to the inpatient rehabilitation unit: medically stable for rehabilitation, ability to tolerate 3 h of rehabilitation therapy daily, and reasonable expectation for functional gain. The 10-item short form of the WCPA was administered to accommodate the time constraints of the inpatient setting. The WCPA-10 was administered as part of standard of care on the inpatient rehabilitation unit by Occupational Therapists for persons who were alert, oriented, able to attend for at least 20 min, able to read and write legibly in English, follow two-step commands, and were cognitively independent in basic self-care activities of daily living (ADL). Exclusion criteria included those who would not be typically given the WCPA-10 during ordinary care such as those with dementia, severe cognitive impairment, language or visual deficits, or required cognitive assistance for basic self-care activities. People with limited English proficiency were also excluded as the test materials were only available in English. All study procedures were approved by the Weill Cornell Medicine Institutional Review Board.

Healthy control participants were obtained from an existing normative database. Participants were recruited *via* snowballing techniques by graduate occupational therapy students from the greater New York City area. Inclusion criteria were those who were living independently in the community, and for participants age over 65, a score >24 on the Montreal Cognitive Assessment (when available, conducted in 46/77 participants). Exclusion criteria were subjective cognitive complaints as measured by a standardized T-score < 35 on the Patient-Reported Outcomes Measurement Information System, (PROMIS) Cognitive Abilities Short-Form Version 2.0, Form 8a (27); reported past history of a neurological condition (e.g., previous stroke, traumatic brain injury, Parkinson's disease, brain tumor), attention-deficit hyperactivity disorder, history of hospitalization for a psychiatric disorder, or inability to read or write in English. Collection of normative data from healthy controls was granted exemption by the Mercy College Institutional Review Board (IRB), because data were recorded such that participants could not be identified. An oral consent script was read aloud, and a written copy of the script was provided to each participant.

Measures

10-item Weekly Calendar Planning Activity

The WCPA-10 is an objective measure of C-IADL performance. The original 17 item version has demonstrated validity, reliability, and sensitivity to executive dysfunction and sensitivity to change (17, 18, 28, 29). The WCPA-10 requires the examinee to input a series of appointments into a mock weekly calendar/schedule while following a set of specific rules and guidelines (**Figure 1**). Appointments are either fixed at a certain date/time or flexible and can be entered on multiple dates/times, and at times conflict, which requires the examinee to manage conflicting appointments. The examinee has to keep track of multiple rules (e.g., cannot enter appointments on a certain day, cannot cross off items once entered) in working memory while shifting between the appointment sheet, calendar, and instructions sheets. The rules are explained verbally just prior to beginning the task. An 8 × 11 paper with task instructions is also placed on the table and can be referred to by the examinee throughout the task. The examiner periodically attempts to distract the examinee with pre-specified questions, which the examinee has to inhibit. The examiner observes the examinee and records specific strategies that he or she uses; the examinee also reports to the examiner at the end of the task any additional strategies that he or she employed in a post-task interview.

In this study, we used the 10-appointment version of the WCPA. The WCPA-10 has the same ratio of fixed and variable appointments (3/7 or 70%) as the original WCPA, but there are only 10 appointments to enter as opposed to 17. The main outcome measure was the percent of appointments entered correctly out of 10 (Percent Accuracy, i.e., number correct/10 × 100%), as it incorporates both accurate performance, errors in managing conflicts, and omission errors. Total Strategies (combination of those observed by the examiner and self-reported by the examinee) was a second measure emphasized in analyses, given the importance of cognitive strategies to cognitive rehabilitation. We also calculated Planning Time (time in seconds from the start of the task to entering the first appointment), Time to Completion, Efficiency Score (time in seconds/weighted accuracy), Total Errors, and the number of Rules Followed correctly out of 5. A lower efficiency score indicates that the client obtained higher accuracy in less time. Efficiency scores were not calculated for those with accuracy scores of 3 or below. Based on the standard WCPA-10 record form, we also documented for each participant whether or not they used one of several different cognitive strategies. Finally, at the conclusion of the WCPA-10, participants were asked "Do you do tasks like this on a regular basis?" to gauge their familiarity and responded "yes" or "no."

Montreal Cognitive Assessment

The MoCA (30) is a 30-item screening measure for general cognitive impairment that is administered on admission as standard of care to all stroke patients on our acute inpatient rehabilitation unit. The MoCA assesses visuospatial/executive skills, naming, attention, language, abstraction, delayed recall, and orientation. Lower scores indicate greater cognitive impairment. The MoCA has demonstrated validity and clinical utility in inpatient stroke rehabilitation (31), and is closely associated with impairments assessed using neuropsychological tests (4).

Statistical Analysis

We used one way analysis of variance (ANOVA) and chi-square tests to evaluate group differences in demographic and clinical variables. We used one-way ANOVAs to evaluate group differences on each of the outcome measures, Percent Accuracy,

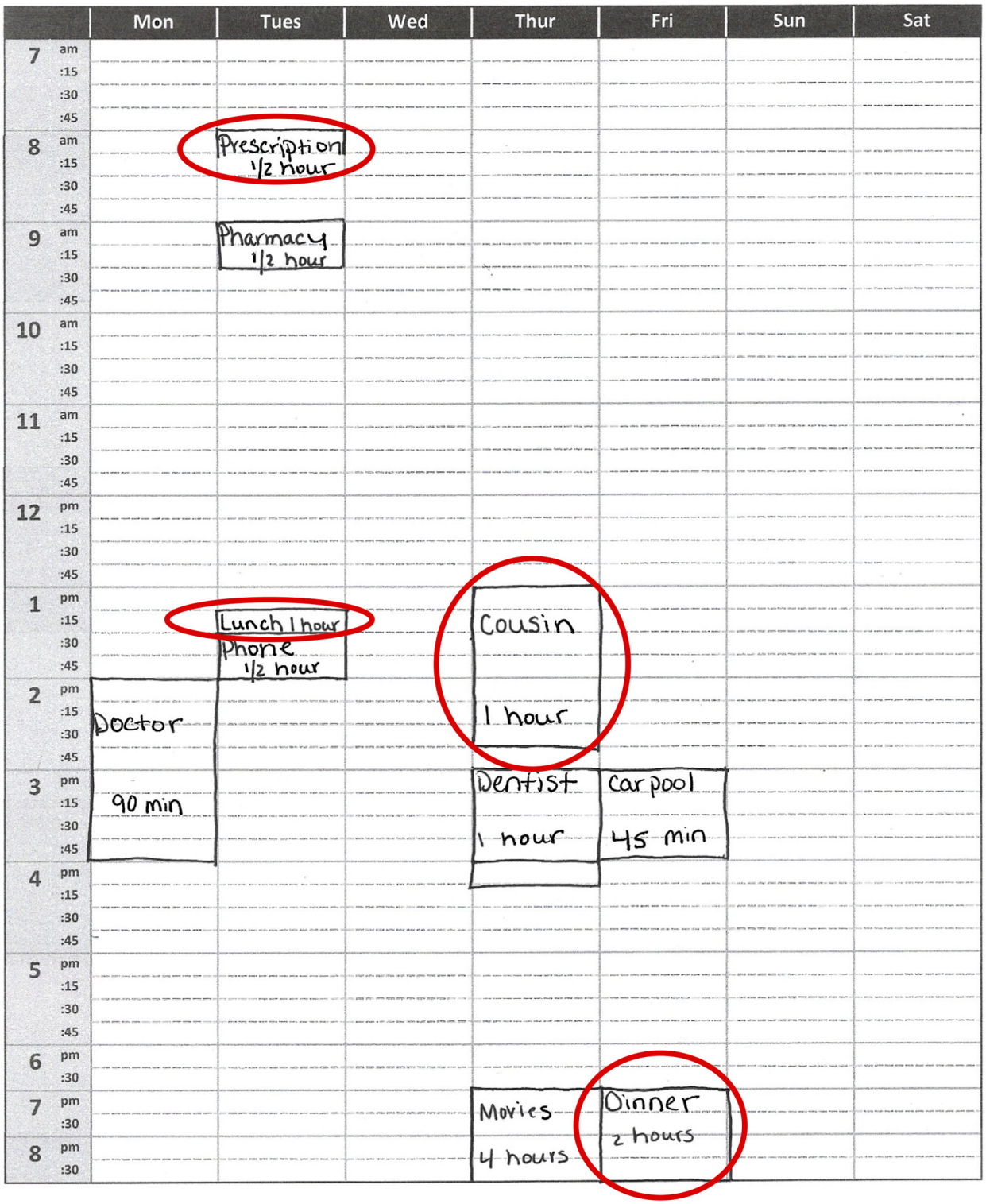

FIGURE 1 | Visual example of the weekly calendar stimulus on the Weekly Calendar Planning Activity. Patients are required to schedule appointments of specific lengths on specific days and times while following multiple rules. Red circles highlight errors, which can include placing the appointment on the wrong day or time ("Prescription ½ h"); marking the appointment with an incorrect duration ("Lunch 1 h"; "Cousin 1 h"); or having a vague description of the appointment ("Cousin," "Dinner").

TABLE 1 | Demographic and clinical characteristics.

	Stroke ($N = 77$)	Healthy control ($N = 77$)	F-value	df	p-value	Effect size η^2
Age	66.1 (14.1)	66.0 (14.0)	0.00	1,152	0.99	0.00
Gender	Female: 38 (49%) Male: 39 (51%)	Female: 41 (53%) Male: 36 (47%)			0.63	–
Education (years)	14.7 (1.9)	14.6 (2.6)	0.04	1,119	0.85	0.00
Race/ethnicity	White: 51 (67%) Black: 16 (21%) Hispanic: 3 (4%) Asian/Pacific Islander: 4 (5%) Native American: 0 (0%) Other: 2 (3%)	White: 49 (64%) Black: 11 (14%) Hispanic: 15 (20%) Asian/Pacific Islander: 1 (1%) Native American: 1 (1%) Other: 0 (0%)			0.02	–
Stroke location	Right hemisphere: 38 (49%) Left hemisphere: 28 (36%) Bilateral: 8 (10%) Unknown/not available: 3 (4%)					
Days post-stroke	18.1 (14.6)	–			–	
Montreal cognitive assessment	23.3 (3.6)	26.2 (1.7)	26.1	1,121	<0.001	0.18

Planning Time, Time to Completion, Efficiency Score, Total Strategies, Total Errors, and Total Rules Followed. Although all WCPA-10 variables differed from normality using the Kolmogorov-Smirnov test (all p's < 0.01), ANOVA is known to be robust against violations of normality (32). The use of non-parametric tests did not change any findings; thus, we report ANOVA results.

For cognitive strategies that were commonly used by the healthy control group (at least $n = 20$ [25%] of the control group used), we compared the frequency of use by individuals with stroke to healthy control participants using chi-square tests. We used a chi-square test to compare the frequency of yes vs. no vs. missing responses to familiarity question by group, and then an independent samples t-test to evaluate separately in stroke and control participants whether there was a difference in accuracy by familiarity (yes or no). We evaluated the association between cognitive impairment and WCPA-10 performance separately in stroke and healthy participants using Spearman rank-order correlations between MoCA scores and Percent Accuracy, Planning Time, Time to Completion, Efficiency Score, Total Strategies, and Total Rules Followed.

We next sought to explore individual differences in the performance of stroke participants relative to the healthy control group, correcting for demographic factors. We first used Spearman rank-order correlations to evaluate in the healthy control group the association between age and education, with Percent Accuracy (as a measure of overall executive skills) and Total Strategies (as a measure of cognitive strategy use). We then used demographic-corrected regression equations—including predictors that exhibited significant correlations with Percent Accuracy and Total Strategies—to obtain the demographic-predicted score for each stroke participant. We subsequently subtracted each participant's demographic-predicted score from his or her obtained score to obtain the residual demographic-corrected score. We reported the frequencies of these residual scores for the entire sample, and for those patients who scored in the normal range on the MoCA (25 or greater out of 30), the latter in order to explore the clinical utility of the WCPA-10 in individuals with stroke who screen as having normal cognitive functioning.

RESULTS

Demographics and Clinical Characteristics

There were no group differences in age, gender, or education (**Table 1**). There was a significant difference in race/ethnicity between groups. Both groups had similar percentages of Caucasian participants, while a greater percentage of Black participants and a smaller percentage of Hispanic participants were observed in the stroke group. Stroke participants had significantly lower MoCA scores than the healthy control group.

Performance on the WCPA-10

On average, the WCPA-10 took ∼12–13 min for stroke participants to complete. Using one-way ANOVAs, relative to control participants, stroke patients had significantly worse Percent Accuracy, Total Strategies, Time to Completion, Efficiency Score, Rules Followed, and Total Errors (**Table 2**). Stroke patients and control participants did not differ in WCPA-10 Planning Time.

The number of strategies used was significantly related to the percentage of accurate appointments on the WCPA-10 ($r_s = 0.37$, $p < 0.001$). The following strategies were used by at least $n = 20$ (25%) of the healthy control group: repeats keywords or instructions out loud; uses finger; crosses off, checks off, or highlights appointments entered; enters fixed appointments first and then flexible appointments; self-checks; talks out loud about strategy or plan; and pauses and rereads. Individuals with stroke less frequently used their finger, crossed/checked/highlighted appointments, entered fixed appointments first and then flexible appointments, and self-checked (**Figure 2**; all $X^2 > 8.1$, p's < 0.04). There was no group difference in frequency of repeating keywords/instructions out loud, or in frequency of pausing

TABLE 2 | Performance of stroke and healthy participants on the WCPA-10.

WCPA-10 measure	Stroke			Healthy control	*F*-value	df	*p*-value	Effect size η^2
	All cases	Low MoCA (<25)	High MoCA (≥25)					
Percent accuracy	49.9 (24.1)	45.7 (24.0)	57.1 (22.9)	71.0 (18.6)	37.2	1, 152	< 0.001	0.20
Total strategies	3.9 (2.0)	3.5 (1.8)	4.6 (2.2)	5.0 (2.5)	10.2	1, 149	< 0.002	0.06
Planning time (s)	89.5 (199.1)	79.8 (128.5)	106.1 (285.1)	62.9 (75.5)	1.2	1, 141	0.29	0.01
Time to completion (s)	767.1 (399.6)	805.4 (399.4)	699.0 (398.3)	552.8 (196.9)	17.7	1, 150	< 0.001	0.11
Efficiency score	266.7 (242.3)	316.4 (283.7)	198.6 (150.5)	120.1 (72.1)	24.4	1, 129	< 0.001	0.16
Rules followed	3.7 (1.0)	3.4 (1.0)	4.0 (0.8)	4.2 (0.8)	13.3	1, 149	< 0.001	0.08
Total errors	5.0 (2.4)	5.4 (2.4)	4.3 (2.3)	2.9 (1.9)	37.2	1, 152	< 0.001	0.20

The statistics provided are for the comparison between all stroke cases and healthy control participants. For the measure Efficiency Score, higher scores indicate lower efficiency.

and rereading. A chi-square test comparing familiarity with a calendar/schedule format by group was significant [$X^2_{(2)} > 7.9$, $p = 0.02$]; however, a z-test comparing cell proportions did not indicate a statistically significant difference in the proportion of the stroke group who stated they were familiar with the calendar (53%) vs. the control group (64%). In the stroke group, there was no difference between those who said they regularly used a calendar/schedule vs. those who said they did not in Percent Accuracy [$t_{(73)} = 0.93$, $p = 0.36$] or Total Strategies [$t_{(70)} = 1.45$, $p = 0.15$]. In the control group, there was no difference between those who said they regularly used a calendar/schedule vs. those who said they did not in Percent Accuracy [$t_{(67)} = 1.48$, $p = 0.15$] or Total Strategies [$t_{(67)} = 0.27$, $p = 0.79$].

Correlation With Cognitive Impairment

In stroke participants, performance on the MoCA was modestly but significantly correlated with Percent Accuracy ($r_s = 0.31$, $p = 0.006$), Rules Followed ($r_s = 0.31$, $p = 0.007$), and Total Strategies ($r_s = 0.30$, $p = 0.009$). MoCA score was not correlated with Efficiency Score ($r_s = -0.25$, $p = 0.06$), Time to Completion ($r_s = -.08$, $p = 0.49$) or Planning Time ($r_s = -0.08$, $p = 0.53$). In healthy participants, performance on the MoCA was modestly but significantly correlated with Total Strategies ($r_s = 0.40$, $p = 0.006$), but not Percent Accuracy ($r_s = 0.14$, $p = 0.34$), Rules Followed ($r_s = -0.03$, $p = 0.84$), Efficiency Score ($r_s = 0.11$, $p = 0.50$), Time to Completion ($r_s = 0.27$, $p = 0.07$) or Planning Time ($r_s = 0.23$, $p = 0.13$).

Exploratory Evaluation of Individual Differences in Performance in Stroke Participants Relative to Control Group After Demographic Correction

In the healthy control group, Percent Accuracy correlated significantly with age ($r_s = -0.38$, $p < 0.001$) but not education ($r_s = 0.16$, $p = 0.19$). Similarly, Total Strategies correlated significantly with age ($r_s = -0.51$, $p < 0.001$) but not education ($r_s = 0.15$, $p = 0.21$). We thus computed regression equations predicting Percent Accuracy and Total Strategies from age. The relationship between Percent Accuracy and age was modeled by $y = 106.3 + (-0.53)$*(age), and the relationship between Total Strategies and age was modeled by $y = 10.5 + (-0.08)$*(age). Using these equations, we calculated each stroke participant's age-predicted Percent Accuracy score and Total Strategies score, and subtracted these values from their obtained scores.

Results are displayed as box plots (median and interquartile range) in **Figure 3**, with negative values indicating performance worse than would be expected by age. As a group, stroke participants had a median Percent Accuracy 19.1% lower than would be predicted by age (range = 79.4% lower to 27.9% higher). 64/77 (83.1%) stroke participants were less accurate on the WCPA than their age prediction. Similarly, stroke participants as a group had a median Total Strategies 1.6 lower than would be predicted by age (range = 7 lower to 6 higher). 55/74 (74%) stroke participants used fewer strategies than their age prediction; three stroke participants were missing data on strategy use.

We then explored individual differences in performance (Percent Accuracy and Total Strategies) using the regression-predicted and age-corrected procedure above, but in stroke participants who scored within normal limits (25/30 or higher) on the MoCA (**Figure 4**). Such participants would be classified clinically as having "normal" cognitive functioning based on standard of care cognitive screening on our inpatient rehabilitation unit. Twenty-eight individuals in our sample scored within normal limits on the MoCA. Within this subgroup, median Percent Accuracy was 11.2% lower than age prediction (range: 61.8% lower to 27.9% higher). 23/28 stroke participants (82.1%) performed below their age-predicted score in Percent Accuracy. Within this subgroup, median Total Strategies was 1.32 lower than predicted by age (range: 4.8 lower to 6 higher). 20/27 stroke participants (74.1%; 1 individual with missing data) performed below their age-predicted score in Total Strategies.

DISCUSSION

The results of this study provide initial support for use of a brief C-IADL assessment,–the WCPA-10–for individuals with stroke undergoing inpatient rehabilitation and highlight the need to use performance based, functional cognitive assessments, even for those who perform well on cognitive screening tools. Specifically, we found that our stroke sample exhibited greater C-IADL deficits, and used fewer cognitive strategies, than did healthy control participants. At an individual level, the majority of stroke patients score below their age-predicted performance on the

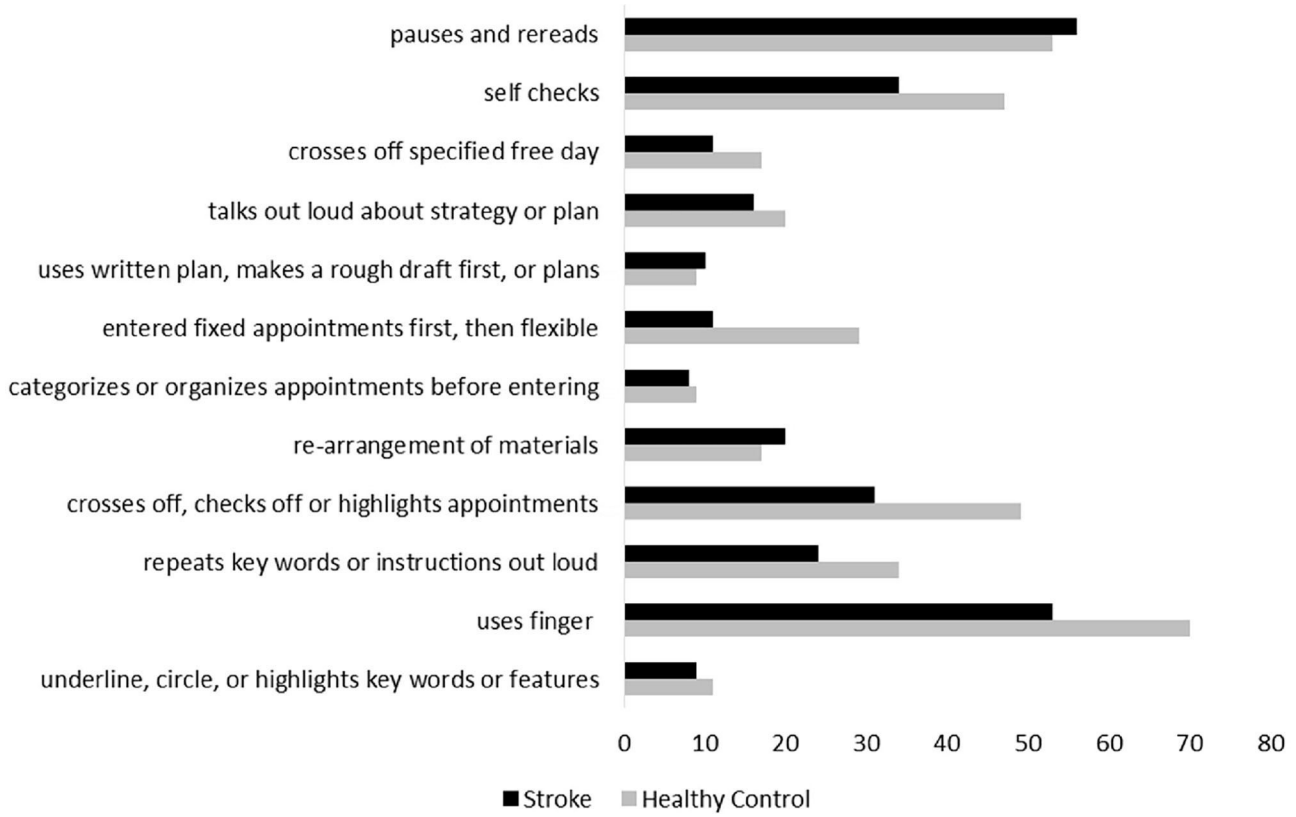

FIGURE 2 | Frequency of strategies used by stroke patients and healthy control participants.

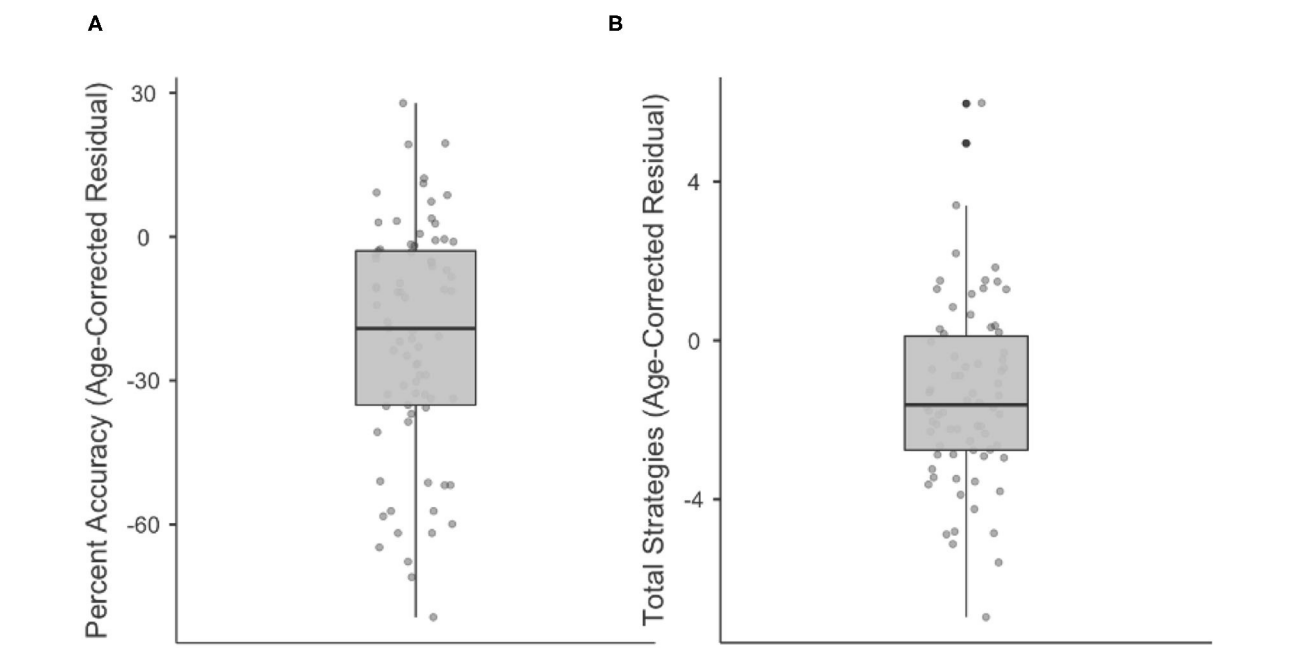

FIGURE 3 | Boxplots showing median, interquartile range, range, and individual datapoints of stroke patient residual scores (raw score—age-predicted score) for percent accuracy **(A)** and total strategies **(B)**. Median/interquartile range of residual scores are below age predictions.

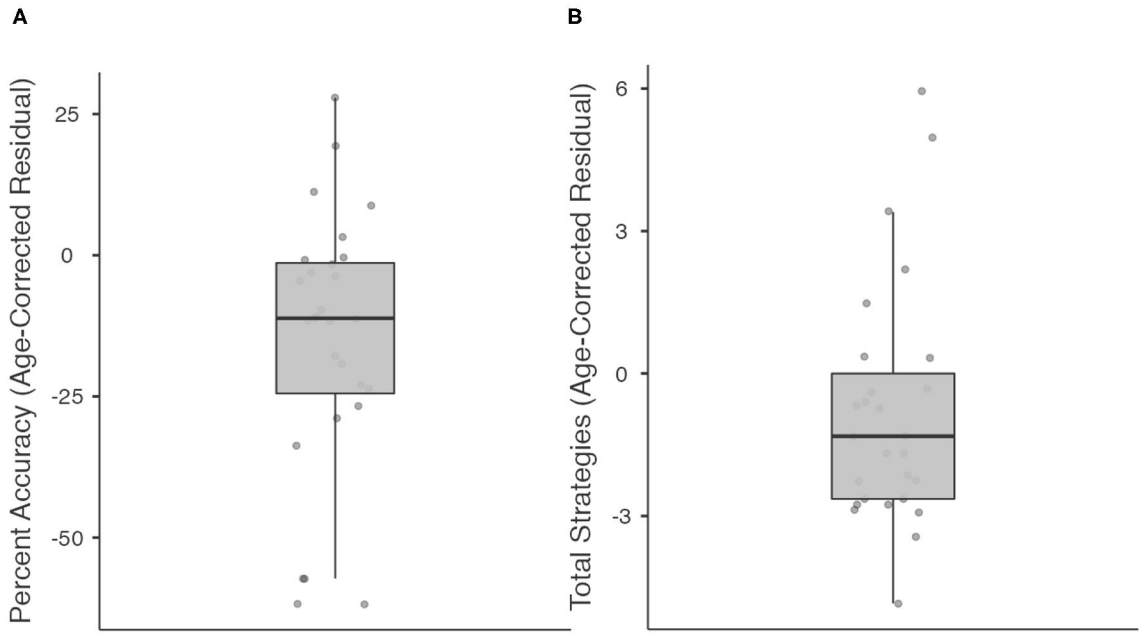

FIGURE 4 | Boxplots showing median, interquartile range, range, and individual datapoints of stroke patient residual scores (raw score—age-predicted score) for percent accuracy **(A)** and total strategies **(B)**, in patients deemed to have "normal" cognitive function on the Montreal Cognitive Assessment. Median/interquartile range of residual scores are below age predictions.

WCPA-10, including overall accuracy and total strategies used. Performance on the WCPA-10 correlated only modestly with an impairment-based screening measure of cognition (MoCA) and identified deficits in patients who would be deemed to have "normal" cognition based on the MoCA.

The WCPA-10 differentiated individuals with stroke from healthy control participants on multiple aspects of C-IADL performance and identified performance deficits that can be easily missed within a structured inpatient rehabilitation setting. Specifically, relative to the control group, our sample of stroke patients had significantly lower accuracy, followed fewer rules, made a greater number of errors, were less efficient, and took longer to complete the WCPA-10. At an individual level, use age-the majority of stroke patients (83%) performed worse on the WCPA-10 than their age prediction. Further, the majority of stroke patients (74%) used fewer cognitive strategies than their age prediction. Because we did not have a detailed cognitive assessment to which we could compare WCPA-10 performance, the specific cognitive impairments contributing to deficient performance are unknown. However, prior research has demonstrated an association between the 17-item WCPA and executive functions (17, 19, 20), suggesting that executive dysfunction may have impacted performance.

Importantly, the WCPA-10 identified C-IADL deficits and worse cognitive strategy use in patients who scored within the normal range on the MoCA. Eighty-two percentage of patients classified as "normal" on the MoCA had worse accuracy than their age prediction and 74% used fewer strategies than their age prediction. This finding underscores the utility of a C-IADL measure such as the WCPA-10 as a complement to traditional impairment-based cognitive screening measures such as the MoCA. Put another way, relying solely on a screen such as the MoCA may result in missing cognitive limitations that have the potential to impact patients' independence in daily activities. Given that it can be administered in on average 12 min, the WCPA-10 can complement the MoCA to assist in identifying and triaging patients most in need of follow-up comprehensive neuropsychological evaluation or higher level functional testing, which can provide information on specific underlying cognitive impairments that may be impacting functional performance. Relatedly, we found only modest correlations between the WCPA and the MoCA. This finding accords with research indicating only partial overlap between impairment-based and functional measures of cognition (26, 33).

Interestingly, the stroke and control groups did not differ in planning time on the WCPA-10. That is, stroke patients on average did not take more or less time relative to control participants to plan their approach to the task, prior to initiating the first appointment entered. This may be because the WCPA-10 goal of entering a list of appointments into a calendar appears deceptively easier than it actually is. Healthy control participants also demonstrated relatively brief planning times; however, they were observed to more frequently stop, pause and readjust task methods once they encountered potential appointment conflicts or recognized task complexities. Pause and stop periods within the task, may thus be better indications of planning than the initial planning time in this particular task.

An advantage of the WCPA-10 is that it enables the objective quantification of cognitive strategy use. This is especially relevant in the inpatient rehabilitation setting where rehabilitation clinicians are teaching patients strategies to optimize performance and maximize independence in C-IADLs in preparation for discharge back to the community. Cognitive strategies are normally used to help people monitor and control performance errors or manage task challenges in cognitively demanding tasks. Healthy people typically use multiple strategies when faced with a cognitive challenge and this was observed with healthy controls on the WCPA. Our findings suggest deficiencies in cognitive strategy use and is consistent with other literature reporting decreases in cognitive strategy use in people with acquired brain injury (34). We found that individuals with stroke less frequently used particular types of cognitive strategies on the WCPA-10. Specifically, they less frequently used their finger (i.e., to focus and maintain attention on salient aspects of the stimuli), less frequently crossed out/checked off/highlighted appointments to keep track of those that had been entered and those that had not been entered, less often entered fixed appointments first and then flexible appointments, and less frequently self-checked for errors. The lower use of these strategies may have increased demands on working memory and cognitive load, thereby contributing to worse performance. This is consistent with studies on the association between strategies and functional performance (34–36). Decreased self-awareness of performance may also be a factor contributing to decreased strategy use (37). For example, if a person doesn't recognize challenges or task difficulties, they also may not perceive the need to use strategies. Future research is needed to examine the cognitive strategy score on the WCPA-10 and its relationship to self-awareness.

Careful analysis of performance and strategy deficiencies within the context of the WCPA-10 can inform the types of strategies and training that may be most useful for clinicians to emphasize during rehabilitation. The WCPA-10 identifies people who have difficulty managing a list and entering information accurately into a weekly calendar. Since use of lists and schedules is an inherent aspect of many everyday tasks, identification of difficulties in these areas provides important targets for rehabilitation intervention. For example, functional cognitive rehabilitation activities that involve managing use of lists in a wide variety of contexts have been described by others (28, 38). The WCPA-10 may also provide more general information on underlying performance deficits, error patterns and deficiencies in strategies that are likely to influence functioning across multiple step activities. Different WCPA-10 result patterns can be observed by analyzing the combination and type of rule breaks, error types, efficiency, strategies used and responses to the after-task interview, along with accuracy. This is illustrated in the original WCPA test manual (17). For example, a person that omits appointments from the list, loses track of rules, and does not to check off appointments or self-check work might also show similar performance errors across other multiple step activities. Cognitive rehabilitation might address general methods to help the person initiate, manage and use efficient strategies to increase the ability to keep track of task variables.

Limitations

Our characterization of clinical stroke characteristics was relatively limited. Because our data were collected in the context of routine clinical care, this limited the ability to collect more comprehensive information such as stroke location or type, lesion size, stroke severity, or medical comorbidities. However, this reflects the realities of clinical research in an acute inpatient rehabilitation setting. Future work on the WCPA-10 will benefit from investigating the relationship between clinical-disease characteristics and performance. Relatedly, the MoCA is a relatively brief screening measure of cognitive impairment. Our stroke sample was not routinely administered comprehensive neuropsychological measures of executive functioning and other cognitive domains to which we could compare performance on the WCPA-10. However, this reflects the reality of integrating assessments on acute inpatient rehabilitation units in which it is not always feasible to conduct extensive neuropsychological testing.

Conclusion

The WCPA-10, a multi-step functional cognitive (C-IADL) task is feasible in an inpatient setting, relatively quick to administer, and captures functional performance deficits in stroke patients relative to age-matched healthy adults, even in those who perform above the normal cut-off score on a cognitive screening tool (Montreal Cognitive Assessment). Relative to healthy adults, individuals with stroke, also use significantly fewer cognitive strategies, both at the group level and commonly on an individual level. This finding emphasizes the importance of analyzing deficiencies in cognitive strategy use and considering methods for promoting strategy use within rehabilitation. C-IADL skills are typically under-assessed in inpatient rehabilitation settings in people with stroke due to time constraints and a focus on physical abilities and self-care skills. This paper is the first to report findings of the 10-item version of the WCPA, thereby contributing to the limited literature on C-IADL assessment and strategy use in stroke inpatients undergoing rehabilitation. The results highlight the potential utility of a higher-level functional cognitive assessment tool like the WCPA-10 to identify cognitive difficulties that may interfere with safety and independence upon discharge to the home and community.

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 Weill Cornell Medicine Institutional Review Board (stroke) and Mercy College (healthy participants). Stroke patients provided their written informed consent and Healthy participants provided oral consent.

AUTHOR CONTRIBUTIONS

AJ: conceptualization, formal analysis, writing-original draft, writing-review and editing, and visualization. CA:

data curation, formal analysis, and writing-review and editing. AL: writing-review and editing and visualization. JT: conceptualization, methodology, writing-original draft, writing-review and editing, supervision, and project administration. All authors contributed to the article and approved the submitted version.

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Predicting Autonomous Shuttle Acceptance in Older Drivers Based on Technology Readiness/Use/Barriers, Life Space, Driving Habits, and Cognition

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Shared autonomous vehicle services (i. e., automated shuttles, AS) are being deployed globally and may improve older adults (≥65 years old) mobility, independence, and participation in the community. However, AS must be user friendly and provide safety benefits if older drivers are to accept and adopt this technology. Current potential barriers to their acceptance of AS include a lack of trust in the systems and hesitation to adopt emerging technology. *Technology readiness, perceived ease of use, perceived barriers,* and *intention to use* the technology, are particularly important constructs to consider in older adults' acceptance and adoption practices of AS. Likewise, person factors, i.e., *age, life space mobility, driving habits*, and *cognition* predict driving safety among older drivers. However, we are not sure if and how these factors may also predict older adults' intention to use the AS. In the current study, we examined responses from 104 older drivers (M_{age} = 74.3, SD_{age} = 5.9) who completed the Automated Vehicle User Perception Survey (AVUPS) before and after riding in an on-road automated shuttle (EasyMile EZ10). The study participants also provided information through the Technology Readiness Index, Technology Acceptance Measure, Life Space Questionnaire, Driving Habits Questionnaire, Trail-making Test Part A and Part B (TMT A and TMT B). Older drivers' age, cognitive scores (i.e., TMT B), driving habits (i.e., crashes and/or citations, exposure, and difficulty of driving) and life space (i.e., how far older adults venture from their primary dwelling) were entered into four models to predict their acceptance of AVs—operationalized according to the subscales (i.e., *intention to use, perceived barriers,* and *well-being*) and the *total acceptance* score of the AVUPS. Next, a partial least squares structural equation model (PLS-SEM) elucidated the relationships between, *technology readiness, perceived ease of use*, *barriers to AV acceptance, life space*, *crashes and/or citations*, *driving exposure, driving difficulty, cognition,* and *intention to use* AS. The regression models indicated that neither age nor cognition (TMT B) significantly predicted older drivers' perceptions of AVs; but their self-reported *driving difficulty* ($p = 0.019$) predicted their *intention to use* AVs: $R^2 = 6.18\%$, F (2,101) = 4.554, $p = 0.040$. Therefore, *intention to use* was the dependent variable in the subsequent PLS-SEM. Findings from the PLS-SEM ($R^2 = 0.467$) indicated the only statistically

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significant predictors of *intention to use* were *technology readiness* ($\beta = 0.247$, *CI = 0.087-0.411)* and *barriers to AV acceptance* ($\beta = -0.504$, *CI = 0.285-0.692).* These novel findings provide evidence suggesting that *technology readiness and barriers* must be better understood if older drivers are to accept and adopt AS.

Keywords: older drivers, predictors, acceptance, automated shuttle, barriers, executive function, cognition

INTRODUCTION

Estimates indicate that older adults are the fastest growing segment of the population, and that they want to continue to drive, or stay mobile in their communities, if driving is no longer an option. Although many of them will continue to drive, we know that some of them are outliving their driving expectancy and need to retire from driving (1). Shared autonomous vehicles services (i.e., automated shuttles, AS) are being deployed globally and may improve older adults' ($\geq$65 years old) mobility, independence, and participation in the community, if they can no longer drive, choose not to drive, or if they are seeking to use alternative forms of transportation. However, AS must be easy to use, provide safety benefits, and instill trust if older drivers are to accept and adopt this technology. General barriers to older drivers' acceptance of AVs includes lack of trust in the systems, fear that driving abilities may decline due to relying on automation, and hesitation to adopting the technologies. Although research is emerging to inform us on the perceptions of older drivers pertaining to their acceptance practices, we are not certain how *demographics, technology readiness, ease of use* of the technology, and the *perceived barriers* related to the technology, may influence their *intention to use* such technology. Moreover, we also expect that a restricted *life space* and *driving history*—may further impact such *intention to use* practices. Finally, *cognitive* status may be a factor underlying older adults' *intention to use* AVs—especially if they need to retire from driving or if they can no longer drive. As such, this study examines how *age, technology readiness, perceived ease of use* of technology, *life space, driving habits,* and *cognition* predict acceptance (*intention to use*) of autonomous shuttles (AS). Understanding the singular and collective impact of such variables, will yield information that will inform city mangers on transportation planning practices for older adults, and assist industry partners with refining, designing, and deployment tactics targeted at older adults.

LITERATURE REVIEW

Older Drivers

Due to increased longevity, worldwide patterns are unfolding suggesting that 703 million persons aged 65-plus lived across the globe in 2019—and that by 2050, one in six people in the world will be over the age of 65 (2). Our aging population in the U.S. at 40.3 million in 2019, will account for one in four adults being 65-plus by 2030—or 80 million older adults in the U.S. (3).

Old age is associated with the onset of chronic conditions, comorbidities, frailty, and increased medication use (4). However, the aging population is a heterogeneous group (5–7) group and may include a mix of healthy and active older adults; people living with chronic disease; people with mild, moderate, or severe cognitive impairment; and people with, e.g., neurodegenerative or other diseases (8). The literature studies on age-related sensory, cognitive, and motor changes and their impact on driving, are very comprehensive and indicate that such underlying factors plausibly affect fitness to drive abilities of older drivers (9–11). Older adults who experience significant cognitive and/or physical declines may reduce or stop their driving (1), limit their out of home or life space activities (12), and consequently feel isolated while also experiencing deteriorating physical and mental health (13), and an impoverished quality of life (14).

Older Drivers and Autonomous Shuttles

The AS—one mode in the family of shared mobility services (15) holds plausible opportunities to allow older drivers who require an alternative to automobile driving, to stay mobile in their communities. Particularly, the use of AS, may preserve independence in community mobility among the aging population with cognitive (and/or other) declines (16). Specific benefits of using AS are related to increased health and safety (e.g., crash prevention, driving stress reduction, increased mobility for those unable to drive); a green environment *via* emission reduction; progressive transportation and city planning; congestion mitigation; infrastructure development; and access to services, leisure, and employment opportunities (17–19). Interestingly, estimates indicate that the over 65-plus group will encompass approximately one third of the mobility marketplace by 2060, with the broader "Silver Economy" majorly contributing to new and related Autonomous Vehicles (AV) business models (17). However, AS must be easy to use and provide safety benefits if older drivers are to accept and adopt this technology (20).

Despite current barriers to older drivers accepting AS that include lack of trust in the systems (21, 22) and hesitation to use the emerging technology (23, 24), research indicates that their perceptions change, positively, after being exposed to an AS, operating at Level 4 of automation (15, 25). Some researchers have assessed user perceptions (alone) *via* survey (26–29), while others have reported on favorable passenger experiences in AS after riding it (30). For example, such riders were positive toward the low travel speeds, observing the shuttle's ability to detect objects (e.g., cyclist next to a shuttle), the control of the shuttle, and access to an emergency button in shuttle. In a recent study, researchers identified specific factors, i.e., using other modes of transportation (e.g., bicycle or public transit), miles driven by car, income, male gender, and living in urban areas, as positive

predictors of older adults' perceptions to use autonomous driving features (31).

Older Drivers' Acceptance and Adoption Practices of Technology

The literature indicates that four constructs are important to consider for older adults' acceptance and adoption practices pertaining to AV technology (32–36). These are: technology readiness, perceived ease of use, perceived barriers, and intention to use the technology, next discussed.

Technology Readiness

The Technology Readiness Index 2.0 [TRI; (32, 37)] is a measure determining optimism, innovativeness, discomfort, and insecurity of participants pertaining to new technologies on a 6-point scale, measuring the variables from 6 = very desirable to 1 = very undesirable. This multi-item scale yields acceptable psychometrics, and although not geared toward the older adults specifically, examines individual's readiness to use technology across the four categories (optimism, innovativeness, discomfort, and insecurity).

Perceived Ease of Use

This factor is contained within the Technology Acceptance Model [TAM; (33)]. The TAM, widely used in the literature to determine older adults' acceptance of information technology, explains about 40% of the variance in individuals' intention to use technology, and helps to understand user ease of use of the technology (34). Limitations, however, pertains to the TAM's lack of predicting cost, cultural differences, and social aspects of decision making in acceptance of such technology (35).

Perceived Barriers of AV Acceptance

The Autonomous Vehicle User Perception Survey [AVUPS; (36, 38)] contains three subscales (i.e., *intention to use, perceived barriers,* and *well-being*) and a total *acceptance* score. The AVUPS showed acceptable face validity and the mean content validity index was 96% (38). The total AVUPS scores for test-retest reliability ($N = 84$) were significantly and strongly correlated with excellent reliability ($\rho = 0.76$, $p < 0.001$, ICC = 0.95). The separate Mokken scale scores for test-retest were also significantly and strongly correlated with excellent reliability: i.e., *intention to use* ($\rho = 0.80$, $p < 0.001$, ICC = 0.93), *perceived barriers* ($\rho = 0.73$, $p < 0.001$, ICC = 0.87), and *well-being* ($\rho = 0.72$, $p < 0.001$, ICC = 0.84) (36). Because the construct validity indicated that either of the three separate Mokken subscales (i.e., intention to use, perceived barriers, and well-being), and/or the total acceptance score can be used to quantify users' perceptions of AVs (36), this tool may be used as a valid indicator for assessing older adults' perceived barriers, as well as their intention to use AVs.

Person Factors as Predictors of AV Technology Acceptance

From the older driver literature, we know that person factors, i.e., age, life space mobility, driving habits, and cognition all predict driving safety among older drivers (6, 12, 39, 40). However—what is not known is if and how these factors will also predict older adults' intention to use the AS as a shared mobility service.

Life Space

Life space mobility indicates patterns of functional mobility that may change over time (6). Particularly, Stalvey et al., defines life space as the "spatial extent of an older person's mobility" (12). These researchers developed the Life Space Questionnaire (LSQ) as a reliable and valid measure to determine the mobility and independence of community-dwelling older populations over time. Life space mobility as a concept, is widely documented in the older driver literature, and is associated with personal, cognitive, functional, environmental, and social factors that affect how people live their day-to-day lives (6, 41). In a comprehensive review of the literature, conducted from 2010 to 2020, Johnson et al. (6) surmise that life space can be understood as an independent or dependent variable in older adults. Particularly, as an independent variable, life space is predictive of cognitive declines, admissions to nursing homes, falls, decreased quality of life, and mortality (42–45). Likewise, as a dependent variable, life space is associated with impairment in walking, various modes of transportation use, and car driving in older male and female adults (40, 46). It seems reasonable to surmise that a decline in life space mobility may lead to an increased desire to use the AS as a viable transportation option.

Driving Habits

Aging is associated with increased adoption of self-regulation strategies (e.g., limiting driving to only drive in optimal conditions, avoiding night driving or driving in traffic, or seeking alternative forms of mobility), driving fewer days per week, failing an on-road assessment, and unsafe driving such as observed in violations, crashes and/or citations, or driving cessation (7, 47–50). Such driving habits are generally assessed in the older driver literature via the Driving Habits Questionnaire [DHQ; (50)]. However, we do not know if declining driving habits, assessed by the DHQ, are associated with AS acceptance practices—and a general review of the literature yielded no findings to support (or not) this statement.

Cognition

Cognitive declines may lead to a deterioration in driving performance and essentially be a plausible factor underlying unsafe driving over time (51). According to researchers (39, 52, 53), cognitive predictors of older drivers failing an on-road evaluation, or being crash involved include: decreased visual attention [i.e., sustained, divided, selective, or switching attention (54)]; decreased visual processing speed [i.e., amount of time needed to make a correct judgment about a visual stimulus (55)]; decreased spatial abilities [i.e., generation, retention, retrieval, and transformation of visual-spatial information (56, 57)]; and decreased reaction time, [i.e., being able to respond quickly and carry out tasks concurrently (58)]. Moreover, impaired executive functioning [i.e., control and coordination of cognitive operations including planning, reasoning, problem solving, decision-making, judgement (59, 60)]—may lead to a degradation of driving tasks in older drivers (16). What is not

clear from the current literature is if and how impaired cognitive abilities predictive of poor driving performance may also be telling of older adults' AV acceptance practices.

Summary

Although some of the aforementioned factors inform us on older driver perceptions pertaining to accepting AV technology, we are less informed about how these factors, combined with person factors, may be predictive of older adults' intention to use the AS as a viable mode of transportation.

Rational and Significance

Our country and the world are aging. Yet, the desire to stay mobile and to participate in their communities are paramount among older adults. Age-related declines are affecting the safety and fitness to drive abilities of older drivers which eventually impair their independence in community mobility and participation in society. Although autonomous vehicle technologies, specifically the AS, a shared mobility service, holds plausible community mobility opportunities for older adults, we do not yet understand the effect of *age, technology readiness/use/barriers*, *life space mobility, driving habits,* and *cognition*—as singular or cumulative predictors of intending to use such technology.

Assumptions

Based on the literature, and our past and current findings on older drivers' acceptance practices of AS, we have formulated four assumptions: (1) older age (vs. younger age) will be a barrier of AS acceptance; (2) decreased cognitive status will be a barrier in AS acceptance; (3) driving habits (i.e., increased driving difficulty, crashes and/or citations) will positively predict AS acceptance; and (4) decreased life space mobility will positively predict AS acceptance. Finally, we anticipated that the predictor variables will singularly or cumulatively explain the eventual acceptance and adoption practices of older drivers—and hence we developed a conceptual model to explore the multi-variate relationships.

Purpose

The primary purpose of this paper is to examine if *age, technology readiness/use/barriers*, *life space, driving habits,* and *cognition* are predictors of older adults' *intention to use the technology*. This information is critical to help inform city managers and transportation planners as they develop AS deployment practices. Likewise, findings will be very relevant to industry partners, who must refine design factors, to provide ubiquitous access and acceptability to older adults if they are to use the AS.

METHODS

The University's Institutional Review Board (IRB#201801988) provided approval for the study and all participants consented to enroll and participate in the study. Participants received $25.00 upon completing the study.

Design

This is a secondary analysis from a pre-posttest experimental design study (15). For this study we utilized surveys at baseline and after exposure to the automated shuttle (AS). We enrolled participants who were recruited from community partner interactions, older driver stakeholders, flyers placed in community settings, and Facebook groups. Detailed methodology and research protocol are discussed in our previous publications (15, 36, 38).

Community-dwelling older drivers ($N = 104$) were included in the parent study if they were 65 years of age or older, had a valid drivers' license, and had driven in the last 6 months. They were excluded if they scored < 18 Montreal Cognitive Assessment (MoCA) or were unable to communicate in English. In this study, older drivers were relatively independent as the eligibility criteria reduced heterogeneity of our sample by excluding individuals that displayed signs of impaired cognition, required routine assistance, and no longer maintained a valid drivers' license or driving exposure.

Equipment

The EasyMile EZ10 automated shuttle (SAE Level 4) operated with a safety operator in the vehicle, on a pre-designated route in a deserted bus depot (see **Figure 1**). The deserted bus depot was located in an urban environment next to a park, restaurants, and a new bus depot with various forms of transportation. The AS operated at roughly 15 miles per hour without the presence of ambient traffic or pedestrians. The AS ride was about 10 min in duration, between the hours of 9 AM and 4 PM, in an area with no traffic, bicyclists, or pedestrians, and in good weather conditions. Initially six participants were allowed in the shuttle, but due to COVID-19, we accommodated two participants in the shuttle. All the participants and research team adhered to CDC guidelines for COVID-19 prevention.

Procedure

The detailed study protocol is available from Classen et al. (25). We are only discussing the procedure relevant to this analysis. As such, during the first visit, participants completed a demographic medical history form (61), TRI 2.0 (37), TAM (33), Automated Vehicle User Perception Survey [AVUPS; (36, 38)], Life Space Questionnaire [LSQ: (12)], DHQ (50), and the TMT A and B (62). Prior to riding in the AS, participants were instructed to remain seated while the shuttle operated. During the route, the safety operator detailed capabilities and features of the AS. The AVUPS was completed again during their final visit, i.e., after being exposed to both the autonomous shuttle and simulator. (Note, the simulator data are not analyzed in this study.)

Measures

Independent variables for the exploratory path model included the following:

Age. The only variable used from the demographic medical history form for this analysis was age.

Technology Readiness. Four items were used from the Technology Readiness Index 2.0 [TRI; (37)], representing the validated domain, *optimism* (see **Table 1**).

Perceived Ease of Use. Four items were used from the Technology Acceptance Model [TAM; (33)], representing the validated domain, *perceived ease of use* (see **Table 1**).

FIGURE 1 | The EasyMile EZ10 automated shuttle (SAE Level 4).

Perceived Barriers to AV Acceptance. Six items were used from the *perceived barriers,* a sub-scale of the AVUPS (36). The items and their loadings are indicated in **Table 1**.

Life Space Questionnaire [LSQ: (12)]. The LSQ, is a valid and reliable measure to ascertain how far older adults venture from their primary dwelling. The LSQ assesses mobility *via* nine space-levels (bedroom/sleep area, external area of the residence, yard/driveway, community, neighborhood, town, county, state, southeast region) accessed in the prior week. Each space level is scored according to the space reached (binary) which is represented by the nine LSQ items. The total score, obtained by summing the score on each level (i.e., each item), ranges from 0 (older adult restricted to the bedroom/sleeping area) to 9 (older adult traveled outside of southeast region). Participants were informed that their study visit should not influence their LSQ responses.

Driving Habits Questionnaire [DHQ; (50)]. The DHQ contains 34 items comprised of six factors, including *self-reported crashes and/or citations, driving exposure*, *driving space, current driving status, driving dependence,* and *driving difficulty*. The *self-reported crashes and/or citations* and *driving space* items are answered yes (1) or no (0). *Driving exposure* indicates the number of self-reported miles driven in the past year. *Driving space* reflects six space-levels (immediate neighborhood, beyond neighborhood, neighboring towns, distant towns, outside the state of residence, outside the region). Current *driving status* was used as a manipulation check for the inclusion criterion, i.e., "driving within the last 6 months with a valid driver's license" and the *dependence on other drivers,* ranges from 1 ("I drive") to 3 ("this person drives me"). *Driving difficulty* (eight items) ranges from 1 ("so difficult I no longer drive in the situation") to 5 ("no difficulty") on a 100-point scale. The mean score of the eight-items is subtracted by 1 and multiplied by 25. A score below 90 suggests driving difficulty. The three factors used for this analysis was *self-reported crashes and/or citations, driving exposure,* and *driving difficulty*.

Cognition: Trail Making Test Part A and Part B [TMT A and TMT B; (62)]. TMT A and B are extensively used among researchers to assess executive functions, visual–perceptual functions and visual–motor tracking of older drivers (5, 47, 63, 64). TMT A requires participants to connect numbers and involves visual scanning, number recognition, numeric sequencing, and motor speed. Trails B requires participants to connect numbers with letters, alternating between the two sequences and measuring set shifting and

TABLE 1 | Items, item factor loading, internal consistency (α), average variance extracted (AVE), and construct reliability (CR) for the PLS-SEM ($N = 104$).

Constructs/items	Item	λ	α	AVE	CR
Technology Readiness			0.791	0.614	0.863
TRI 1	New technologies contribute to a better quality of life	0.846			
TRI 2	Technology gives me more freedom of mobility	0.777			
TRI 3	Technology gives people more control over their daily lives	0.821			
TRI 4	Technology makes me more productive in my personal life	0.680			
Perceived ease of use			0.736	0.555	0.831
TAM 7	My interaction with the autonomous vehicle is clear and understandable.	0.822			
TAM 8	Interacting with the autonomous vehicle does not require a lot of my mental effort.	0.579			
TAM 9	I find the autonomous vehicle to be easy to use.	0.798			
TAM 10	I find it easy to get the autonomous vehicle to do what I want it to do.	0.756			
Barriers to AV acceptance			0.780	0.532	0.790
AVUPS 5	I am suspicious of automated vehicles	0.679			
AVUPS 14	It will require a lot of effort to figure out how to use an automated vehicle	0.678			
AVUPS 16	I would rarely use an automated vehicle	0.722			
AVUPS 19×	My driving abilities will decline due to relying on an automated vehicle	<0.05			
AVUPS 26	I believe that automated vehicles will increase the number of crashes	0.734			
AVUPS 28	I feel hesitant about using an automated vehicle	0.825			
Intention to use			0.917	0.554	0.931
AVUPS 4	I am open to the idea of using automated vehicles	0.700			
AVUPS 6	I believe I can trust automated vehicles	0.683			
AVUPS 7×	I will engage in other tasks while riding in an automated vehicle	<.05			
AVUPS 8	I believe automated vehicles will reduce traffic congestion	0.759			
AVUPS 9	I believe automated vehicles will assist with parking	0.703			
AVUPS 13	I expect that automated vehicles will be easy to use	0.782			
AVUPS 15	I would use an automated vehicle on a daily basis	0.551			
AVUPS 17×	Even if I had access to an automated vehicle, I would still want to drive myself	<0.05			
AVUPS 20	I will be willing to pay more for an automated vehicle compared to what I would pay for a traditional car	0.585			
AVUPS 21	If cost was not an issue, I would use an automated vehicle	0.840			
AVUPS 22	I would use an automated vehicle if National Highway Traffic Safety Administration (NHTSA) deems them as being safe	0.868			
AVUPS 25	When I'm riding in an automated vehicle, other road users will be safe	0.813			
AVUPS 27	I feel safe riding in an automated vehicle	0.833			

λ, Item Factor Loading (Criteria: > 0.5); ×, item was removed due to poor factor loading; PLS-SEM, Partial least squares structural equation modeling; TRI, Technology Readiness Index; TAM, Technology Acceptance Model; AVUPS, Autonomous Vehicle User Perception Survey. α, Cronbach's alpha; AVE, Average Variance Extracted; CR, Construct Reliability. Items for the Barriers of AV Acceptance construct are from the AVUPS Perceived Barrier scale.

mental flexibility. TMT B, a proxy variable for executive functioning (subtracting TMT A from TMT B), is a predictor of on-road performance in community-dwelling older licensed drivers (65).

Dependent Variable

Intention to Use

The AVUPS contains *intention to use* as one of the sub-scales that demonstrated excellent reliability and validity (36, 38). The 13 items used in the *intention to use* subscale, are indicated in **Table 1**.

Data Analysis

Descriptive statistics were conducted for participants' age and sex. Continuous data were presented as mean (M) and standard deviation (SD). Categorical data were presented as count (n) and percentage (%).

A series of multiple linear regressions, with backward stepwise selection, were conducted to predict the outcome variables,

three AVUPS subscales and the total AVUPS acceptance score. The post-exposure AVUPS scores were used as our dependent variables. The best model for each outcome variable was selected based on simplicity and Akaike information criterion (AIC). The independence of residuals was assessed via a Durbin-Watson test. The linearity was assessed *via* partial regression plots and a plot of studentized residuals against the predicted values. Multicollinearity and collinearity were assessed using bivariate correlations and comparison of tolerance values and variance inflation factors [>2; (66)]. The final model was cross-validated using k-fold cross validation. The predictors for all four models included age (continuous), TMT B (continuous), four domains from the driving habits questionnaire: i.e., [driving dependence (ordinal), driving exposure (continuous), driving difficulty (continuous), crashes and/or citations (binary; no vs. yes)], and life space (ordinal). MoCA scores were not entered as predictors into our models as they were used as an exclusion criterion for participant selection. The AVUPS scores were assessed for normality *via* visual examination (i.e., histograms and probability plots) and statistical tests (i.e., Fisher's skewness, kurtosis, and Shapiro-Wilk test). The *p*-values were adjusted to control for multiple comparisons using the Benjamini-Hochberg procedure (67). A *p-value* of <0.05 was considered significant. Data were analyzed in RStudio (68) using R version 4.0.4 (69) and the tidyverse ecosystem (70).

An exploratory path model was formulated to elucidate the relationships between, *age, technology readiness, perceived ease of use, barriers to AV acceptance*, *life space, driving habits,* and *cognition* to *intention to use.* Specifically, PLS-SEM was deployed using SEMinR software (71). All scores were used from participants' baseline intake (i.e., pre-exposure) other than *intention to use,* which was collected after riding in the AS. The exploratory path model (**Figure 2**) displays the hypothesized relationships between *technology readiness* (TRI optimism domain), *perceived ease of use* (TAM domain), *barriers of AV acceptance* (AVUPS subscale)*, life space* (LSQ total score), *crashes and*/or *citations* (DHQ), *driving exposure* (DHQ driving exposure domain), *driving difficulty* (DHQ driving difficulty domain), *cognition* (Time to complete Trails B) to *intention to use* (AVUPS intention to use subscale). PLS-SEM was used due to the exploratory nature of our study, relatively small sample size, and its ability to builds upon multiple regression to investigate complex relationships between dependent and independent variables (72, 73). All scores entered into the PLS-SEM were normalized using the Blom transformation (74, 75), the most commonly deployed rank-based inverse normal transformation. Criteria used to evaluate the constructs were as follows: the (a) factor loading coefficients must be >0.5, (b) average variance explained (AVE) in each construct must be >0.5, and (c) composite reliability of each construct must be >0.7 (73). The structural model was evaluated by interpreting the magnitude of each path coefficients (β). The 95% Confidence Interval (CI) of each path coefficient was estimated by bootstrapping using the Monte Carlo method, whereby 5,000 random sub-samples were drawn with replacement from the item scores.

RESULTS

The study sample ($N = 104$ older drivers; $M_{age} = 74.3 \pm 6.0$) was predominantly White ($n = 93$; 89%) and consisted of 47 (45%) males and 57 (55%) females, ranging from 65 to 91 years old. The three AVUPS domain scores and *total acceptance* score did not differ between genders (binary) (15); thus, gender was not used as a covariate in the models. Descriptive statistics for participants' *age, driving habits*, and *cognition* are displayed in **Tables 2**, **3**.

Four multiple linear regression models with backward stepwise selection were conducted to predict AVUPS subscales (i.e., *intention to use, perceived barriers,* and *well-being*) and

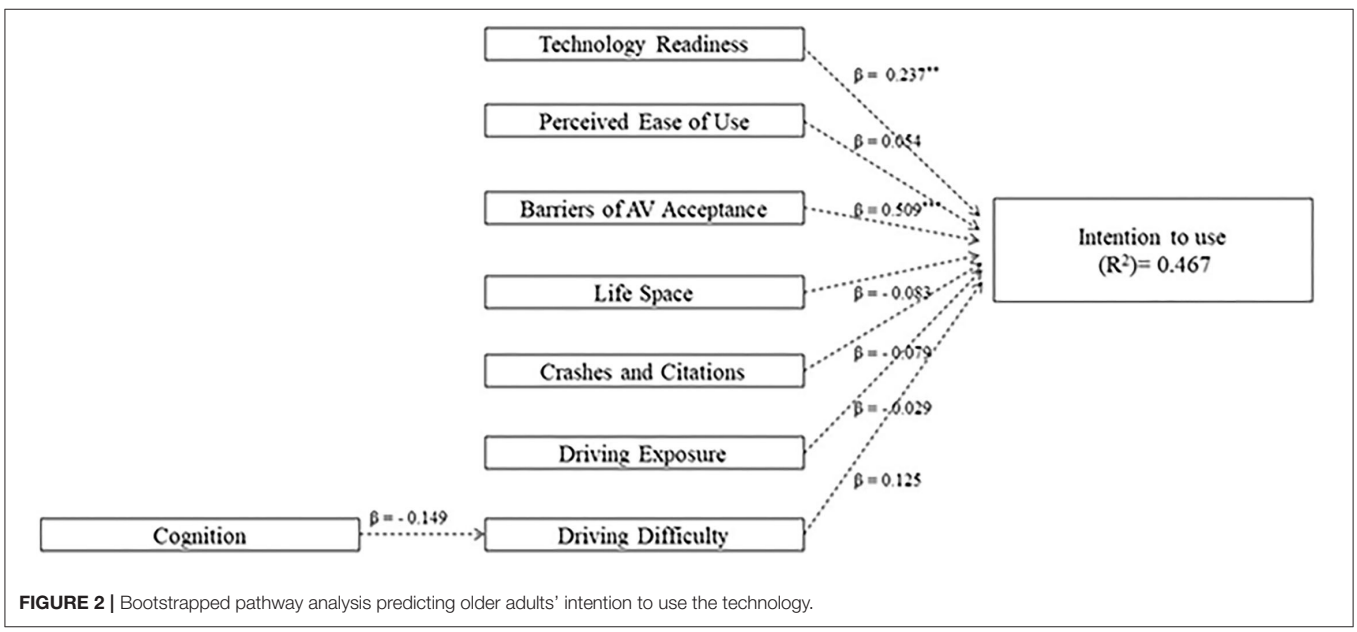

FIGURE 2 | Bootstrapped pathway analysis predicting older adults' intention to use the technology.

TABLE 2 | Indicators of continuous independent variables: Age, cognition, and self-reported driving habits ($N = 104$).

Variables	*M*	*IQR*	*SD*	Range (min-max)
Age (years)	74.30	70-78	5.95	65-91
TMT B (s)	78.66	50-91	41.26	29-257
MoCA score	26.91	25-29	2.23	21-30
Driving exposure* (DHQ domain: miles/year)	6657.5	2,158-7,930	6694.7	208-35,360
Driving difficulty*(DHQ domain)	81.21	75-91	15.24	16-100

**DHQ domain; DHQ, Driving Habits Questionnaire; IQR, Inter quartile range; M, Mean; min, minimum; max, maximum; MoCA, Montreal Cognitive Assessment; SD, standard deviation; s, seconds; TMT B, Trail Making Test Part B.*

the *total acceptance* score. Histograms displayed negatively skewed AVUPS scores and difficulty with driving (i.e., DHQ domain) which were normalized using a reflect and square root transformation. For the first model, older drivers' self-reported *driving difficulty* ($p = 0.019$) and *crash and/or citation* involvement ($p > 0.05$) predicted their *intention to use* AS: $R^2 = 6.18\%$, $F_{(2,101)} = 4.554$, $p = 0.040$ (see **Table 3**). For the second model, *dependence on other drivers* ($p = 0.052$): $R^2 = 3.67\%$, $F(1,102) = 3.875$, $p = 0.052$ did not predict older drivers' *perceived barriers* to AS. For the third model, involvement in a *crash or citation* ($p = 0.072$): $R^2 = 2.18\%$, $F_{(1,102)} = 3.297$, $p = 0.072$ did not predict older drivers' *well-being* related to AS acceptance. Lastly in the final model, *driving difficulty* ($p = 0.081$): $R^2 = 1.99\%$, $F_{(2,101)} = 3.101$, $p = 0.081$ did not predict older drivers' *acceptance of AS.*

Discriminant validity was assured by the factor loading coefficients of each individual indicator used to identify *technology readiness* (0.680-0.846), *perceived ease of use* (0.579-0.822), *barriers of AV acceptance* (0.678-0.825), and *intention to use* (0.551-0.868) were consistently >0.5 (see **Table 1**). To meet this criteria, 2 of 13 items were removed from *intention to use* and one of six items was removed from *perceived barriers*. Convergent validity was assured by exceeding criteria for average variance extracted (AVE > 0.5), internal consistency ($\alpha > 0.7$) and composite reliability (>0.7) for each construct (i.e., *technology readiness, perceived ease of use, barriers of AS acceptance, and intention to use)* with multiple indicators (see **Table 1**). **Figure 2** displays the bootstrapped model, including the β coefficients, effect size (R^2), loading coefficients (criteria: >0.5) for each construct. The effect size ($R^2 = 0.467$) indicates that 47% of the variance in *intention to use* was accounted for by the predictors. **Table 4** displays the significance of the path coefficients in **Figure 2**.

Table 4 indicates the statistical significance of the path coefficients in the structural bootstrapped model. From this model the only statistically significant differences occurred between *technology readiness* and *intention to use to use;* and *barriers to AV acceptance* and *intention to use*.

TABLE 3 | Indicators of categorical independent variables: Driving dependence, driving space, and crashes and/or citations ($N = 104$).

Variables	*N* (%)
Driving dependence (DHQ domain)	
"I drive"	47 (45%)
"Split between being driver and passenger"	40 (38%)
"This person drives me"	17 (16%)
Driving space (DHQ domain)	
Immediate neighborhood	0 (0%)
Outside neighborhood	6 (6%)
Neighboring towns	13 (12.5%)
Distant towns	39 (37.5%)
Outside of Florida	15 (14%)
Outside of southeast region	31 (30%)
Crashes and/or citations (DHQ domain)	
Yes	18 (17%)
No	86 (83%)

DHQ, Driving Habits Questionnaire.

TABLE 4 | Statistical significance of path coefficients in the structural bootstrapped model ($N = 104$).

Path	Effect (β)	Confidence Interval (95%)	*t*-statistic
Technology readiness to intention to use	0.247**	0.087-0.411	2.875
Perceived ease of use to intention to use	0.070	−0.129-0.288	0.511
Barriers to AV acceptance to intention to use	−0.504***	0.285-0.692	4.967
Life space to intention to use	−0.085	−0.241-0.064	1.102
Crashes and/or citations to intention to use	−0.069	−0.191-0.064	1.199
Driving exposure to intention to use	−0.031	−0.208-0.153	0.317
Driving difficulty to intention to use	0.126	−0.040-0.292	1.485
Cognition to driving difficulty	−0.151	−0.341-0.054	1.475

*β, path coefficient; **$p < 0.01$, ***$p < 0.001$.*

DISCUSSION

The primary purpose of this paper is to examine if *technology readiness, ease of use, technology barriers*, *life space mobility, driving habits,* and *cognition* are predictors of older adults' *intention to use* the AS.

Based on the literature, and our past and current findings on older drivers' acceptance practices of AS, we have formulated

and tested four assumptions. The first assumption postulated that older *age* (vs. younger age) will be a barrier of AS acceptance—and this did not hold true. No obvious differences were observed between age (or genders) for AV acceptance despite the age range among the older adults with a spread from 65 to 91 years of age.

The second assumption postulated that decreased *cognition* will be a barrier in AS acceptance—which also was not supported by the findings. The MoCA score ($M = 26.91$, $SD = 2.23$) indicated that overall, the general cognition of the group was reasonably intact, and as such we did not detect a wide range in cognitive functioning, even given that the MoCA score of <18 was used as an exclusion criterion. The TMT B score ($M = 78.66$, $SD = 41.26$) indicates that the group had on average a faster completion time of the test (cut-off 180 s)—which is also better than the reported TMT B scores (108 s) with a statistically significant area under the curve of 0.86 to predict on-road failure in people with Parkinson's (76). However, wide variability ($SD = 41.26$) was noted in the TMT B scores of the older adults, suggesting that at least some of them were very likely to have had lower cognitive functioning. Yet, at least in our sample, cognition was not a predictor of the *intention to use* practices of older drivers.

The third assumption postulated that *driving habits* (i.e., crashes and/or citations, driving exposure, and increased driving difficulty) will positively predict *intention to use*. Just under 20% of the group had evidence of self-reported crashes and/or citations—yet this variable did not predict *intention to use.* Although projections from Lyman et al. indicate that future crash counts are hard to predict, they propose evidence indicating that older drivers will make up a substantially larger proportion of drivers involved in crashes (77), partly due to their increasing age, driving exposure, and need to continue to drive. Of course, a necessary mitigation strategy for avoiding crash risk is to suggest the use of an AS as a safer mode of transportation—but, it is clear that being crash and/or citation involved did not predict *intention to use* in our study. Likewise, even though we observed a big spread in miles driven per year (208-35,360) the older adults' exposure did not predict *intention to use.* Although the driving difficulty score ($M = 81.21$, $SD = 15.24$), slightly below the criterion of 90, suggests that some may have experienced a decline in fitness to drive abilities—this variable also did not predict the older adults' *intention to use.* From these findings, at least as they pertain to our sample, we learn that *driving habits* does not predict acceptance practices and as such, should not be used in such a fashion in future research.

The fourth assumption postulated that decreased *life space* will positively predict *intention to use*, which again was not the case in our study. More than half of the drivers in this study was either somewhat or totally dependent on someone to drive them, but only a minority indicated life space restrictions, as they did not travel further than "outside" their neighborhood. What is clear is that *intention to use* technology, especially as it pertains to autonomous vehicle technology, requires a different set of assumptions and preconditions to understand older adults' motivation to engage in such technologies. Thus, researchers need to focus on constructs that are much more telling of the indicators of older adults' successful engagement with AS.

Interestingly, our first regression model indicated, that from all the variables entered across the four models, only the first model was significant. Specifically, in this model older drivers' self-reported *driving difficulty* ($p = 0.005$) positively predicted their *intention to use* (**Table 3**). This is actually a very good sign that older drivers who are at risk, demonstrate as a group, the insight to want to use a safer mode (than driving) of transportation. However, this finding did not hold up as a significant predictor in the final SEM.

Finally, the fifth assumption postulated that predictor variables will singularly or cumulatively explain the eventual acceptance and adoption practices of older drivers—and hence we developed a conceptual model to explore the multi-variate relationships. Based on the PLS-SEM (**Figure 2**; **Table 5**), the results indicated that the path model can be used to generate hypotheses as discussed next.

First, increases in *technology readiness* are associated with an increase ($p < 0.01$) in *intention to use* ($\beta = -0.247$). Not surprising, this finding indicates a positive relationship between those who are ready to use technology and their intention to use the AS. Specifically, the items in the optimism domain indicate that new technology "contributes to better quality of life" (item 1), "gives more freedom of mobility" (item 2), "gives people more control over their daily lives" (item 3) and "makes me more productive in my personal life" (item 4). These items set the stage for planners, policy makers and industry partners to create opportunities for older adults to experience the benefits of the current AS technologies. Such experiences may positively impact the acceptance and adoption practices of older adults as they engage with AS, as early research is starting to illustrate (15, 25).

Second, when *perceived ease of use* increased, there was no change in *intention to use* ($p > 0.05$). It is not clear why *perceived ease of use* did not predict *intention to use*, especially because the items indicate that: interaction with the AV is clear (item #7), does not require a lot of mental effort (item #8), easy to use (item #9), and get the AV to do what one wants to do (item #10; **Table 5**). One potential reason for explaining the non-significant finding is that the older adults had only one exposure—and that occurred not in traffic, but in a bus depot, which may suggest that the true ease of use was not experienced in the context of daily life.

Third, a decrease in *barriers to AV acceptance* (meaning fewer barriers) was associated with a statistically significant increase ($p < 0.001$) in *intention to use* ($\beta = -0.504$). This finding has important implications for stakeholders of the AV industry. These stakeholders can make a significant contribution to reducing barriers for the older drivers pertaining to AS technology. For example, some of the AVUPS items underlying

TABLE 5 | Predicting intention to use with driving difficulty and self-reported crashes and citations using backward stepwise selection.

Variable	*β*	*SE*	*t statistic*	*p*
Driving difficulty	0.162	0.077	2.109	0.037**
Crashes and/or citations	0.536	0.366	1.464	0.146

*β, path coefficient; SE, Standard Error; **p < 0.05.*

the *perceived barriers* include item # 5 "being suspicious of AV," item #14 "require a lot of effort to use AV," item # 26 "I believe AV will increase number of crashes," and #28 "I feel hesitant about using AV" (36). Addressing these barriers, *via* education, exposure to the technology, demonstration rides, show-and-tell rides, workshops, roundtable discussions with drivers who had (vs. not had) exposure to AS, informational videos, and neighborhood trail rides, may go a long way in helping older adults be more prone to use the AS.

Fourth, when *life space* increased (meaning older adults ventured further away from their residences) there was no change in *intention to use* ($p > 0.05$). This result suggests that as older drivers are able to engage in a wider life space, that they do not have the need or intent to use the AS. City managers and industry partners can play an important role here in exposing older drivers to experience the benefits of using these AS technologies, while they are still independent (and driving), vs. having to wait until they can no longer drive—and are potentially more compromised, before exposing them to the AS technology.

Fifth, when *self-reported crashes and/or citations decreased*, when *driving exposure increased*, or when *driving difficulty* decreased (less driving difficulty), there was no change in *intention to use* AS ($p > 0.05$). Crash and/or citation involvement, that is not predictive of *intention to use,* is a bit perplexing to the research team. One phenomenon to consider is that the self-reported number of crashes may be underrepresented as we did not verify the self-reports with state or police reports of crashes and/or citations (78). On the other hand, less *driving difficulty* and increased *driving exposure* may indirectly indicate that older adults are more involved in their communities, which is very favorable. This may also suggest that the older adults may not necessarily have an *intention to use* the AS, as long as they can continue to be independent in their driving abilities, and venture in and outside of their communities.

When *cognition* increased (meaning better cognitive functioning), there was no significant change in *driving difficulty* or *intention to use* ($p > 0.05$). We were very surprised that cognition did not predict other sub-domains and/or *intention to use* in the model. Some of the reasons may include that our measure, TMT B, was just not adequately sensitive to detect actual changes; or that executive functions are not as important for *intention to use* as other domains of the cognitive construct. It is important to note that all participants were interested and willing to participate in the study, and thus had a baseline acceptance of riding in the AS. Finally, our sample had spectrum bias pertaining to cognition, as older drivers could only participate after meeting the MoCA criterion of <18 (out of 30). Other study limitations include self-selection bias due to COVID-19 pandemic, convenience sampling due to targeting one city area in FL, participants' interest to ride in the AS, and demographics that limit generalization to other diverse populations in the state, or across other states, in the U.S.

The strengths of our study, beyond what are already discussed in previous publications (15, 25, 36, 38, 39, 65, 79) pertain to revealing important exploratory information. Particularly, we have generated knowledge telling of the role of person factors (demographics, driving habits, cognition, life space), not previously examined in the AV and older driver literature. We have also demonstrated that the assessments or questionnaires, used to determine older drivers' declining driving abilities, are not necessarily predictive of their intention to use AS. Moreover, the PSL-SEM provides an important foundation to quantify core predictors of older driver performance, as cited in the literature, including their paths, coefficients and variance, for laying the founding for hypothesis generation and follow up studies in the older adult and AS industry.

Perhaps the greatest take home message of this study is the confirmation that city planners and policy makers, as well as industry partners and health care professionals, can play a role

in the AS acceptance and adoption practices of older adults. Such actions may be proactive and overcome the current problem of intervening when older adults are experiencing too many comorbidities or declines, to actively learn and engage, in new transportation options, including the AS (80).

CONCLUSION

This study examined personal predictors and aspects of technology readiness, ease of use, and barriers of intention to use AS. Although *cognition*, more specifically executive functions, are not identified as a predictor of such practices, *driving difficulty* did significantly predict *intention to use* AS in a linear model—but the results did not hold up in the final SEM. The PLS-SEM indicated that 47% of the variance in *intention to use* is explained by the predictor variables—even though only *technology readiness* and *barriers to AV acceptance* singularly predicted *intention to use*. Finally, we have identified opportunities for city managers, planners and policy makers, as well as industry partners, to institute proactive strategies to facilitate positive AS acceptance and adoption practices among older drivers.

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 University of Florida's Institutional Review Board (IRB#201801988) provided approval for the study and all participants consented to enroll and participate in the study. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SC and VS: study conception and design. SH and JM: data collection and data input. JM: data management. JM and SC: analysis and interpretation of results. SC, JM, and VS: draft manuscript preparation. All authors reviewed the results and approved the final version of the manuscript.

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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.2021.798762/full#supplementary-material

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Differences in Dual Task Performance After Robotic Upper Extremity Rehabilitation in Hemiplegic Stroke Patients

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Background: Cognitive–motor interference is a phenomenon in which the concomitant performance of cognitive and motor tasks results in poorer performance than the isolated performance of these tasks. We aimed to evaluate changes in dual-task performance after robotic upper extremity rehabilitation in patients with stroke-induced hemiplegia.

Methods: This prospective study included patients with left upper limb weakness secondary to middle cerebral artery stroke who visited a rehabilitation hospital. Participants performed a total of 640 robot-assisted planar reaching movements during a therapist-supervised robotic intervention that was conducted five times a week for 4 weeks. Cognitive and motor performance was separately evaluated in single- and dual-task conditions. The digit span test and Controlled Oral Word Association Test (COWAT) were used to assess cognitive performance, whereas motor performance was evaluated through kinematic assessment of the motor task.

Results: In single-task conditions, motor performance showed significant improvement after robotic rehabilitation, as did the scores of the COWAT subdomains of animal naming ($p < 0.001$), supermarket item naming ($p < 0.06$), and phonemes ($p < 0.05$). In dual-task conditions, all motor task performance variables except mean velocity showed improvement after robotic rehabilitation. The type of cognitive task did not affect the dual-task effect, and there were no significant differences in the dual-task effects of motor, cognitive, or the sum of motor and cognitive performance after robotic rehabilitation.

Conclusion: Post-stroke robotic rehabilitation has different effects on motor and cognitive function, with more consistent effects on motor function than on cognitive function. Although motor and cognitive performance improved after robotic rehabilitation, there were no changes in the corresponding dual-task effects.

Keywords: cognitive-motor interference, dual-task, motor skills, robotic rehabilitation, stroke

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INTRODUCTION

Most people commonly experience situations in which they need to perform dual tasks, such as walking while talking with others, or choosing items in the market while calling on their mobile phones. Thus, the ability to perform dual tasks simultaneously is a necessary skill in daily life. Cognitive–motor interference (CMI) is manifested as dual-task effects (DTEs), in which the concomitant performance of both cognitive and motor tasks is reduced as compared to when performing isolated cognitive or motor tasks (1, 2). CMI occurs because performance capacity, which is comprised of both cognitive and motor performance, is limited. This phenomenon is particularly pronounced among stroke patients because of the diminished capacity for dual tasks secondary to stroke (3, 4).

Most studies on CMI among stroke patients have reported lower extremity performance, such as gait and posture control (1, 5–7). CMI in upper limb performance is also important, as most stroke patients with hemiplegia after a stroke have difficulty using the upper limb. Recently, CMI has also been reported in the upper limbs of stroke patients (8, 9). We have also investigated upper extremity motor CMI during various cognitive tasks, in participants with stroke who have undergone robotic rehabilitation (10). However, most studies on CMI, including our previous studies, have focused on only one aspect of cognitive or motor performance. It has been recommended that changes across absolute and relative dual-task performance and the interaction between cognition and motor performance be investigated, to consider treatment effects on overall dual-task performance and to improve understanding of CMI (11, 12). Therefore, it is necessary to explore longitudinal changes in CMI considering the concomitant reciprocal interaction between cognitive and motor performance, in order to assess treatment effects.

Modality transfer, in which training for a specific task improved learning of a novel task, has been reported (13). In particular, physical training has shown modality transfer on various aspects of cognitive function (14). Therefore, we hypothesized that rehabilitation focusing on motor function might improve motor as well as cognitive performance, and that CMI may be changed when using a different strategy between cognitive and motor performance. Therefore, we applied robotic rehabilitation, focusing on upper limb motor function, and explored concomitant changes in motor and cognitive performance, and the concomitant DTEs on both motor and cognitive performance, in order to gain insight regarding overall dual-task performance.

METHODS

Participants

Participants were consecutively selected from the inpatient department of our rehabilitation center. The inclusion criteria for study participation were as follows: (1) left upper limb weakness secondary to a first unilateral middle cerebral artery stroke, affecting the right hemisphere, as evidenced by brain imaging or medical records; (2) age 18–65 years; and (3) a score $\geq$ 25 on the Mini-Mental State Examination (MMSE) (15). The exclusion criteria were as follows: (1) orthopedic or neurological conditions other than stroke; (2) aphasia, which would prevent language-related cognitive tasks in the present study; and (3) visual or auditory problems that prevented participation in the study protocol. Based on these criteria, of the 53 participants admitted to our rehabilitation center, 13 participants in the chronic phase of a first-ever stroke were selected for this study.

This study was approved by the Ethics Committee of the Institutional Review Board of our center, and all participants provided informed written consent before enrollment, in accordance with the Declaration of Helsinki.

Tasks

Motor performance was assessed using a kinematic assessment from the point-to-point task embedded in InMotion 2. We collected data on motor performance variables, including smoothness (SM), mean velocity (MV), path error (PE), and reach error (RE). For SM and MV, a higher value indicates better performance, whereas for PE and RE, a lower value indicates better performance. Detailed explanations of these variables have been described in a previous study (10).

Cognitive performance was measured with two different cognitive task types: (1) the digit span test (DST) and (2) the Controlled Oral Word Association Test (COWAT) from the Seoul Neuropsychological Screening Battery (SNSB-II) (16). The DST, which consists of a forward (DST-for) and backward test (DST-back), was used to assess attention or the central executive component of working memory. The COWAT was a measure of fluency in meaning (animal names: COWAT-animal, supermarket item naming: COWAT-supermarket, and text phoneme naming: words that start with Korean character ㄱ, ㅇ, ㅅ; COWAT-phonemic), indicating language proficiency and executive function. In addition to the raw score, we used *z*-scores that were standardized according to the age and educational criteria of the SNSB-II based on a nationwide sample (1,100 people) (16). The order of cognitive tasks was randomized across participants.

Interventions

For the robotic intervention, an InMotion 2 (Interactive Motion Technologies Inc., Watertown, MA, USA), which was specifically designed for upper limb rehabilitation, was used (2), as described previously (10).

Participants sat in a chair with their trunk restrained to minimize compensatory movement, and their affected arm was placed in an arm support attached to the handle of the robotic arm. With a computer monitor presenting visual feedback in front of the participant, the therapist guided the participant to hold the robot handle and direct the patient to complete moving the handle to one of eight equally spaced points on the perimeter of a 14-cm radius circle from the central object, to complete a 640

Abbreviations: CMI, Cognitive-motor interference; COWAT; Controlled Oral Word Association Test; DTE, dual-task effects; DST, Digit span test; DLT, dual task loss; MANOVA, multivariate repeated-measures analyses of variance.

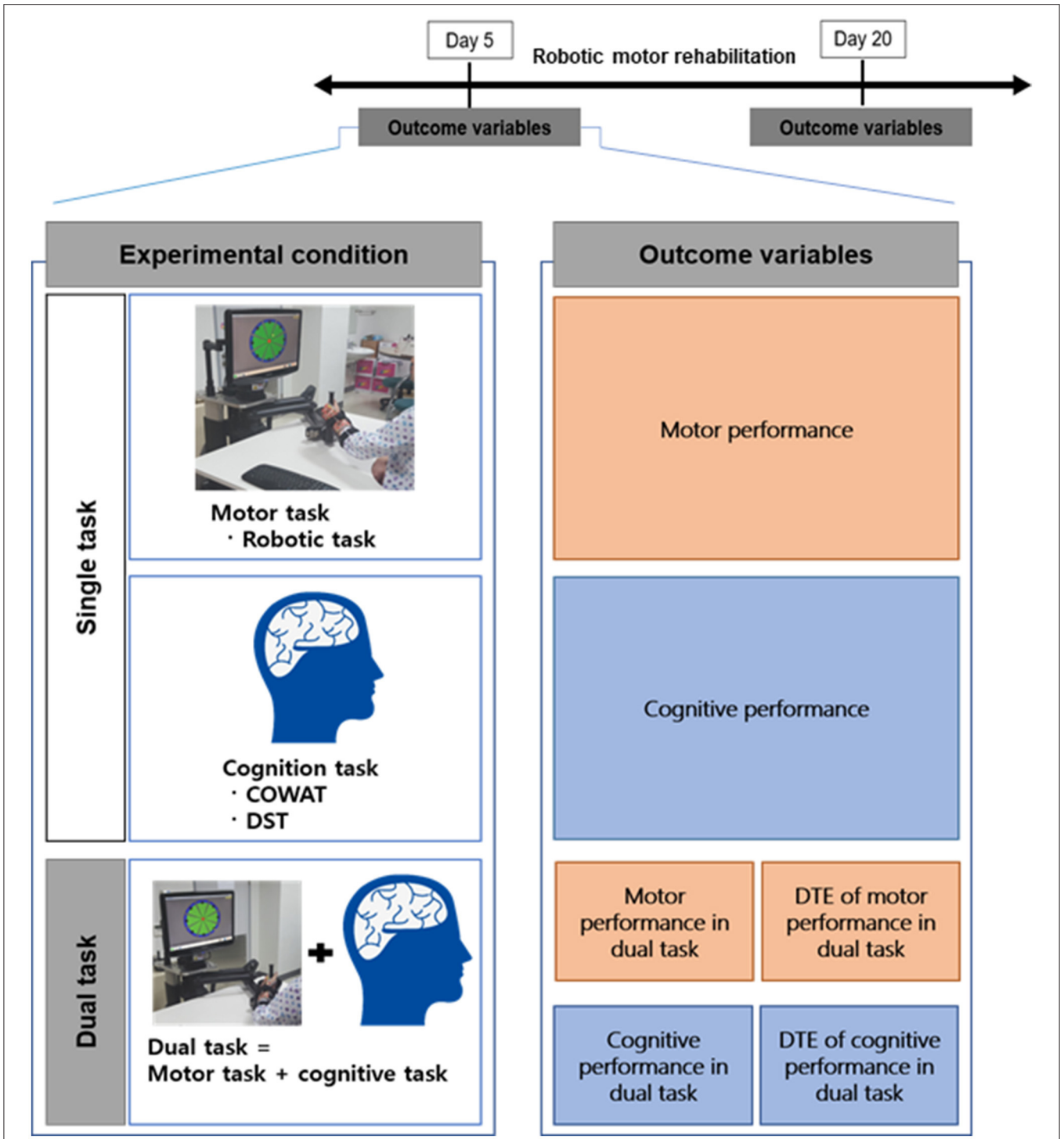

FIGURE 1 | Schematic diagram of the research methodology used. Schematic diagram of the research hypothesis on capacity changes according to motor and cognitive performance. COWAT dual performance and motor performance improved from day 5 to day 20, but not for DTE. DST dual performance did not change from day 5 to day 20, only motor performance improved, but DTE did not change.

planar point-to-point reach movement. The therapist instructed and assisted the patient from the front of the patient's unaffected side.

The task was performed at a comfortable speed without time limitation and the robotic intervention was conducted five times a week for 4 weeks under the supervision of a physical therapist.

It has been reported that a large amount of high-dose intensive training and repeated execution of specialized functional tasks play an effective role to activate neural plasticity through robotic intervention (17). In addition, because the functional levels of the upper extremities of the subjects in this study were similar, the number of repetitions was controlled rather than the time of robotic intervention.

Outcome Measures

We evaluated both motor and cognitive performance, during single and dual tasks separately, on days 5 and 20 of the robotic intervention. Dual cognitive interference was performed under two conditions: (1) during the DST and (2) COWAT. The order of application of cognitive task types was randomly assigned. In the dual task condition, the participants were asked to focus on the motor task. All cognitive performances during dual tasks were recorded while the participant performed the point-to-point motor task, while motor performances during dual tasks were recorded only during the COWAT-phonemic and DSC-back tasks (**Figure 1**).

Dual task loss (DTL) of performance involved analyzing the effect of the cognitive task on dual-task interference and was calculated as follows: DTL (%) = [(performance in dual-task – performance in a single task)/performance in a single task] × 100% (18). For clarity, we transformed DTL into DTEs, so that higher values indicated better performance in the dual-task condition relative to the single-task condition in the following manner: DTEs of SM, MV, and cognitive performance: MV = DTL, and DTEs of RE and PE = –DTL (10).

Statistical Analysis

We used PASW v.18.0 (SPSS Inc., Chicago, IL, USA) for statistical analysis. Descriptive statistics were used to analyze the demographic and clinical characteristics of the participants. We compared changes in cognitive or motor performance across days 5 and 20 in the single and dual tasks, respectively, using repeated-measures one-way analysis of variance (RM ANOVA). Then, repeated-measurement multivariate analysis of variance (RM MANOVA) was used to assess cognitive and motor performances during the dual task across days 5 and 20 to assess the concomitant effects of cognitive and motor tasks. Then, RM ANOVA and RM MANOVA were performed to assess the DTE of cognitive and motor performances on days 5 and 20 of robotic rehabilitation.

RESULTS

Thirteen stroke patients (10 males) with middle cerebral artery infarction, with a mean age of 45.9 ± 11.9 years, were enrolled in the present study. Their mean education level was 12.4 ± 4.4 years and their MMSE score was 28.2 ± 2.7.

Below, we present results for cognitive and motor performance in the context of a single task (only cognitive or motor task, without another concomitant task) and a dual task (concomitant cognitive and motor task).

Performance in a Single Task

Table 1 demonstrates the change in motor or cognitive performance on days 5 and 20 of robotic rehabilitation. Motor performance in a single task (without a concomitant cognitive task) showed significant improvement in SM, RE, and PE, except MV.

Cognitive performance in a single task (without a concomitant motor task) demonstrated improvements in COWAT-animal, COWAT-supermarket, and COWAT-phonemic, while the DST-for and DST-back did not change.

Performance in the Dual Task

Table 2 shows the change in motor performance between day 5 and day 20 during the dual task, in which the motor task was performed with each cognitive task (COWAT-phonemic and DST-back). RM ANOVA showed improvement in all motor performance variables except MV, in both dual tasks with COWAT and DST tasks. The COWAT performance during a concomitant motor task showed improvement, while neither DST-for or DST-back changed.

TABLE 1 | Single cognitive or motor task performance at day 5 and day 20 of robotic rehabilitation of the upper limb.

Task performance		5 days		20 days		Within-subject comparisons				
	N	Mean	SD	Mean	SD	Type III sum of squares	df	Mean square	*F*	*P*
DST-for	13	0.011	1.674	0.339	1.237	1.429	1	1.429	2.842	0.105
DST-back	13	−0.319	1.161	−0.499	1.261	0.495	1	0.495	1.017	0.323
COWAT-animal	13	−1.309	0.985	−0.736	1.154	6.169	1	6.169	17.256	<0.001
COWAT-supermarket	13	−1.282	0.795	−0.985	1.114	1.067	1	1.067	4.109	0.054
COWAT-phonemic	13	−0.422	1.247	−0.202	1.569	1.070	1	1.070	5.494	0.028
Smoothness	13	0.447	0.124	0.486	0.086	0.022	1	0.022	17.035	<0.001
Reach error	13	0.051	0.059	0.035	0.035	0.004	1	0.004	7.448	0.012
Mean velocity	13	0.098	0.049	0.098	0.038	0.000	1	0.000	0.572	0.457
Path error	13	0.025	0.029	0.018	0.013	0.001	1	0.001	5.419	0.029

COWAT-animal, naming an animal; COWAT-supermarket, naming items in the supermarket; COWAT-phonemic: speaking with consonance "ㄱ," "ㅇ," "ㅅ" of the Korean language, DST, digit span test, for, forward; back, backward; SD, standard deviation.

TABLE 2 | Dual-task performance involving cognitive and motor performance (subdomains of cognition and motor function) at day 5 and day 20 of robotic rehabilitation of the upper limb.

Task performance		5 days		20 days		RM ANOVA					RM MANOVA				
						Within-subject comparisons					Within-subject comparisons				
	N	Mean	SD	Mean	SD	Type III sum of squares	df	Mean square	*F*	*P*	Type III sum of squares	Df	Mean square	*F*	*P*
COWAT-animal during motor task	13	−1.407	0.949	−0.602	1.099	6.169	1	6.169	17.256	<0.001					
COWAT-supermarket items during motor task	13	−1.682	0.990	−1.405	0.728	1.067	1	1.067	4.109	0.054					
COWAT-phonemic during motor task	13	−0.765	1.212	−0.442	1.436	1.070	1	1.070	5.494	0.028	1.621	1	1.621	4.212	0.063
Smoothness during COWAT-phonemic	13	0.434	0.121	0.483	0.086	0.026	1	0.026	22.970	<0.001	0.032	1	0.032	15.947	0.002
Reach error during COWAT-phonemic	13	0.056	0.054	0.044	0.041	0.003	1	0.003	4.120	0.054	0.002	1	0.002	1.428	0.255
Mean velocity during COWAT-phonemic	13	0.089	0.041	0.103	0.047	0.001	1	0.001	1.718	0.202	0.003	1	0.003	2.369	0.150
Path error during COWAT-phonemic	13	0.027	0.024	0.020	0.013	0.001	1	0.001	4.288	0.049	0.001	1	1.866	1.866	0.197
DST-for during motor task	13	0.621	1.460	1.045	1.056	1.429	1	1.429	2.842	0.105	2.159	1	2.159	2.369	0.152
DST-back during motor task	12	−0.572	0.989	−0.880	0.743	1.517	1	1.517	1.527	0.230	1.137	1	1.137	1.060	0.325
Smoothness during DST-back	12	0.432	0.122	0.477	0.095	0.022	1	0.022	17.035	<0.001	0.025	1	0.025	8.852	0.013
Reach error during DST-back	12	0.058	0.058	0.038	0.037	0.004	1	0.004	7.448	0.012	0.005	1	0.005	4.809	0.051
Mean velocity during DST-back	12	0.095	0.048	0.101	0.042	0.000	1	0.000	0.572	0.457	0.000	1	0.000	1.012	0.336
Path error during DST-back	12	0.027	0.027	0.020	0.014	0.001	1	0.001	5.419	0.029	0.001	1	0.001	3.223	1.00

COWAT-animal, naming an animal; COWAT-supermarket, naming items in the supermarket; COWAT-phonemic: speaking with consonance "ㄱ," "ㅇ," "ㅅ" of the Korean language, DST, digit span test; for, forward; back, backward; RM-ANOVA, repeated-measures analysis of variance; RM-MANOVA, multivariate analysis of variance; SD, standard deviation. All cognitive function scores are presented with a z-score.

TABLE 3 | Dual-task effects in cognitive and motor performance at day 5 and day 20 of robotic rehabilitation of the upper limb.

Dual-task effects during dual task	5 days			20 days		RM ANOVA Within-subject comparisons					RM MANOVA Within-subject comparisons				
	N	Mean	SD	Mean	SD	Type III sum of squares	df	Mean square	F	P	Type III sum of squares	df	Mean square	F	P
DTE of DST-back	13	−1.817	5.243	−0.671	1.067	8.536	1	8.536	0.610	0.450	2.858	1	2.858	0.693	0.423
DTE of COWAT-phonemic	13	0.192	0.853	−0.059	0.577	0.378	1	0.378	1.098	0.317	0.756	1	0.756	1.098	0.317
DTE of smoothness at DST	12	−0.016	0.097	−0.016	0.089	<0.001	1	<0.001	0.000	0.993	<0.001	1	<0.001	<0.001	0.993
DTE of smoothness at COWAT-phonemic	13	−0.023	0.095	−0.004	0.062	0.002	1	0.002	0.418	0.530	0.004	1	0.004	0.418	0.530
DTE of DST-back + DTE of smoothness	12	−2.069	5.469	−0.751	1.067	2.867	1	2.867	0.690	0.424					
DTE of COWAT-phonemic + DTE of smoothness	12	0.171	0.847	−0.062	0.576	0.621	1	0.651	1.104	0.316					

DTE, dual task effect; DST, digit span test; COWAT, Controlled Oral Word Association Test; RM-ANOVA, repeated-measures analysis of variance; RM-MANOVA, multivariate analysis of variance; SD, standard deviation.

RM MANOVA was performed to examine the change in the concomitant interaction between cognition and motor performance after robotic intervention. RM MANOVA demonstrated that SM ($p = 0.002$) and COWAT-phonemic ($p = 0.063$) concomitantly improved during the dual task. In addition, there was a concomitant change in SM ($p = 0.013$), but not in the SM and DST during the dual task.

DTEs

There were no significant differences in the DTE across all cognitive tasks on day 5 ($p > 0.300$). **Table 3** depicts the change in the DTE of cognitive or motor performance between day 5 and day 20 during the dual task, in which the motor task was performed with a cognitive task (COWAT-phonemic and DST-back) (**Figure 2**). There were no significant changes in the DTE on motor, cognitive, or the sum of motor and cognitive performance between day 5 and day 20.

DISCUSSION

Robotic rehabilitation improved motor performance during single and dual task environments (19, 20), while cognitive performance showed different patterns of change between the DST and COWAT during single and dual tasks. However, there was no change in the DTE on motor performance, cognition performance, or the sum performance of both tasks. These results suggest that robotic rehabilitation improved performance depending on the cognitive task without altering the strategy for coping with the dual task.

We investigated changes in cognition and motor performance after robotic rehabilitation under two conditions: single-task and dual-task conditions. As our intervention involved robotic rehabilitation targeting motor function recovery rather than cognitive function, we hypothesized that performance improvement would mainly be seen in motor rather than cognitive performance regardless of single or dual task conditions. As expected, motor task performance consistently improved after robotic rehabilitation, except for mean velocity in both single and dual task conditions.

On the other hand, cognitive task performance showed a different pattern of change after robotic rehabilitation, unlike motor performance. In the single task, cognitive performance improvements were seen in every COWAT domain, but not in the DST. With the dual task, the cognitive performance in the COWAT-animal and COWAT-phonemic domains improved, while that in the COWAT-supermarket domain and DST did not. Thus, robotic rehabilitation could improve cognitive performance in some, but not all cognitive tests. These effects of robotic rehabilitation on cognitive function could be understood when considering robotic rehabilitation as a type of exercise. Exercise is known to improve multiple domains of cognitive function, but with varying effects across cognitive tasks or exercise types (21, 22). Robotic rehabilitation may have enhanced beneficial effects on cognitive function, because robotic rehabilitation places a greater attentional demand on participants to pay more attention than other exercise. Robotic rehabilitation in this study required continuous attention to the target on the

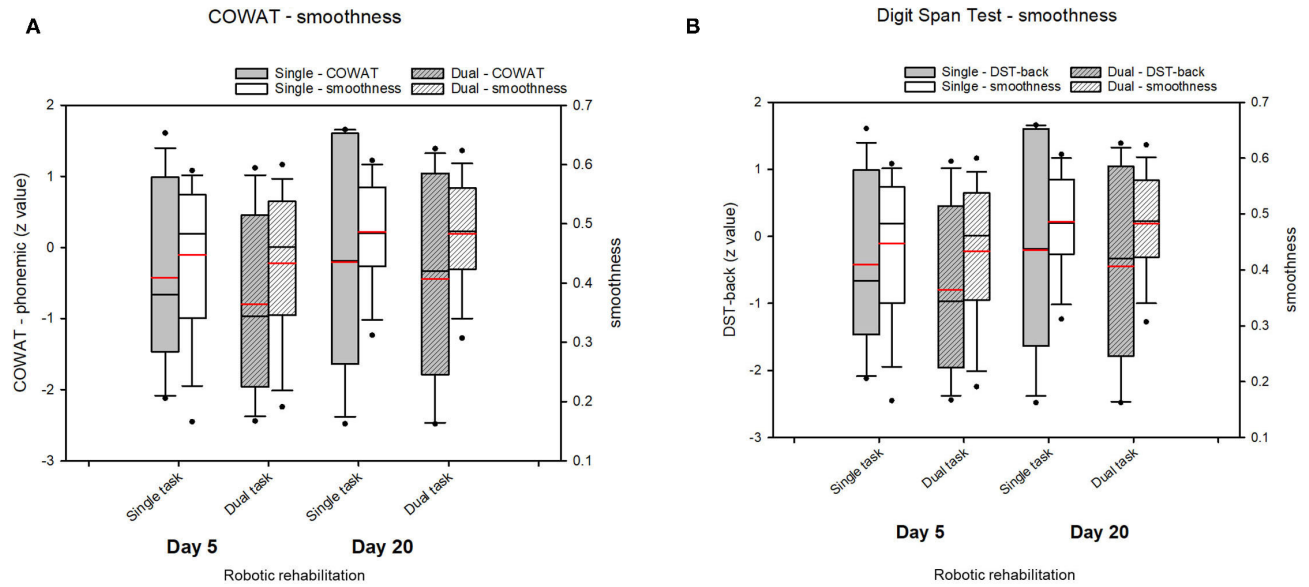

FIGURE 2 | Change of the dual-task effect (DTE) value after robotic rehabilitation of the upper limbs. **(A)** COWAT_phonemic and smoothness, **(B)** Digit Span Test and smoothness. The change in the DTE of cognitive or motor performance between day 5 and day 20 during the dual task did not indicate significant changes in the DTE on motor, cognitive, or the sum of motor and cognitive performance. Boxplots represent the mean of *z*-value for each group over the course of robotic rehabilitation. Boxplots display lower and upper extremes, lower and upper quartiles, and medians. Red line in boxplots indicates the mean. The black whiskers mark the 5th and 95th percentiles.

screen. In addition, we inferred that robotic rehabilitation had greater effects on executive function than on working memory, as DST is related to working memory and the COWAT is more directly related to executive function (23–25).

We performed RM MANOVA using concomitant dependent variables: motor performance and COWAT-phonemic or DSC-backward was included to explore the interaction between cognitive and motor performance during robotic rehabilitation. We demonstrated significant improvement in motor performance and a marginally significant change in cognitive performance ($p = 0.063$ for the COWAT-phonemic group). Thus, robotic rehabilitation improved mainly motor, rather than cognitive performance, and these improvements were more evident during the dual-task condition. Therefore, we inferred that the task specificity of robotic rehabilitation is consistent with both dual-task and single-task conditions.

Next, we investigated the DTE of cognitive and motor performance (smoothness), in order to explore strategies for allocating weight between motor and cognitive tasks in dual tasks. We hypothesized that if more weight was given to the motor task, the weight allocated to the cognitive task might be reduced, or vice versa (**Figure 1**). In the present study, we did not find statistically significant changes in the DTE of cognitive performance and the DTE of motor performance across all cognitive tasks after robotic rehabilitation, in contrast to the improvement of performance. In addition, the DTL sum for cognitive and motor function did not change (**Figure 3**). Therefore, we concluded that robotic rehabilitation cannot change dual-task interference, but does affect absolute performance. This is in contrast with previous results, in which executive function training improved DTE-cognitive performance rather than DTE-motor performance (11). This difference might be explained as follows. First, our rehabilitation training was composed of point-to-point tasks that required attention as well as motor performance, thus blurring the effects of motor training effects by developing cognitive performance as well as motor performance. Second, our intervention, focusing on motor performance, might have failed to change both DTE-motor performance and DTE-cognitive performance. Interventions targeting cognitive function might easily improve DTE-cognitive performance, because cognitive function, including attention, plays an important role in controlling motor function during dual task performance (26, 27). Third, our study focused on upper extremity rehabilitation, in contrast to a previous study on gait or balance training, where participants may be injured by falling down. Therefore, the participants in our study were likely to place relatively less emphasis on motor tasks. Fourth, the DTE is known to be related to various cognitive functions; thus, the various patterns of cognitive impairment in our patients might have affected the results, in contrast to the patterns in the homogeneous older group involved in a previous study (28).

This study had several limitations. We only included a small number of participants in the single-center, which affected our results, although we achieved statistical significance. Although a normality test was not performed, statistical analysis was performed using ANCOVA analysis considering covariances by repeated measurements. The participants were stroke patients with various patterns of cognitive impairment. To overcome these limitations, we explored kinematics, using a

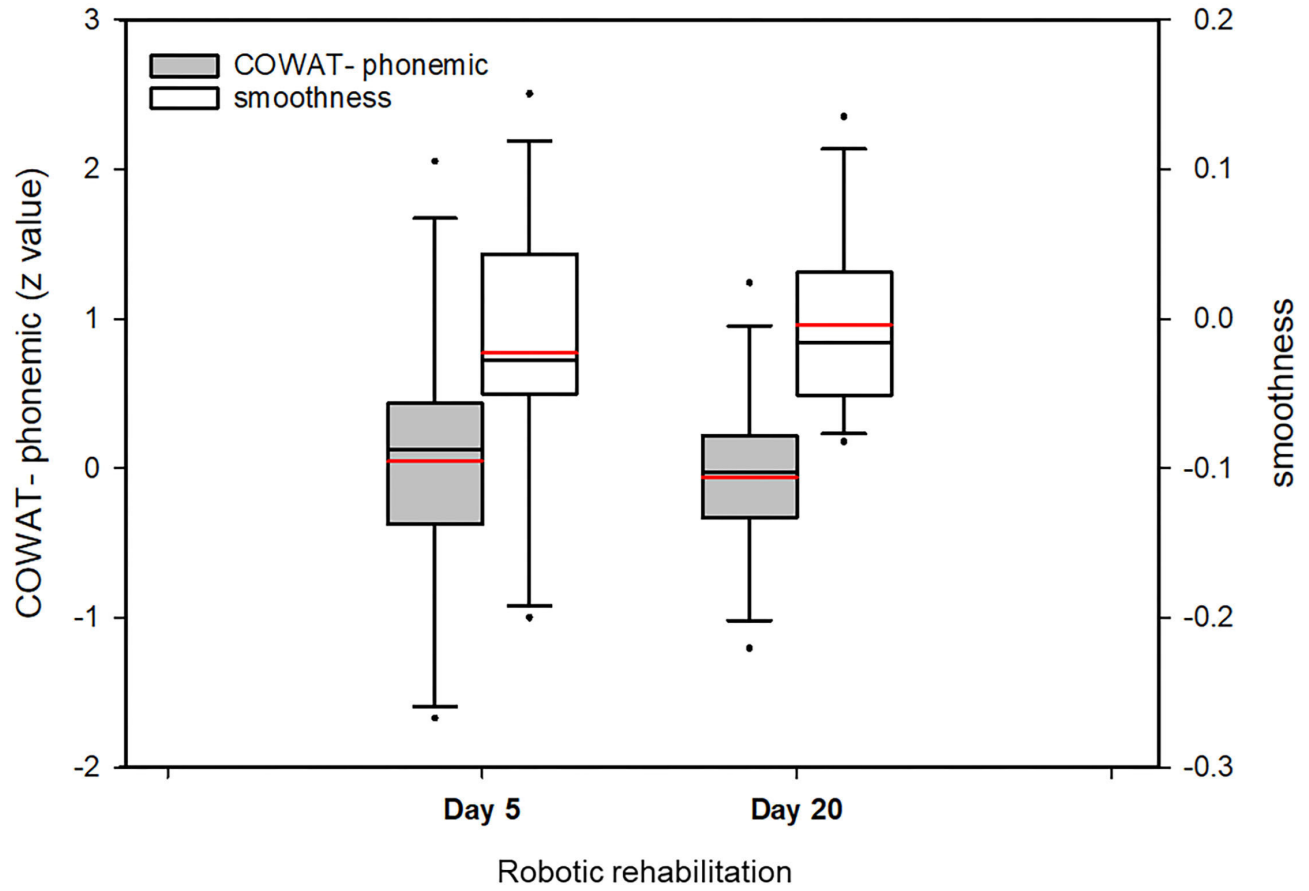

FIGURE 3 | Change of the dual task loss (DTL) value (COWAT_phonemic and smoothness) after robotic rehabilitation of the upper limbs. The DTL sum for cognitive and motor function did not change. The DTL sum for cognitive and motor function did not change. Boxplots represent the mean of *z*-values for each group during the course of robotic rehabilitation. Boxplots display lower and upper extremes, lower and upper quartiles, and medians. Red line in boxplots indicates the mean. The black whiskers mark the 5th and 95th percentiles.

rehabilitation robot, and only included stroke patients with right hemispheric lesions. In addition, in the statistical analyses, we adjusted for cognitive performance using standardized Z-scores according to age and educational level. Further studies in a large number of participants including a comparator group with diverse cognitive functional measurements are needed.

In the present study, modality transfer of robotic upper limb rehabilitation to cognitive performance was not consistent depending on the cognitive task. This finding could be one factor to guide the selection of optimal candidates for robotic rehabilitation; thus, patients with motor deficits might be an optimal target population. Moreover, this limited result could indicate the need for dual task robotic training that targets both motor skills and cognition as a preferred option for patients with both motor and cognitive impairments. However, it has not been confirmed; therefore, we sought to determine the usefulness of dual task robotic rehabilitation.

CONCLUSIONS

In this study regarding stroke patients, robotic rehabilitation changed the motor performance; however, the cognitive function differed depending on the cognitive task implemented. The rehabilitation had limited effects on motor and cognitive DTEs. Robotic rehabilitation has different effects on motor and cognitive function, with more consistent effects on motor function than on cognitive function. Although motor and cognitive performance improved after robotic rehabilitation, there were no changes in the corresponding dual-task effects.

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 Institutional Review Board of the National Rehabilitation Center in South Korea. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

J-HS contributed to conception and design of the study and organized the database. GP conducted experiment. KL performed the statistical analysis. J-HS and KL wrote the first draft of the manuscript and wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Perspective: Balance Assessments in Progressive Supranuclear Palsy: Lessons Learned

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Many studies have examined aspects of balance in progressive supranuclear palsy (PSP), but guidance on the feasibility of standardized objective balance assessments and balance scales in PSP is lacking. Balance tests commonly used in Parkinson's disease often cannot be easily administered or translated to PSP. Here we briefly review methodology in prior studies of balance in PSP; then we focus on feasibility by presenting our experience with objective balance assessment in PSP-Richardson syndrome and PSP-parkinsonism during a crossover rTMS intervention trial. We highlight lessons learned, safety considerations, and future approaches for objective balance assessment in PSP.

Keywords: progressive supranuclear palsy, balance, posturography, wearable sensors, gait

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INTRODUCTION

Many studies have examined aspects of balance in progressive supranuclear palsy (PSP) (1–12), but guidance on the feasibility of standardized objective balance assessments in PSP is lacking. Balance tasks commonly used in Parkinson's disease (PD) often cannot be administered in or directly translated to PSP, and the nine subtypes of probable and possible PSP (13) show various degrees of balance deficits. Here we briefly review methodology in prior studies of balance in PSP; then we focus on feasibility by presenting our experience with objective balance assessment in PSP-Richardson syndrome (PSP-RS) and PSP-parkinsonism (PSP-P) during a crossover rTMS intervention trial.

Clinical Scales for Balance in PSP

Clinical scales are the most common method of balance assessment in PSP. The PSP Rating Scale (PSPRS) (14) is a general scale addressing PSP symptoms, activities of daily living, mentation, speech and swallow, eye movements, dexterity, and gait and balance. Out of a total of 100 scale points, 16 are devoted to gait and balance tasks on exam (arising from a chair, gait, postural stability, and sitting down). An additional history item asks about estimated fall frequency if the subject attempts to walk unaided, i.e., with no access to a walking aid, such as a walker. Because many subjects already require regular walking aid use at the time of testing, we find that this answer skews to the maximum item score and is thus less useful for tracking in longitudinal or intervention studies. The PSPRS

exceeds at capturing the full spectrum of PSP symptoms, but lacks granularity to objectively investigate changes in balance. For example, the PSPRS-gait subscore does not correlate with total sway path on objective posturography (3). The motor section of the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (15) is often used in studies that contrast PSP and PD but the MDS-UPDRS is weighted more heavily for tremor than is needed in PSP, lacks relevant postural control tasks of standing without using arms and controlled standing to sitting, and provides a less granular assessment of postural stability compared to the equivalent pull test task on the PSPRS. The Balance Evaluation System Test (BESTest) (16) and its shorter version (Mini-BESTest) (17) target different balance control systems so that specific rehabilitation approaches can be applied for different balance deficits. The BESTest was shortened based on a factor analysis to improve clinical utilization (17). The Mini-BESTest is a 14-item test scored on a 3-level ordinal scale assessing 4 aspects of balance: sensory integration, anticipatory postural adjustments, automatic postural responses, and dynamic balance during gait. Although both the BESTest and Mini-BESTest are highly sensitive tests of balance, certain items may be too difficult to perform in PSP (i.e., the lateral push and release, standing on foam with eyes closed, etc). For this reason, the Mini-BESTest has not been consistently applied or validated in PSP. The Berg balance scale (18), commonly used in stroke and geriatric balance studies, addresses fourteen easily-implemented balance tasks, but lacks reactive postural control tasks and uneven support surface items. It has a ceiling effect (19), and it is not validated in PSP.

Review of Laboratory Measurement of Balance in PSP

Various technologies have been used to assess aspects of balance in PSP. Early studies (2) used the Sensory Organization Test (SOT) on the Neurocom Balance Manager System (Clackamas, OR) to assess sensory integration of postural control (20) by combining a moveable force plate platform with moveable surrounding walls (for platform and visual sway, respectively). Static force plate posturography tests sagittal and medio-lateral sway in PSP (3, 4, 6, 7, 9), and can examine limits of stability the maximum excursion or lean without taking a step or losing balance (5, 8). Dynamic force plate posturography records center of pressure (CoP) shifts after platform perturbations, such as forward translations and toes-up (backward) tilts, to assess motor control in PSP (5). Wearable sensors can examine a variety of movements on normal ground in PSP and overcome the restrictions of force plates. For example, triaxial accelerometers have measured gait acceleration and vertical displacement in PSP (10). Motion analysis systems combine force plates with patient markers and video tracking to capture a breadth of gait and balance tasks in PSP (11), including joint kinematics (12), and have demonstrated high inter-lab reliability (21), but come with significant drawbacks including high cost, time-consuming marker placement, lengthy pre-processing to assign each marker to its corresponding biomechanical model, followed by lengthy data processing and analysis (22).

OUR EXPERIENCE WITH OBJECTIVE BALANCE TESTING IN PSP

During our ongoing repetitive cerebellar controlled TMS crossover trial in PSP (NCT04468932), in which subjects receive multiple sessions of multi-modal balance testing, we have learned important lessons about feasibility in PSP. We focus on probable PSP-RS and PSP-P subtypes (13). We do not yet have experience with objective balance testing in other variants of PSP, such as PSP-speech and language. We are sharing our experience in order to encourage safe practices and facilitate more objective balance testing in PSP; this is not meant to be an exhaustive recommendation of procedures. To capture the known backward postural instability in PSP-RS, we focus on postural sway in the sagittal plane (see sections Dynamic Posturography on the Neurocom System and Selected Mini-BESTest Items, Two-Minute Walk Test, and a 360-Degrees Turning in Place With Opal Sensors below). We also collect sway in the medio-lateral plane as it is important for fall prevention, and we include perturbation tasks to challenge stability (see sections Dynamic Posturography on the Neurocom System and Selected Mini-BESTest Items, Two-Minute Walk Test, and a 360-Degrees Turning in Place With Opal Sensors below). Finally, our assessment captures straight walking and turning (see section Selected Mini-BESTest Items, Two-Minute Walk Test, and a 360-Degrees Turning in Place With Opal Sensors below) for overall clinical relevance, and because a subset of patients with PSP have freezing of gait.

Figure 1 shows our comprehensive balance assessment protocol for PSP: the Sensory Organization Test (SOT) and Motor Control Test (MCT) with forward platform translation and toes-up perturbations on a Neurocom Balance Manager system, anticipatory postural adjustments, reactive postural control and sensory orientation aspects of the mini-BESTest (17), a two-minute walk test (23, 24), and a 360-degree turning in place task (25). The mini-BESTest, two-minute walk, and 360-degree turning task are all performed while wearing six Opal inertial measurement sensors (APDM Wearable Technologies, Portland, OR) (26). We administer two balance quality of life questionnaires: the Activities-Specific Balance Confidence (ABC) Scale (27, 28) and Falls Efficacy Scale (FES-I) (29).

Dynamic Posturography on the Neurocom System

We perform dynamic posturography on the Neurocom system to quantify sagittal and medio-lateral sway under various sensory conditions and with platform perturbations. The standard provided Neurocom output is an equilibrium score during each test, a sensory analysis score, and a strategy analysis (20). It is important to note that these outcomes purely rely on the sagittal sway during the tests, ignoring the medio-lateral sway. However, it is possible to download the force plate recording during the SOT tests and calculate both sagittal and medio-lateral COP excursion in all conditions. We also perform the large forward translations of the Motor Control Test (MCT). We include a customized toes-up platform tilting task because we previously

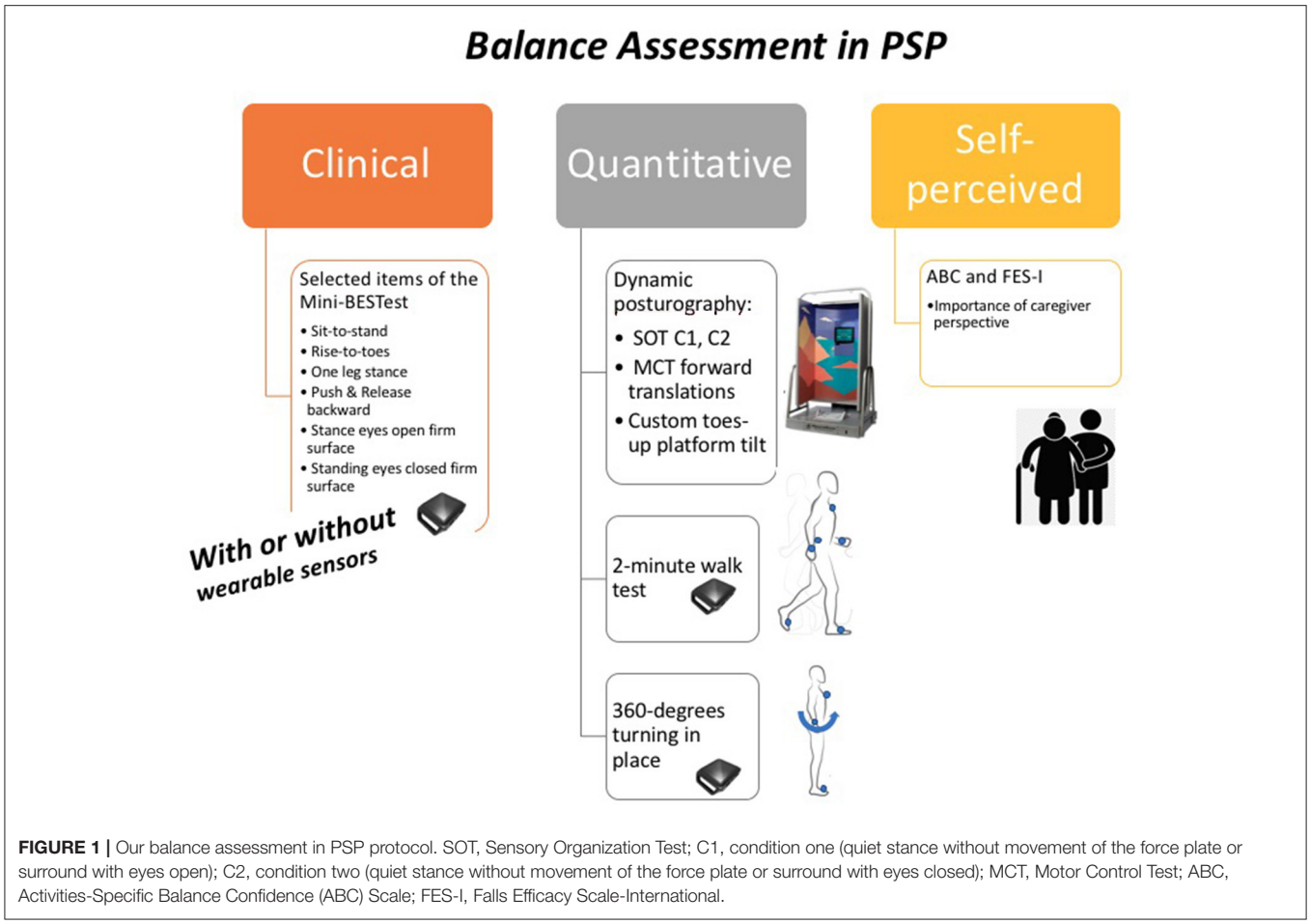

FIGURE 1 | Our balance assessment in PSP protocol. SOT, Sensory Organization Test; C1, condition one (quiet stance without movement of the force plate or surround with eyes open); C2, condition two (quiet stance without movement of the force plate or surround with eyes closed); MCT, Motor Control Test; ABC, Activities-Specific Balance Confidence (ABC) Scale; FES-I, Falls Efficacy Scale-International.

found it differentiated subjects with PSP from PIGD-matched PD (5). Safety is ensured by a lightweight harness and an assistant for spotting. Trials are invalidated if subjects shift their feet on the surface of the force plate.

Feasibility

We learned that the conditions most consistently completed without foot shifting during the SOT in PSP are conditions one through three (quiet stance without movement of the force plate or visual surround with eyes open, quiet stance without movement of the force plate or visual surround with eyes closed, and stance *with* movement of the visual surround with eyes open). See **Figure 2** with representative center of pressure sway excursions in condition one before and after cerebellar repetitive TMS compared to sham TMS. The other elements of the SOT that involve force plate movement with or without eyes closed are generally challenging in our PSP subjects, though some subjects have shown individual improvements after our intervention. For example, 50% of our subjects were able to complete a condition of the SOT after rTMS that they could not complete without falls before rTMS, regardless of order of intervention. These individual improvements were not seen after sham TMS. For this reason, we suggest at least attempting to complete all aspects of the SOT, particularly in less impaired individuals. Our PSP subjects have generally tolerated perturbations with forward platform translations of the MCT and with toes-up platform tilts. While they may shift their feet during these perturbations and invalidate certain trials, a majority of trials are successfully completed and yield analyzable data. We find that the duration of posturography testing on the Neurocom system for more impaired subjects with PSP is 30 min, but the time becomes considerably shorter for less impaired subjects who are able to transfer in and out of the machine more efficiently.

Lessons Learned

1. Eye mask. It is necessary to use a comfortable eye mask to blindfold subjects for the eyes-closed portions of assessment, since abnormal eyelid function (caused by conditions such as apraxia of eyelid closing) can impair consistent eye closure in PSP. Subjects may not be able to close their eyes on command.
2. Standardized foot placement is essential. We recommend marking optimized foot placement on the force plate with tape. Geriatric neurological subjects may have concomitant chronic orthopedic issues (such as foot eversion) that prevent perfect alignment, so consistency during and between testing sessions is the goal.
3. Ensure subjects are consistently tested without footwear or socks, and either exclude or account for significant

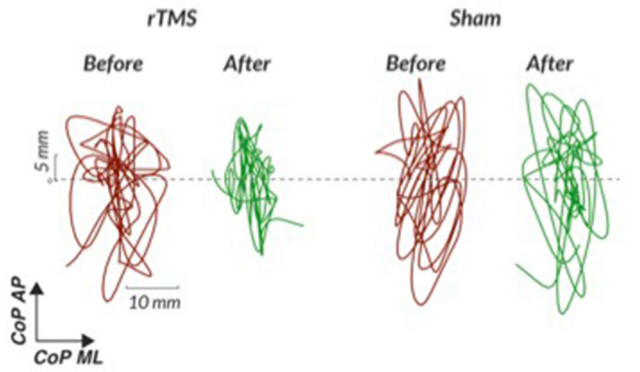

FIGURE 2 | Representative center of pressure sway excursions in quiet stance without movement of the force plate or surround (condition one of the Sensory Organization Test) before and after cerebellar repetitive TMS compared to sham TMS. rTMS, repetitive transcranial magnetic stimulation; CoP, center of pressure; AP, anterior-posterior; ML, medio-lateral; C1, condition one.

lower extremity proprioceptive deficits, such as loss of toe proprioception on neurological examination, in the study design.

4. Ensure that safety harness straps have some slack. Subjects with PSP often lean forward during testing to compensate for their backward postural instability. When leaning they may place sufficient tension on the harness straps to provide sensory input and mechanical support that invalidates posturography results.
5. Spotting during balance testing and assistance entering and exiting the Neurocom are essential for safety; the safety harness is necessary, but not sufficient. While the harness prevents full falls, subjects with PSP risk injuring themselves on the walls of the Neurocom during perturbations. Subjects often need assistance stepping into and out of the machine.
6. Clearly marking "falls" or foot shifting that invalidate trials in the study case report form assists in data analysis.

Selected Mini-Bestest Items, Two-Minute Walk Test, and a 360-Degrees Turning in Place With Opal Sensors

Compared to posturography confined to the Neurocom machine, these tests are more representative of real-life challenges to static and dynamic balance. For this mobile testing we equip patients with six lightweight Opal sensors (APDM Wearable Technologies, Portland, OR) (26) (one on each wrist, one on each ankle, one on the chest and one over the lumbar area with Velcro straps). The inertial sensors combine accelerometer, gyroscope, and magnetometer technology along three axes. We then "instrument" the mini-BESTest by performing it while subjects wear the mobile sensors. The full mini-BESTest is a fourteen-task scale addressing anticipatory postural adjustments, reactive postural control, sensory orientation, and dynamic gait. We perform portions of the mini-BESTest with Opal sensors in PSP as noted in the Feasibility section below. Then, in the 2-min unassisted walk, subjects walk uninterrupted with mobile sensors back and forth down a hallway. Spatio-temporal gait characteristics, such as stride length, gait speed, angle of the foot at heel-strike, and upper body arm swing and trunk angle while walking are calculated from the 2-minute walk test (26, 30). Both average and variability are reported. For the separate instrumented 360 degrees turning in place task, subjects are instructed to turn in place for a total of 1 min, 360 degrees to the right, then 360 degrees to the left (and so on) at a comfortable speed (25). This turning protocol elicits potential freezing of gait in a controlled manner.

Feasibility

Thus, far in six subjects with PSP (each with multiple testing sessions), we find that subjects diagnosed with probable PSP-RS or PSP-P are unable to complete all portions of the mini-BESTest without adjustments that invalidate results. We suggest limiting mini-BESTest tasks to the following: sit-to-stand, rise to toes, stand on one leg, compensatory stepping correction backward, stance with eyes open on a firm surface, and stance with eyes closed on a firm surface. All six tasks will not be feasible in all patients, but all are worth attempting. In our experience, even with two highly trained assistants per subject for safety spotting, the following mini-BESTest tasks are generally not feasible and may be eliminated: compensatory stepping correction forward, compensatory stepping correction lateral, stance with eyes closed on a foam surface, and stance with eyes closed on an incline. We have been surprised that compensatory stepping correction backward is more feasible than compensatory stepping forward in PSP, but this mainly relates to reluctance of subjects to sufficiently transfer their weight to the examiner at the beginning of the forward compensatory stepping task, invalidating any results. We find the dynamic gait portion of the mini-BESTest, which includes items such as straight walking with head version, too difficult in PSP; instead, we recommend incorporating mobile sensor testing into separate 2-min unassisted walking and 360 degree turn tasks to obtain quantitative spatio-temporal parameters of gait and turning. The average duration to complete the instrumented mini-BESTest items, the 360 degrees turning in place task, and the 2-min walk test is 45 min.

Lessons Learned

1. We modified instructions for selected tests of the mini-BESTest to account for the wider base of balance often necessary in PSP, even in less advanced subjects. For example, during the eyes open standing on a firm surface test we use a template to maintain a consistent distance between the feet at different sessions, as opposed to a variable patient-selected stance width. The original mini-BESTest instructions of standing with feet nearly touching is often not feasible in this population. We first try standing with eyes open using a template between the feet. If subjects are able to complete this task, we then add the more challenging task of standing on a firm surface with eyes closed and feet together.
2. Consistency in subject testing with shoes and socks off is important for validity.
3. Two spotters are often required for all mobile sensor testing in order to safely push most subjects to the limits of their balance capabilities. A gait belt is required.

4. Monitor for impulsivity during the unassisted gait test. Certain patients with PSP may walk quickly and precariously with a high initial acceleration (10). We caution subjects to "walk at your normal pace; you do not have to rush," rather than instructing them to walk as quickly as they can. We are more interested in quality metrics such as gait variability than total distance covered.
5. During unassisted gait, some subjects with PSP may move their head more than a healthy age matched control in an to attempt to overcome their oculomotor deficits and visually scan their surroundings. This can distract subjects from the task. If this behavior occurs, we gently correct and remind subjects to keep looking straight ahead during the gait testing.

Patient-Rated Balance Questionnaires

We collect the Activities-Specific Balance Confidence (ABC) Scale (27, 28) and Falls Efficacy Scale-International (FES-I) (29) questionnaires from both the subject and caregiver. We have not seen improvement in either the ABC or FES-I that corresponds to static posturography improvements. This could either mean that static postural tasks do not capture clinically relevant and dynamic balance skills, *or* that questionnaires are not sensitive enough to detect objective instrumented improvements that would continue to improve with a longer intervention or training. Future longitudinal studies are needed.

Lessons Learned

1. We find that subjects may overestimate their balance abilities, particularly in intervention trials, so it is important to separately collect the caregiver perspective.
2. ABC and FES-I scales are scored in opposite directions, such that a 100% on the ABC represents total confidence in one's balance abilities, while a high score on the FES-I represents low confidence that one could do various activities without falling. Due to executive dysfunction and perseveration in PSP (31), certain subjects become confused and report answers that are the opposite of their intended answers. It is important to remind subjects of the instructions, to consider using only one scale, or to separate administration of the scales with other study tasks.
3. The average time for caregivers to complete the ABC and FES-I scale is 10 min. The subjects themselves may take up to 20 min to complete the scales with examiner assistance due to (1) bradyphrenia and (2) speech impairments that require them to repeat themselves or to point to answers for interpretability.

General Safety Considerations and Patient Comfort

Consideration of fall prevention at every point of contact in studies of PSP is paramount. The study team must consider fall prevention during patient transport to and from their vehicle, while navigating large research facilities, during bathroom breaks, in the MRI suite, etc. As caregivers know, this is not a trivial task. We recommend transporting patients in a wheelchair to and from their vehicle as well as while navigating the research facility. Normalizing wheelchair transport as a standard study procedure improves safety and prevents excessive subject fatigue, an important benefit because fatigue may confound balance testing results. It is important to be mindful to test subjects at consistent times of the day to minimize confounding affects related to alertness level. Because a subset of subjects with PSP may be on levodopa, ensuring consistent assessment times related to medication administration times is essential, especially since levodopa can increase postural sway (32). During testing and transport we recommend constant use of a lightweight gait belt without metal parts. In the case of a study with a MR imaging component, gait belts without metal fasteners can safely enter the MR suite without last minute awkward reconfigurations. It is imperative that MR technicians be trained in fall risk in PSP, and it is additionally recommended that research assistants are present in the MR suite and available to assist the MR tech with patient transfer in and out of the scanner. Regarding patient comfort during testing, we find that most patients prefer on-ground testing with mobile sensors and two spotters to being in the Neurocom with a harness and one spotter.

FUTURE DIRECTIONS

Alternative methodologies may better target balance deficits in PSP in the future. Dynamic posturography will benefit from force plates with seated testing capabilities, such as the Hunova system (Movendo Technologies, https://www.movendo.technology/en/) (33, 34). Seated assessment will be especially beneficial for more advanced subjects and for sit-to-stand training. The ZeroG Gait and Balance system (Aretech llc, https://www.aretechllc.com/) is a dynamic body-weight support system that has the potential to increase the safety of targeted rehabilitation programs for postural instability in PSP. Video motion analysis systems capture a breadth of movement tasks with high reliability (21), but we believe that inertial sensors and marker-less technologies reduce data processing time systems with similar accuracy and without the need for trained personnel for pre-processing (22). Turning is especially difficult to measure in video motion analysis systems because markers can become obstructed during transitions unless special measures are implemented (22). Intricate lab-based video motion analysis systems will not transition as easily as mobile sensors to home based or telehealth assessments in future clinical trials.

CONCLUSION

Balance testing in PSP is quickly moving beyond scale-based ratings to more objective assessments. Objective assessments in PSP should ideally capture multiple aspects of balance, including static balance, gait, turning, joint kinematics, and cognitive aspects of mobility. Safety can be ensured by consistent implementation of careful protocols by trained teams of neurologists, PTs, and study personnel familiar with PSP. Data integrity in future multi-center trials of balance in PSP will depend on consistent methodologies and patient instructions. Future studies are needed to examine balance deficits in the

less common subtypes of PSP, and recruitment in early PSP is essential.

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 Oregon Health and Science University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MD: conception, data gathering, and writing. AP, GH, and GM: data gathering and reviewing. MM: organization, writing, and reviewing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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A Lifespan Approach to Balance in Static and Dynamic Conditions: The Effect of Age on Balance Abilities

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Postural control is a complex sensorimotor skill that is fundamental to our daily life. The abilities to maintain and recover balance degrade with age. However, the time decay of balance performance with age is not well understood. In this study, we aim at quantifying the age-dependent changes in standing balance under static and dynamic conditions. We tested 272 healthy subjects with ages ranging from 20 to 90. Subjects maintained the upright posture while standing on the robotic platform hunova®. In the evaluation of static balance, subjects stood on the fixed platform both with eyes open (EO) and eyes closed (EC). In the dynamic condition, subjects stood with eyes open on the moving foot platform that provided three different perturbations: (i) an inclination proportional to the center of pressure displacements, (ii) a pre-defined predictable motion, and (iii) an unpredictable and unexpected tilt. During all these tests, hunova® measured the inclination of the platform and the displacement of the center of pressure, while the trunk movements were recorded with an accelerometer placed on the sternum. To quantify balance performance, we computed spatio-temporal parameters typically used in clinical environments from the acceleration measures: mean velocity, variability of trunk motion, and trunk sway area. All subjects successfully completed all the proposed exercises. Their motor performance in the dynamic balance tasks quadratically changed with age. Also, we found that the reliance on visual feedback is not age-dependent in static conditions. All subjects well-tolerated the proposed protocol independently of their age without experiencing fatigue as we chose the timing of the evaluations based on clinical needs and routines. Thus, this study is a starting point for the definition of robot-based assessment protocols aiming at detecting the onset of age-related standing balance deficits and allowing the planning of tailored rehabilitation protocols to prevent falls in older adults.

Keywords: postural control, aging, static and dynamic assessment, standing balance, age-dependent changes, perturbations

INTRODUCTION

Postural control is a complex sensorimotor skill fundamental to maintain, achieve, or restore a state of balance during any daily life activity (1). The generation of effective and appropriate postural control commands requires the central nervous system to process sensory information and to integrate them with motor, premotor, and brainstem afferent signals (2). Aging alters postural control as it affects the central structures (3), the sensory system, both in terms of unimodal processing (4–6) and multisensory integration (7), and the motor functions, affecting both movement and force control (8).

However, while the decline due to age is well characterized when considering, for example, the number of mechanoreceptors (9) or the brain volume loss (10), there are limited studies that systematically evaluate the time decay of balance abilities with age.

Indeed, most studies investigating the effects of aging on postural control assessed the difference in performance between well age-separated groups of subjects, namely, young, middle aged, and old adults either in static (11–13) or in dynamic conditions (14–21). Unfortunately, all the above-mentioned studies include different age ranges, making their comparison difficult and introducing bias due to the specific selection of the age ranges for each group. This also prevents a clear identification of the onset and the deterioration rate of the balance abilities associated with aging.

Only recently, two studies looked at a wider age range compared to previous studies, trying to assess how different postural and walking parameters change over a continuum of age (22, 23). These two studies used a lifespan approach to provide a quantification of the decline of balance with age by combining linear regression and qualitative observations. Virmani et al. (23) studied to what extent age affects walking in different conditions (i.e., steady-state gait, dual-task walking, and tandem gait). Park et al. (22) analyzed the effect of age both on static balance and on gait, focusing on (a) balance during quiet stance, (b) anticipatory postural adjustments in gait initiation, and (c) dynamic balance during walking. However, the reactive components of postural control, such as postural adjustments to external perturbations or in the presence of unstable environmental conditions, are not studied despite these reactive components being fundamental to detect balance impairments and the risk of falling (2, 15, 24–27).

To the best of our knowledge, no studies evaluated the ability to maintain the upright posture both in static and dynamic conditions, focusing on the reactive components of postural control, as a function of age, considering a large cohort of subjects and spanning an interval of 70 years, i.e., from 20 to 90 years of age.

This study aims at filling this gap by describing the deterioration of balance performance in adulthood by considering the reactive components of balance, and has a two-fold purpose:

- Describe the deterioration of balance abilities as a mathematical function depending on age in both static and dynamic conditions;
- Determine the potential of different types of perturbations on probing balance abilities.

Also, in this study, we used a robotic platform that allowed us to investigate the reactive postural components of balance in a reliable, repeatable, and well-controlled manner. Importantly, the assessment protocol proposed in this work is designed for clinical evaluation. Thus, our testing conditions are intended to be quick and easy to perform. First, we assessed postural control in static condition with both eyes open (EO) and eyes closed (EC). We specifically investigate the role of visual feedback and the interplay between vision and aging while maintaining standing balance. Indeed, this is still a debated issue as some research (12, 28, 29) demonstrated that old adults rely more on vision, while others (20, 30) concluded that the rate of change due to EC is independent of age. Then, to test the reactive components of balance, we assessed postural control in three different dynamic conditions (2): (i) the perturbations depended on the subject himself and were proportional to the oscillation of the subject, (ii–iii) the perturbations were imposed by the robotic device and independent from the subjects. Specifically, those were continuous and predictable in (ii) and unpredictable and unexpected in (iii). In these dynamic tasks, which are more challenging than the static tasks, we expect to have a better-defined relationship between balance performance and age and/or a higher decay of the measured abilities.

MATERIALS AND METHODS

Subjects

A total of 272 healthy subjects (48 participants 19–30 years, 25 participants 31–40. 28 participants 41–50. 21 participants 51–60. 39 participants 61–70. 80 participants 71–80. 31 participants 81–90; see **Figure 1** for the age distribution) participated in this study and matched the following criteria:

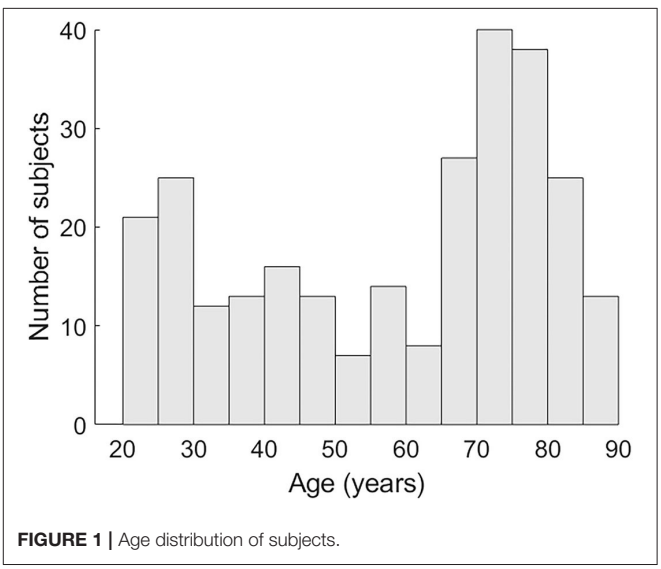

FIGURE 1 | Age distribution of subjects.

- age ranging from 19 to 90 years;
- absence of any neurological disorders (from the anamnesis) and/or moderate-severe cognitive impairment [subjects with more than 4/10 wrong answers to the Short Portable Mental Status Questionnaire (31) were excluded from the study];
- absence of any other condition that could affect balance;
- ability to stand and walk independently without assistive aids;
- absence of speech and/or aphasia disorders;
- absence of severe heart disease or respiratory failure.

Also, subjects that had a bone fracture in the 6 months (12 months in case of femoral fracture) prior to the evaluation were excluded. Participants were enrolled by the Department of Geriatric Care, Orthogeriatrics and Rehabilitation of Galliera Hospital (Genoa, Italy) in collaboration with the University of Genoa and the Italian Institute of Technology.

The study procedures conformed to the Declaration of Helsinki and were approved by the local ethical committees [Comitato Etico DIBRIS, reference number: CE DIBRIS: 012/2020 and Comitato Etico Regionale (CER) Liguria, reference number: 169REG2016]. All subjects included in the study signed a consent form that conforms to these guidelines and approved to publish individual data.

Robotic Device

All subjects were tested using the medical robotic device hunova® from Movendo Technology srl, already described in previous studies (32, 33). Briefly, it has two electromechanical platforms: one under the feet and one under the seat (not used here) with two rotational degrees of freedom as described in (34). Behind each platform, a six-axis force-torque sensor allows the estimation of the center of pressure, while an optical incremental encoder allows the measurement of the inclination of the platforms. The device integrates an Inertial Measurement Unit (IMU) synchronized by software with the device. The IMU sensor in this experiment was placed on the sternum of the user for monitoring trunk motion, as previously done in previous studies (33, 35).

Robotic Exercises and Protocol

During all tests, participants stood on the platform while wearing the IMU sensor on the sternum. At the beginning of each test, they were positioned on the platform with the heels separated by about 2 cm, the feet abducted at 20 degrees, and the arms relaxed along the sides of the body.

Participants were requested to stand still, avoiding any significant motion in all tests independently of the state of the foot platform. Before starting the experiment, subjects underwent a familiarization phase, where they become acquainted with the device and the proposed exercises by experiencing the platform movements and trying each exercise until they felt comfortable.

The protocol included five tests (see **Figure 2**), as follow:

Test 1 and 2. Static condition, i.e., the platform was kept fixed for the entire duration of the test. Participants had their eyes either open (EO—Test1) or closed (EC—Test2).

Test 3-4-5. Dynamic condition, i.e., the foot-platform was moving in three different ways described below. Participants always had their eyes open. Specifically:

Test 3. Subjects were asked to stand still on an unstable surface. The platform tilted in response to the weight shift of the subject. The platform responded as a plate on a pivot, with an additional low elastic rotatory force field that opposed to the movement induced by the subject weight shift and tended to restore the platform parallel to the floor.

Test 4. Subjects were asked to stand on the platform that was moving according to a preprogrammed and continuous circular trajectory (not influenced by the subject motion). The platform was tilting around the x and z axes, generating a circular trajectory given by the following equations [as previously described in a previous study (36)]:

$$\theta_z = A \sin(\pi \omega t)$$
$$\theta_x = A/2 \sin(2\pi \omega t)$$

where θ_z and θ_x are the angular tilt around the medio-lateral (ML) and antero-posterior (AP) directions, respectively, and A is the maximum angular rotation and ω is the angular velocity. In our specific case, A = 6; $\omega = 0.15$.

Test 5. Subjects were asked to stand on the platform while experiencing unpredictable perturbations. The platform tilted forward or laterally, along the z and x rotational axes, respectively. Thus, there were three possible perturbations: (i) "toes down" along the positive z-axis (i.e., forward perturbation), (ii) "right-foot down," and (iii) "left-foot down" along the x-axis (i.e., rightward perturbation; leftward perturbation, respectively). In this exercise, the platform rotated following a Gaussian profile trajectory, as to respect the minimum jerk trajectory, with the peak of 5.5° at 330 ms after the perturbation onset (mean velocity ∼16.5°/s). A total of nine perturbations, three for each perturbation direction, were presented in random order and with a jittered time interval between each one (4.7 + 0.6 s) to avoid anticipation or guessing.

In all the eyes open conditions, participants were asked to fix a single point on a wall 1 m away. In case participants did not finish one of the proposed exercises because they used the handles of hunova® to restore balance or opened their eyes in the EC test, they were requested to repeat the exercise after a break to prevent fatigue.

Notice that the coordinate reference system is the same commonly used for gait analysis with the positive *x*-, *y*-, and *z*-axes, respectively, pointing forward (AP direction), up, and right (ML direction), defining a right-handed system [for clarification, see (33)]. Positive rotations are counterclockwise about the axis of rotation. The center of the system is in the middle of the platform.

Based on *a priori* assumptions of clinicians, each performed exercise within the protocol (exception made by test 5) lasted 20 s. While this is not the classical balance test duration, clinicians believed this was sufficient to highlight the signs of decline in balance performance due to age that may qualify as risk biomarkers for preventable fall. This complied with

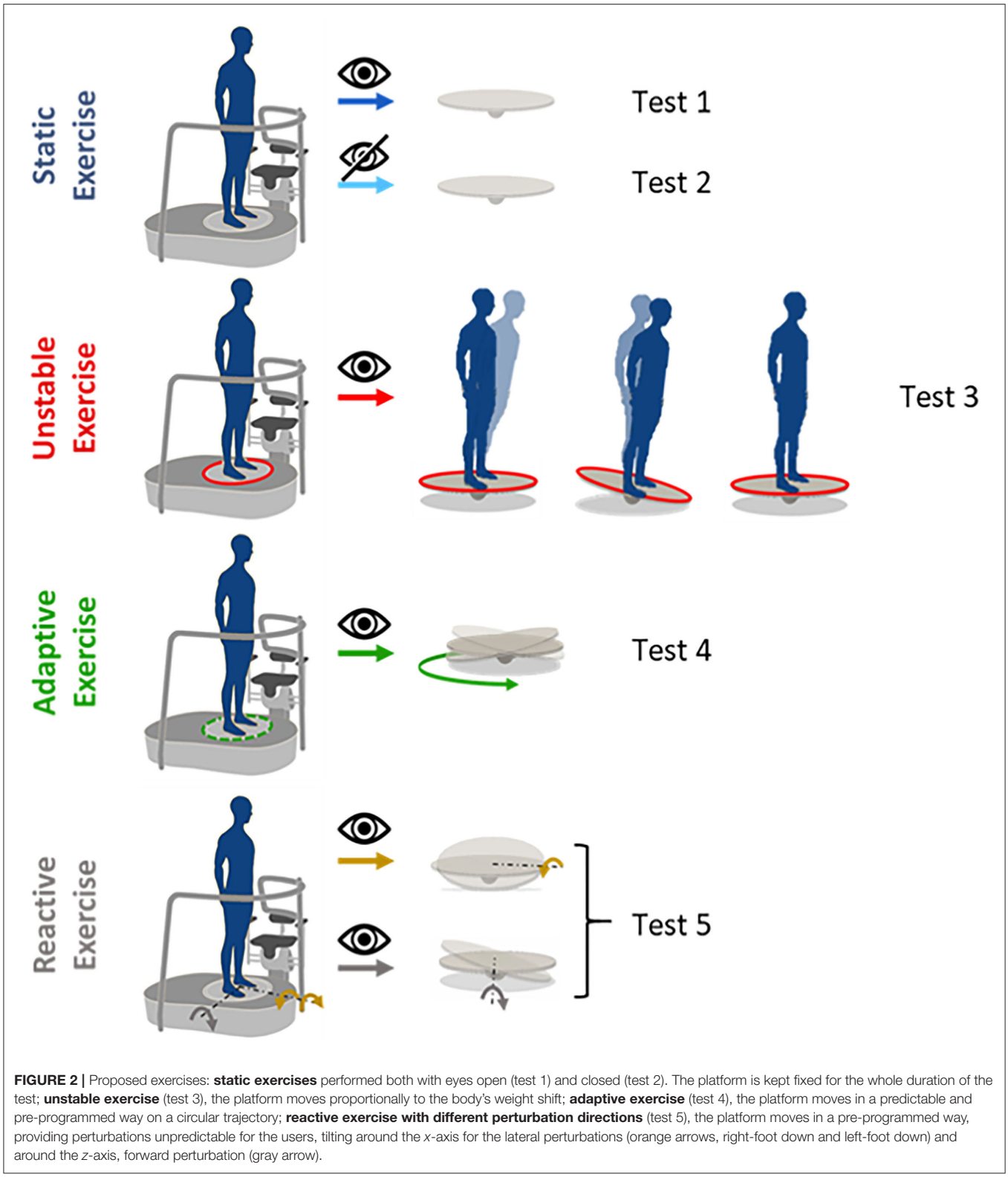

FIGURE 2 | Proposed exercises: **static exercises** performed both with eyes open (test 1) and closed (test 2). The platform is kept fixed for the whole duration of the test; **unstable exercise** (test 3), the platform moves proportionally to the body's weight shift; **adaptive exercise** (test 4), the platform moves in a predictable and pre-programmed way on a circular trajectory; **reactive exercise with different perturbation directions** (test 5), the platform moves in a pre-programmed way, providing perturbations unpredictable for the users, tilting around the *x*-axis for the lateral perturbations (orange arrows, right-foot down and left-foot down) and around the *z*-axis, forward perturbation (gray arrow).

the final aim of a clinically applicable and safe protocol that: (a) included different conditions but was also administrable in a reasonable time (i.e., around 10 min), (b) avoided the risk of falling in dynamic conditions which in their experience, could occur in some older participants under longer exposure.

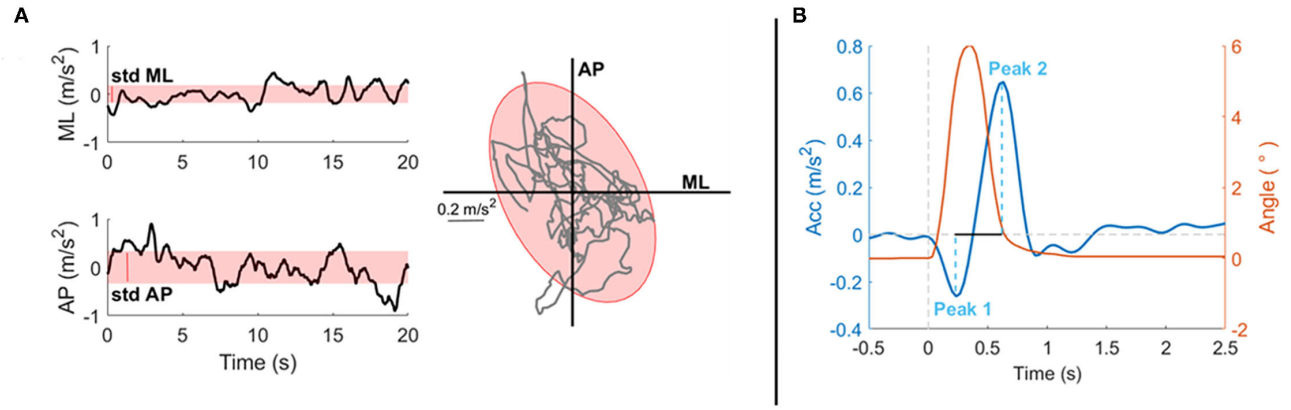

FIGURE 3 | Experimental data from a representative subject to explain the parameters selected for the analysis of the proposed tasks. Parameters are based on readings of an Inertial Measurement Unit (IMU) placed on the sternum of the subject, i.e., parameters are extracted from the acceleration measures. **(A)** On the first column, the stabilograms (black line) and the variability (red shaded area, STD) of a 20-s exercise both in the ML (up) and AP (bottom) directions are shown. In the second column, the statokinesigram (gray line) together with the fitted confidence ellipse (red shaded area) representing the sway area are shown. Those parameters are computer for tests 1, 2, 3, and 4. **(B)** This panel shows the postural response after a perturbation of a representative subject for test 5: in red the perturbation trajectory, in blue the postural response along the perturbation's direction. Here, the peaks amplitudes are highlighted (light blue dashed line) together with the peak-to-peak time difference (black line).

For completeness, since in the literature a duration of 30 s is more common, in the **Supplementary Figures S1**, **S2**), data supporting the hypotheses that the posturographic analysis does not lead to different results when based on 20 and 30 s of recording are provided.

Data Analysis

The trajectory followed by the platform in its motion and the signals from the IMU sensor were simultaneously recorded at a sampling frequency of 30 Hz and saved by hunova®. As previously explained in previous studies (33, 36), we used the IMU accelerations to evaluate balance performance. The acceleration measures from the IMU were firstly corrected to have them referred to a true horizontal-vertical Cartesian coordinate system (37) and then filtered with a 12 Hz cut-off low-pass Butterworth filter.

From the trunk acceleration signals, different spatio-temporal parameters were computed (see below). For tests 1, 2, 3, and 4, the following parameters were extracted [as previously done in previous studies (33, 38) and as shown in **Figure 3**]:

- Mean velocity (MV, m/s): the mean value of the speed on the horizontal plane (39), i.e., the 2-norms of velocity along the x–z-axes, obtained by the integration of the corresponding components of the acceleration (40);
- Anterior-Posterior variability (STD AP, m/s^2): standard deviation of the trunk acceleration along the AP direction (z-axis): the bigger this value, the more subjects moved in this direction;
- Medio-Lateral variability (STD ML, m/s^2): standard deviation of the trunk acceleration along the ML direction (x-axis): the bigger this value, the more subjects moved in this direction;
- Sway area (SA, m^2/s^4): the area of the 95% confidence ellipse of the statokinesigram of the trunk accelerations in the horizontal plane (i.e., the surface that contains 95% probability of the individual points that make up the statokinesigram).

All the above parameters provide a comprehensive spatio-temporal description of the postural sway in the proposed tasks.

For test 5, data were segmented in 1.75 s lasting epochs, from −0.25 to 1.5 s after each perturbation onset. For each perturbation, the acceleration measure had the first peak in the direction of the perturbation and then, a rebound peak in the opposite direction. Hence, the following parameters were computed (**Figure 3B**):

- Peak$_1$: amplitude of the first peak following the perturbation in the direction of the perturbation;
- Peak$_2$: amplitude of the rebound peak in the opposite direction;
- P2P$_{amp}$: peak-to-peak amplitude, amplitude distance between Peak$_1$ and Peak$_2$;
- P2P$_{time}$: peak-to-peak time, time distance between Peak$_1$ and Peak$_2$.

The proposed measures considered both the first oscillations performed to counteract the platform inclination and the postural adjustment following the platform inclination, together with a comprehensive measure that considered both strategies. For each direction, the three repetitions were averaged, as we expected no adaptation after only three repetitions. Since no effect was found between left and right lateral perturbations (see **Supplementary Figure S3**), the two lateral perturbations were averaged together to distinguish only forward and lateral perturbations.

Each computed parameter in each exercise was described and modeled as a function of age. To perform a comparison between all the parameters, each parameter was normalized in a relatively normalized performance index P_i, *with* $i = 1, .. N$, where N is

TABLE 1 | *a_i-value*, reported with its confidence interval (with 95% confidence bounds).

	MV	STD AP	STD ML	Area
Static EO	0.012 (0.001–0.022)	0.024 (0.008–0.039)	0.055 (0.037–0.074)	0.121 (0.089–0.152)
Static EC	0.001 (0.000–0.002)	0.080 (0.061–0.099)	0.045 (0.025–0.064)	0.070 (0.038–0.102)
Unstable	0.154 (0.136–0.172)	0.174 (0.150–0.198)	0.377 (0.340–0.415)	0.643 (0.565–0.720)
Adaptive	0.164 (0.147–0.182)	0.138 (0.118–0.158)	0.171 (0.149–0.193)	0.301 (0.257–0.344)
	$P2P_{time}$	**$P2P_{amp}$**	**$Peak_1$**	**$Peak_2$**
Reactive, FWD	0.009 (0.000–0.017)	0.358 (0.324–0.392)	0.156 (0.138–0.174)	0.572 (0.497–0.646)
Reactive, lateral	0.031 (0.024–0.039)	0.157 (0.141–0.174)	0.127 (0.114–0.140)	0.225 (0.199–0.252)

The a_i -value is the coefficient of the second-order curve that fits the postural parameter P_i expressed as a function of age. Higher values of a_i indicate faster changes, i.e., greater decline of balance ability throughout the adult life span. Each a_i -value is referred to a specific parameter and a specific exercise. Each row is referred to the exercise reported in the corresponding row of the first column, namely, static EO, static EC, unstable, adaptive, reactive FWD, and reactive lateral. In the upper part of the table, each column is referred to the parameter indicated in the first row: MV (mean velocity), STD AP (Antero-Posterior variability), STD ML (Medio-Lateral variability), and SA (sway area). In the lower part of the table, each column is referred to the parameter indicated in the seventh row, i.e. $P2P_{amp}$ (peak-to-peak amplitude), $P2P_{time}$ (time distance between $Peak_1$ and $Peak_2$), $peak_1$ (amplitude of the first peak), and $peak_2$ (amplitude of the second peak).

the number of parameters computed in the analysis. To do this, each measured parameter m^i was subtracted and then divided by a reference value m_0^i, obtained by the average value of all the subjects with an age under 25:

$$P_i = \frac{m^i - m_0^i}{m_0^i}$$

Then, each performance index, P^i was modeled as a function of age (y) using a second-order polynomial fitting curve:

$$P_i(y) = a_i \left(\frac{y - y_0}{y_0} \right)^2$$

where y_0 represented the reference age value that we consider equal to 25. This procedure kept the model simple and dependent only on one fitting parameter, a_i, which represented the rate of changes in performance due to age. Higher a_i were related to faster changes in performance throughout the lifespan. In our case, as we expected a negative impact of age, higher a_i meant a greater balance deterioration.

Statistical Analysis

Each performance index was described by a second-order polynomial function that we defined fitting our data. As this study aimed at evaluating the effect of age on different balance performances over a wide healthy population and the focus was on the average subjects' performance, not on individual subjects, we used a robust fitting method to reduce the effects of outliers (41). Specifically, robust fitting weighs the contribution of each single data point to the fitting curve with a weight ranging from 0 to 1, and we excluded data with weights lower than 0.1, considering them outliers.

For each parameter of each exercise, the fitting was completely characterized by a_i, which is reported with its confidence interval (with 95% confidence bounds). To evaluate the goodness of fit, we computed both the coefficient of determination (R^2) and the square root of the variance of the residuals (RMSE).

Also, we divided our population into two groups, considering subjects under 50 and over 50 as in a previous study (23) to: (a) make our study comparable with other works and with (22, 23) (i.e., the other two works that assessed balance abilities considering age as a continuum) which also split their population into groups; and (b) make sure of the significance of our mathematical function. To test the significance of our results, we then tested the differences in performance in these two age groups, running either an unpaired t-test or a Wilcoxon rank-sum test (42) depending on the results of the normality test [Anderson Darling test (43)]. Significance was set for all statistics at the family-wise error rate of $\alpha = 0.05$. Finally, we confirmed the strength and validity of our results by computing and reporting (in the **Supplementary Material**) the power analysis related to this comparison. Given the effect size, the sample size, and α, we computed the power of our result.

RESULTS

All subjects successfully completed all the proposed exercises without experiencing fatigue.

We found that a quadratic function was suitable to describe the relationship between balance performance and age during most postural tasks, with a better fit for the dynamic conditions (see also **Supplementary Material** for comparison with different fitting functions). The fact that this function well describes the changes in balance abilities with age, considering the entire adult lifespan and without abrupt changes at a specific age, suggested that balance abilities have a continuous smooth degrade with age, with a higher decline later in life (i.e., at an older age), especially in dynamic conditions. **Table 1** shows the fitting parameter, a_i, which represents how fast performance changes due to age: higher values of a_i indicate faster changes, i.e., greater decline of balance ability throughout the adult life span. **Tables 2**, **3** show the coefficient of determination to describe the goodness of fit, R^2, and the square root of the variance of the residuals, RMSE, both for each parameter in each exercise. The deterioration due to age of balance performance was highly dependent on the

TABLE 2 | Goodness of fit, R^2, for the second order curve that fits a postural parameter P_i, expressed as function of age.

	MV	STD AP	STD ML	Area
Static EO	0.161	0.039	0.110	0.265
Static EC	0.090	0.125	0.110	0.203
Unstable	0.328	0.393	0.445	0.616
Adaptive	0.393	0.358	0.350	0.456
	$P2P_{time}$	$P2P_{amp}$	$Peak_1$	$Peak_2$
Reactive, FWD	0.535	0.366	0.375	0.360
Reactive, lateral	0.326	0.424	0.539	0.371

Higher values of R^2 indicate better fit. Each R^2 is referred to the fitting of a specific parameter in a specific exercise. Each row is referred to the exercise reported in the corresponding row of the first column, namely static EO, static EC, unstable, adaptive, reactive FWD, and reactive lateral. In the upper part of the table, each column is referred to the parameter indicated in the first row: MV (mean velocity), STD AP (Antero-Posterior variability), STD ML (Medio-Lateral variability), and SA (sway area). In the lower part of the table, each column is referred to the parameter indicated in the seventh row, i.e. $P2P_{amp}$ (peak-to-peak amplitude), $P2P_{time}$ (time distance between $Peak_1$ and $Peak_2$), $peak_1$ (amplitude of the first peak), and $peak_2$ (amplitude of the second peak).

TABLE 3 | Square root of the variance of the residuals, RMSE.

	MV	STD AP	STD ML	Area
Static EO	0.271	0.406	0.467	0.801
Static EC	0.267	0.487	0.487	0.784
Unstable	0.461	0.584	0.900	1,711
Adaptive	0.450	0.503	0.563	1,052
	$P2P_{time}$	$P2P_{amp}$	$Peak_1$	$Peak_2$
Reactive, FWD	0.219	0.885	0.473	1,931
Reactive, lateral	0.199	0.436	0.338	0.684

Specifically, each row is referred to the exercise reported in the corresponding row of the first column, namely static EO, static EC, unstable, adaptive, reactive FWD and reactive lateral. In the upper part of the table, each column is referred to the parameter indicated in the first row: MV (mean velocity), STD AP (Antero-Posterior variability), STD ML (Medio-Lateral variability) and SA (sway area). In the lower part of the table, each column is referred to the parameter indicated in the seventh row, i.e., $P2P_{amp}$ (peak-to-peak amplitude), $P2P_{time}$ (time distance between $Peak_1$ and $Peak_2$), $peak_1$ (amplitude of the first peak), and $peak_2$ (amplitude of the second peak).

testing conditions, i.e., on the task (**Figure 4**; **Table 1**). **Table 4** shows the results of the comparison between the performance of subjects under and over 50. These results are described in detail below.

Static Tasks

In the static tasks, the deterioration of balance performance due to age was smaller and with a slower deterioration compared to all the dynamic tasks, i.e., overall aging had smaller effects on static than on dynamic performance. In the static test with EO, the age-dependent changes in the SA were due to the amplitude of the oscillations in the ML direction, while those in the AP changed with a slower rate (smaller *a-value* in the STD AP, as shown in **Table 1**). Also, the MV had negligible changes due to age (**Table 1**; **Figure 4**), as also confirmed by the comparison between under and over 50 (**Table 4**) which shows no statistical difference. In the EO condition, it is important to notice that all the parameters but the MV show a statistically significant difference between under and over 50 (**Table 4**).

Differently, in the static test with EC, the age-dependent changes of the SA were smaller compared to the EO (smaller *a-value*) as the relative difference between young and old adults is less marked as confirmed from the differences in performance of subjects under and over 50. Also, the variability of the oscillation in the mediolateral direction (STD ML) was equal in the EO and in the EC condition, i.e., the *a-value* defining the function that describes the decline with age of this parameter did not change depending on the availability of visual feedback. Instead, the oscillations in the anteroposterior direction (STD AP) changed depending on the EO–EC testing conditions. Specifically, the *a-value* for this parameter was higher in the EC condition (with also a statistical difference between under and over 50), indicating a greater change with respect to EO, i.e., the performance explained by this parameter degraded more in absence of visual feedback.

Dynamic Tasks

In the unstable exercise, where the platform motion depended on the weight shift of the subject, and in the adaptive, where the subject needed to adapt to a continuous and predictable platform motion, the age-dependent changes were relevant for all parameters and statistically different when comparing under and over 50. Specifically, the unstable exercise had bigger changes (higher *a-value*) also associated with higher values of the goodness of fit. In addition, the SA, accounting for changes in both AP and ML directions, was the parameter that has the best fit with the parabolic curve for all the testing conditions.

Conversely, in the reactive exercise, the timing of the postural responses ($P2P_{time}$) after a perturbation was not or was minimally affected by age (**Tables 1**, **4**). Instead, $P2P_{amp}$ had age-dependent changes marked more for perturbations in the forward direction. The difference was mainly due to the amplitude of the second peak ($Peak_2$) which significantly changed with age and with a faster rate for perturbations in the forward directions. However, for the amplitude measures, the goodness of fit was always slightly better for the lateral than for the forward perturbations (**Table 2**).

Performance of the Adults Under 25 Years of Age in the Different Testing Conditions

The performances of subjects under 25 have been considered as reference (i.e., normalization factor, as explained in the Method section). Subjects under 25 had a motor performance that depended on the task (**Figure 5**). All the parameters we selected had the same trend: lower values were typical of the easiest testing condition, i.e., the static with EO, and increase with the difficulties of the task following this order: static exercise with EC, unstable, and adaptive exercises. As for the reactive exercise, subjects under 25 had different results depending on the two perturbation directions: in the forward, both the first and the second peaks were bigger when compared to the lateral perturbations, along with the peak-to-peak timing. Indeed, the postural responses after an impulsive perturbation were

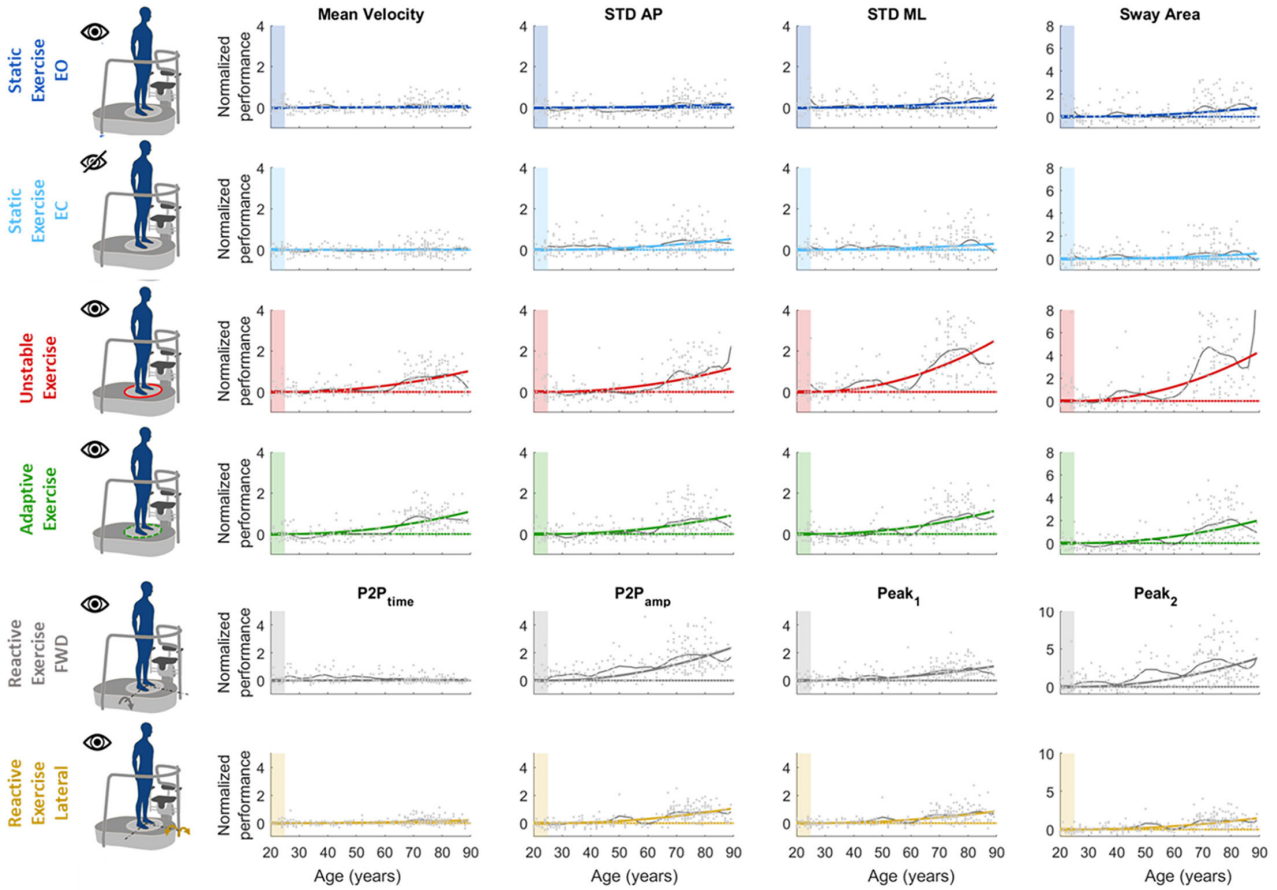

FIGURE 4 | Computed parameters for all the performed tests. Each graph represents how each single parameter changes with age [*x*-axis: age (years), *y*-axis: normalized performance indexes]. In each graph, dots represent single subjects' performance; colored line is the parabolic fitted curve; black line represents the age by age mean curve; dashed color line is the reference performance ($y = 0$). The colored shaded patch highlights the reference age windows used for normalization (age between 20 and 24). Each row is relative to a different test: namely (from top to bottom) static EO, static EC, unstable, adaptive, reactive exercise (forward and lateral perturbation). Each column is relative to a specific computed parameter, namely, (from left to right) mean velocity (MV), STD AP, STD ML, sway area (SA, for test 1–4), and $P2P_{time}$, $P2P_{amp}$, $Peak_1$, and $Peak_2$, (for test 5).

longer when the perturbation is along the AP direction (i.e., forward perturbation).

DISCUSSION

In this study, we proposed a setup and a protocol to test balance abilities in different testing conditions, focusing on the reactive components of balance. The ability to maintain equilibrium when facing perturbations and environmental challenges is a fundamental component of balance that is necessary to avoid falls (2, 15, 24–27). Here, we considered the entire adult age span, and we highlighted that the decline of balance abilities with age could be described by a quadratic curve. Especially in the dynamic tests where the reactive component plays a major role, we observed an increase in the rate of decline with age, suggesting that a quadratic curve better describes than a linear fitting the decline with age. To comprehensively quantify the age-dependent changes in balance abilities, we also evaluated the influence of visual feedback while maintaining the standing posture in the static condition. We decided *a priori* to discard from this study the assessments in the dynamic condition in absence of visual feedback. This choice was motivated by the desire of the clinicians to define a safe protocol to test subjects without the risk of falling. Based on clinical practice, they judged the dynamic tasks with eyes closed associated with a high risk of falls, and they wanted *a priori* to exclude this condition from the protocol.

The effect of age on postural control was also clear from previous studies (11–18) that, differently from our approach, assessed balance differences dividing the population in few "age-groups," e.g., considering young, middle age, and old subjects, with different definitions on the ranges across studies. Indeed, Allum et al. (19) assessed postural control after unexpected perturbations in the four directions including healthy subjects from 20 to 75 years of age, and they split the population into three groups: the first with age ranging between 20 and 34 years,

TABLE 4 | Mean ± std of each measured parameter m^i before normalization.

		MV (m/s)	STD AP (m/s^2)	STD ML (m/s^2)	Area (m^2/s^4)
Static EO	Under 50	0.270 ± 0.075	0.083 ± 0.030	0.043 ± 0.016	0.065 ± 0.040
	Over 50	0.279 ± 0.077	0.104 ± 0.040	0.050 ± 0.021	0.090 ± 0.055
Static EC	Under 50	0.280 ± 0.061	0.097 ± 0.034	0.053 ± 0.018	0.100 ± 0.058
	Over 50	0.320 ± 0.097	0.119 ± 0.047	0.060 ± 0.028	0.126 ± 0.084
Unstable	Under 50	0.446 ± 0.129	0.108 ± 0.049	0.077 ± 0.037	0.157 ± 0.143
	Over 50	0.670 ± 0.237	0.181 ± 0.079	0.158 ± 0.076	0.473 ± 0.332
Adaptive	Under 50	0.612 ± 0.192	0.159 ± 0.055	0.118 ± 0.040	0.351 ± 0.204
	Over 50	1,044 ± 0.340	0.255 ± 0.101	0.210 ± 0.086	0.903 ± 0.570
		$P2P_{time}$ (s)	$P2P_{amp}$ (m/s^2)	$Peak_1$ (m/s^2)	$Peak_2$ (m/s^2)
Reactive, FWD	Under 50	0.409 ± 0.132	1,139 ± 0.461	0.739 ± 0.262	0.413 ± 0.283
	Over 50	0.365 ± 0.084	2,033 ± 0.893	1,111 ± 0.402	0.926 ± 0.612
Reactive, lateral	Under 50	0.307 ± 0.052	0.814 ± 0.226	0.360 ± 0.071	0.455 ± 0.188
	Over 50	0.324 ± 0.078	1,385 ± 0.462	0.531 ± 0.174	0.855 ± 0.370

The colors are used to report statistical results of the comparison between subjects under 50 and subjects over 50: in red the values which resulted statistically significant ($p < 0.001$), in gray parameters with a non-statistically significant p, but with $p \sim 0.1$. Specifically, for each exercise, for each parameter, we reported mean ± std both for subjects under and over 50. Each row is referred to the exercise reported in the corresponding row of the first column, namely static EO, static EC, unstable, adaptive, reactive FWD, and reactive lateral. In the upper part of the table, each column is referred to the parameter indicated in the first row: MV (mean velocity), STD AP (Antero-Posterior variability), STD ML (Medio-Lateral variability), and SA (sway area). In the lower part of the table, each column is referred to the following parameters: $P2P_{amp}$ (peak-to-peak amplitude), $P2P_{time}$ (time distance between $Peak_1$ and $Peak_2$), $peak_1$ (amplitude of the first peak), and $peak_2$ (amplitude of the second peak).

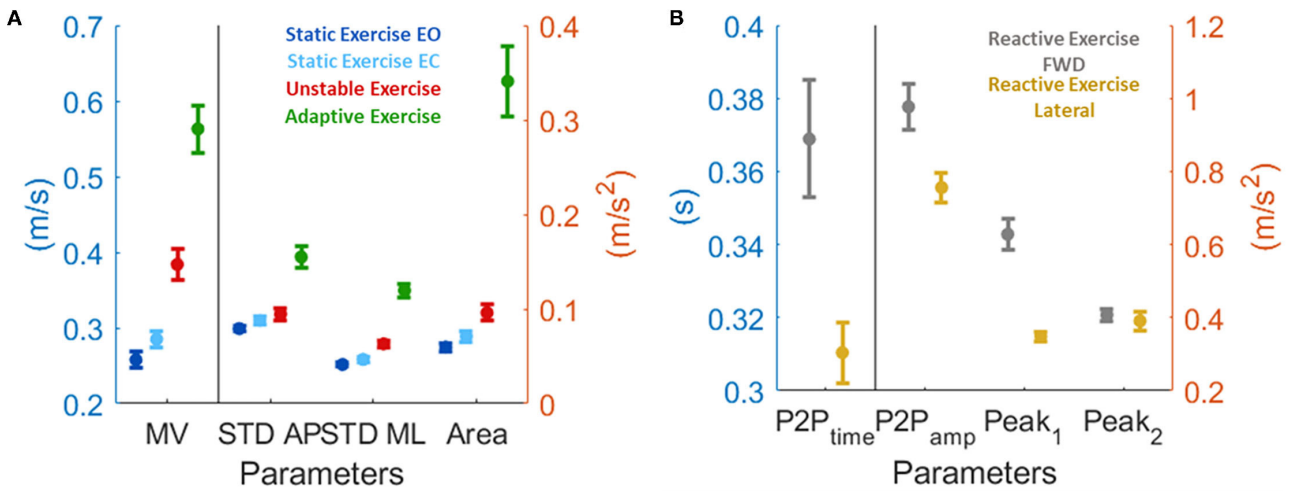

FIGURE 5 | Motor performance of the subjects under 25 expressed as mean and standard deviation. This is the normalization factor we used before applying the fitting (see methods section for more details). **(A)** for test from 1 to 4, and **(B)** for test 5.

the second 35–55, and the third 60–75. Liaw et al. (21) studied balance on a static platform with both eyes open and closed, dividing the population into three "age groups": the first 18–39, the second 40–59, and the third 60–80 years old. Moreover, Freitas et al. (18) split the middle age group into two subgroups and studied postural responses after forward perturbation in young adults (20–25), middle age 1 (40–45), middle age 2 (50–55), and old adults (60–65). Differently, Colledge et al. (13) divided the over 60 into two different groups: 60–70 and over 70. Moreover, the lack of a single definition for "young" and "old" led to different results. For this reason, here, we considered age as a continuous factor with no division in "age-groups."

Before quantitatively assessing the age-dependent deterioration of balance abilities, we selected the best curve to fit our data. A previous study from Park et al. (22) studied the effect of age both on static balance and gait. They computed 37 different parameters and underlined three different typical trends depending on age: linear deterioration, decline after plateau, and no or minimal worsening. Differently, in our study, we found that there is a smooth deterioration of performance with age that could be described by a parabolic curve especially in dynamic conditions. This fitting allowed us to maintain a simple, i.e., depending on a single parameter, and easy-to-use model.

We found that the rapidity with which the performance changes depends on the selected postural parameter and the testing condition.

In the static condition, we compared performance with EO and EC. In literature, there is no unique opinion on the strategy subjects adopt to compensate for the absence of visual feedback. Sarabon et al. (30) concluded that older adults do not rely on vision more than young adults, while Benjuya et al. (29) highlighted the different strategies old and young adults adopt to compensate for the absence of visual feedback. From this study, the authors concluded that young adults compensate for the absence of vision with the use of other sensory information, while old adults stiff the ankles and co-contract agonist and antagonist leg muscles (29). Our results support the hypothesis of dependence on visual feedback of the deterioration of static balance performance with age. Indeed, we found bigger changes with age in the EC condition than in EO condition for the postural sway in the AP direction, i.e., the changes due to age were bigger in the EC condition. Instead, the age-dependent changes were not significantly different between the two feedback conditions for all the other parameters despite that subjects had a worse performance with eyes closed as expected, as shown by the normalization factor, i.e., the performance of subjects under 25 years of age. In summary, our results support the conclusion that older adults rely more on vision than younger adults in static standing balance tasks, and this is mainly observable in the AP postural sway.

As for the dynamic exercises, we included in our experiment three dynamic conditions to test different aspects related to reactive balance: the postural responses after unpredictable and unexpected external-perturbations, after predictable and continuous external-perturbations, and after auto-induced perturbations, i.e., the weight shift of the subject caused a tilt of an unstable platform. In all these exercises and in all the computed parameters, we found evident age-related changes. More precisely, among the dynamic tests, the unstable exercise was the most challenging one. Here, the small postural adjustments, if not optimally controlled, can cause auto-induced perturbations as each weight shift is transformed in a platform inclination. This exercise was the one that causes the biggest changes in performance with respect to young adults. Concerning the reactive exercise, the forward perturbation was the one that induced a bigger postural response with the biggest age effect.

Similar dynamic exercises are proposed in other studies (15, 18). However, several previous works mainly aimed at deeply understanding specific mechanisms underlying postural control and mainly focused on the comparison of performance between healthy subjects and people with well-known impairments. An example is a study on de-afferent subjects that clarified the role of sensory feedback (44–46). Alternatively, postural control was also described depending on its sensory processing and how it changed when the information of at least one of the sensory modalities (i.e., visual) was unavailable or modified (i.e., when we close our eyes). Other studies isolated single aspects of postural control, as defined in a previous study (2), investigating balance only under specific conditions as: (i) balance during quiet stance, (ii) reactive postural adjustments to external perturbations, (iii) anticipatory postural adjustments in preparation for voluntary movements, and (iv) dynamic balance during movements.

Here, we proposed a comprehensive, exhaustive, and short evaluation, suitable for assessment in clinical settings targeting different balance components, i.e., considering the role of visual feedback and specific aspects of the reactive postural control as defined in previous studies (2, 47), namely, the reactive postural adjustments to external perturbations, and dynamic balance during movements. All our metrics have been computed from the IMU placed on the sternum that provides reliable measures of balance abilities as demonstrated by Marchesi et al. (33), Mancini et al. (38, 48). In addition, in our exercises, we used a mobile feet force platform to provide different dynamic interactions in a controlled manner. The use of a robotic platform in our setup allowed us to expose subjects to different environmental conditions that can be repeatable and well-controlled. Indeed, robotic platforms are powerful tools offered to clinicians allowing for standardized assessments. This latter is a fundamental requirement when testing, as in our case, a large population to assess the decline of reactive balance abilities with age. Also, the use of robotic tools and platforms allows quantifying performance in an accurate and precise manner, reducing the subjective component added by the clinical test based on the evaluation of the operator.

In this work, we characterized how age affects balance describing the physiological changes of balance due to age. We concluded that, as expected, those changes are continuous. However, as balance degrades with age, strength and the ability to precisely control handgrip force are also well known to decrease with age. In addition, dynamic balance and handgrip strength seem to be correlated (49), and we could expect a correlation that is worth investigating in future studies, also with a lifespan approach.

Lastly, in clinics, the performance of subjects is normally compared with normality ranges which highly depends on the age ranges that have been considered for the normality definition. Our approach and results may be adopted in clinical practice to assess whether individual balance performance in static and dynamic conditions is in line with the average performance of age-matched people. Indeed, our choice to use a robust fitting method to reduce the effects of outliers (41) allowed us to focus on the average performance of subjects, and not on individual subjects. However, the fitting we are proposing may be used to detect anomalous performance and highlight the early appearance of motor impairments.

To conclude, we highlight a twofold reason why this study could be useful in the clinical environment:

1) It provides a framework—set up and protocol—to assess, in a well-controlled and repeatable manner, balance control in presence of different perturbations as the instability, the predictable, and the unpredictable motion of the surface where one stands.
2) It provides a mathematical description of the decline with age of balance abilities under static and dynamic conditions,

providing data from a large population and covering the entire adult lifespan. This approach can be used to evaluate the possible onset of balance problems, separating them from a normal decay of the balance abilities due to age. In fact, subjects who can be considered outliers, falling at the margins or outside of the range of variability of the proposed fitting could have a specific balance problem and must be carefully monitored. This could also allow for early detection of specific balance problems and to plan a timely rehabilitative intervention.

LIMITATIONS

We acknowledge that we did not randomize the proposed five testing conditions, and this could potentially bias the presented results. However, subjects underwent a familiarization phase in which they experienced all the exercises to avoid effects due to initial exposure to a specific exercise and to the device. Also, the exercises were different and kept short. Thus, we did not expect or observe the effects of fatigue or of learning. Nevertheless, if the performance in a specific exercise could be biased by the order of the presentation of tests, we could expect the same effects on the entire population since all subjects were tested following the same order of the five exercises.

Also, in this study, we did not include dynamic tests with eyes closed. Knowing when subjects would fall could be another way to probe balance abilities and the relation with age. However, in designing the study, we decided to keep the protocol safe without forcing participants to face difficult and stressful conditions.

All these *a priori* choices allowed us to have a protocol suitable for testing more conditions, each highlighting different aspects of postural control for a comprehensive and exhaustive assessment, lasting around 5 min.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed for this study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by CE DIBRIS: 012/2020 and Comitato Etico Regionale (CER) Liguria, reference number: 169REG2016. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GM, ADL, VS, MC, and AC: contributed to the methodology. GM, MC, and AC: contributed to the software, conducted the formal analysis, and contributed to the writing and original draft preparation. AC, ADL, MC, and GM: contributed to the investigation. AC and MC: supervision. All authors contributed to the conceptualization of the study writing, reviewing, and editing. All authors have read and agreed to the published version of the manuscript.

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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.2022.801142/full#supplementary-material

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Association Between Turning Mobility and Cognitive Function in Chronic Poststroke

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Turning difficulties are common in patients with stroke. The detrimental effects of dual tasks on turning indicate a correlation between turning and cognition. Cognitive impairment is prevalent after stroke, and stroke patients with mild cognitive impairment had a poorer turning performance than did stroke patients with intact cognitive abilities. Therefore, we investigated the association between turning mobility and cognitive function in patients with chronic poststroke. Ninety patients with chronic stroke (>6 months post-stroke) were recruited. Angular velocity was assessed using wearable sensors during 180° walking turns and 360° turning on the spot from both sides. Global cognition and distinct cognitive domains were assessed using the Mini-Mental State Examination. In patients with stroke, turning mobility was significantly associated with global cognitive function and distinct cognitive domains, such as visuospatial ability and language. The balance function and lower limbs strength were mediators of the association between cognition and turning. The association highlights the complexity of the turning movement and dynamic motor and cognitive coordination necessary to safely complete a turn. However, our findings should be regarded as preliminary, and a thorough neuropsychological assessment to provide a valid description of distinct cognitive domains is required.

Keywords: cognitive domains, cognitive function, stroke, turning mobility, wearable sensors

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INTRODUCTION

The turning mobility frequently causes falls in patients with stroke (1). The incidences of hip fractures caused by falls that occurred while turning is 8 times higher than that occurring while walking (2). More than 40% of walking involves making turns (3). Thus, turning safely is crucial for maintaining independence in the activities of daily living. Numerous studies have revealed that, compared with age-matched healthy controls, patients with stroke require a longer time and more steps to turn (4–6). Furthermore, patients with stroke covered a longer distance while turning than their healthy counterparts and also exhibited a different trajectory for their center of gravity (7).

Their center of gravity moves at a slower speed and is maintained at the base of support of the body during turning (8). Their body segments exhibit the *en bloc* turn phenomenon when turning while walking, indicating instability during turning (9). Thus, patients with stroke have substantially more difficulties in turning than normal adults.

Research on the effects of dual tasks on turning in patients with stroke was the first to identify a correlation between turning and cognition. Hollands and colleagues revealed that patients with stroke demonstrated a longer turn time, greater step width, and longer single limb support phase when turning 90° while walking and performing arithmetic tasks than while performing only a turning task, indicating that two tasks interfere with each other and both tasks are assumed to compete for the same cognitive resources in the brain (10). Manaf et al. conducted a full-body kinematic analysis and reported that patients with stroke had earlier axial segment reorientation latency with respect to the turn onset while performing a dual-cognitive task (a counting backward task during turning) than while performing a single task (only a turning task) and a dual-motor task (holding a glass of water during turning) (11). Cognitive interference requires increased attentional resources and therefore generates a greater dual-task interference, greatly affecting turning.

Recent evidence has further shown that turns are associated with processing speed and executive function in healthy adults (12), and correlate with attention (13), and visuospatial ability (14) in patients with Parkinson's disease. Attentional demands might be required when performing a challenging motor task such as turning. Processing of different visuospatial and afferent inputs might also necessary to enable clear directional movement. These cognitive domains direct higher-order cognitive control of gait and posture, and are responsible for some levels of planning, organization, and orientation in space. However, this has not been investigated in patients with stroke. Cognitive impairment is prevalent after stroke, and approximately 80% of patients exhibit impairment in at least one cognitive domain (15). Impairments were found most frequently in memory, visuospatial and executive functions, which could be an important contributor to turning dysfunction in patients with stroke (15). Stroke patients with mild cognitive impairment have been reported to have a longer time to turn around in the timed up and go (TUG) test than did stroke patients with intact cognitive abilities (16, 17). Stroke combined with cognitive decline may have a greater influence on turning performance than stroke itself (16, 17).

Previous studies investigated the correlation of cognition and turning but the majority focused on turning while walking. None of studies compared the differences between turning while walking and turning on the spot in terms of the cognitive demands. Investigating different turning tasks and turning angles may be needed because various turning tasks may have different motor programming and turns at different angles are executed during daily activities. Falling is one of the most common complications of stroke patients and turning is an activity that frequently causes falls. However, turning has only been explored in recent years compared with the investigation on straight walking. It is essential for improving our understanding of turning mobility among stroke patients. Physical functions such as muscle strength, motor recovery in the lower limbs, functional balance, and walking capacity (6, 18, 19), have been reported to associate with turning, cognition may also be a contributor to turning difficulties in stroke patients. Therefore, this study investigated the association between turning mobility and cognitive function in patients with chronic poststroke.

MATERIALS AND METHODS

Participants

This cross-sectional observational study was conducted from October 2019 to January 2021 at Shuang-Ho Hospital, Wan Fang Hospital, Taipei Medical University Hospital, and Taipei Tzu Chi Hospital in Taipei and New Taipei city, Taiwan. The inclusion criteria were (1) age 20 to 99 years, (2) survivors of a single unilateral stroke with hemiparesis for at least 6 months before recruitment to the study, (3) ability to walk >10 m independently, and (4) ability to provide informed consent and follow oral command. Patients meeting the following criteria were excluded: (1) additional musculoskeletal conditions or hemineglect that could affect the evaluation and (2) dementia or aphasia that could prevent participants from following instructions. All participants had undergone medical treatment and rehabilitation before the study and had stable stroke conditions throughout the study. All eligible participants provided written informed consent before their participation in the study, which was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (Reference No. 08-XD-051), and Taipei Medical University Joint Institutional Review Board (N201912127).

Procedures

Demographic data, namely age, sex, and body mass index; medical history (stroke type and lesion side); poststroke duration; and walking device use were extracted from the medical record of patients with stroke, and their physical function was examined using the Berg Balance Scale (BSS; for lower limb balance) and five times sit-to-stand (FTSTS; for lower limb strength). The BBS is a reliable and valid measure for people with stroke (20), and it is composed of 14 balance-related tasks individually scored from 0 (inability to perform task) to 4 (independent ability to perform task). The highest total score is 56, which indicates the optimal balance function. In individuals with stroke, scores of 0 to 20 represent balance impairment, of 21 to 40 represent acceptable balance, and of 41 to 56 represent good balance. The FTSTS test was reported to be reliable and valid in patients with stroke (21). Participants were seated on a 45-cm-high standard chair without armrests and instructed to perform the sit-to-stand motion as rapidly as possible 5 times. The time to complete the task was recorded, with a cutoff value of longer than 12 s for poor lower limb strength Finally, the turning performance and cognitive function of all participants were evaluated. All assessments were conducted individually in the laboratory of the

hospital within 1 h by a well-trained research assistant with a health care–related background.

Turning Performance

Turning performance was measured using APDM Opal wireless sensors and Mobility Lab software (APDM, Portland, OR, USA). The Opal is a lightweight (22 g) inertial sensor with a battery life of 16 h and 8 GB of storage. Three Opal inertial sensors were attached to the participant by using Velcro elastic bands, with one on the middle lower back (fifth lumbar vertebra process) and one on the top of each foot. Data were recorded at 128 Hz, stored in the internal memory of the Opal sensor, and subsequently uploaded to a personal computer for offline analysis. The data were exported directly as reported from the APDM system.

Participants were instructed to perform 2 turning tasks [180° walking turns (4) and 360° turn on the spot (6)] at a self-selected pace. Turning 180° while walking is commonly assessed using the TUG test (22), and turning 360° on the spot is one of the items in the BBS assessment (23) and Tinetti motor assessment (24). Before the tests, the researcher demonstrated the procedure to the participants. All participants performed a practice trial to familiarize themselves with the test before the 2 actual trials. Participants wore their regular footwear during the tests. The researcher noted the direction in which the participants opted to turn and asked them to repeat the procedure in the opposite direction.

The angular velocity (°/s) of both 180° and 360° turns were recorded for the analysis; angular velocity represents the mean angular velocity of the trunk along the rotation axis during turning, and decreased angular velocity indicates increased instability although there has been no normative value reported previously (25). This parameter was selected for the study because our previous research indicated that the turning velocity may be more sensitive than the time duration and number of steps required for representing the quality of the turning performance (26). The horizontal rotational rate of the lumbar sensor was used with a minimum of 45° accompanied by at least one right and one left foot stepping to detect turns. Humans find it challenging to make more than a slight turn in <0.5 s or to complete an extremely slow turn in >10 s while walking. Therefore, only turns within a duration of 0.5 to 10 s and turn angles of $>45°$ were considered (27). The algorithm for detecting and characterizing turning has been detailed previously (27, 28).

Cognitive Function

To assess cognitive function, we used the Mini-Mental State Examination (MMSE), which is a 30-point questionnaire extensively used in clinical and research settings. The MMSE is a reliable and valid measure for research in people with stroke (29). It is composed of 5 cognitive domains and 11 individual items. The 5 domain are as follows: (1) Orientation: temporal orientation (5 points) and spatial orientation (5 points); (2) Memory: immediate memory (3 points) and delayed recall (3 points); (3) Attention: serial subtraction (5 points); (4) Language: naming (2 points), verbal repetition (1 points), reading (1 points) and writing (1 points) a sentence, and verbal comprehension (3 points); and (5) Visuospatial ability: construction (1 points). Any score of 26 or more (out of 30) indicates a normal cognition. Below this, scores can indicate severe ($\leq$9 points), moderate (10–19 points) or mild (20–25 points) cognitive impairment.

TABLE 1 | Demographic characteristics, cognitive function and turning performance of patients with stroke ($N = 90$).

Participants' characteristics	
Age (years)	59.40 ± 10.53 (35–93)
Sex (male, *n*, %)	61 (68%)
Body mass index (kg/m^2)	24.64 ± 3.82 (16.02–37.64)
Lesion side (right, *n*, %)	46 (51%)
Post-stroke duration (month)	42.73 ± 46.47 (6–207)
Lesion type- Infarction (*n*, %)	60 (67%)
Lesion type- Hemorrhage (*n*, %)	30 (33%)
Assistant devices (*n*, %)	49 (54%)
Five Timed Sit-to-Stand (s)	22.35 ± 14.03 (5.91–109.00)
Berg Balance Scale (score/56)	44.74 ± 7.67 (19–56)
Cognitive function	
Mini-Mental State Examination Score (score/30)	26.93 ± 2.91 (16–30)
Orientation (score/10)	9.53 ± 1.56 (0–10)
Memory (score/6)	5.26 ± 0.82 (3–6)
Attention (scor /5)	4.35 ± 0.97 (1–5)
Language (score/8)	7.13 ± 1.09 (3–8)
Visuospatial (score/1)	0.72 ± 0.45 (0–1)
Turning performance	
180° turns toward paretic side (°/s)	119.59 ± 36.31
360° turns toward non-paretic side (°/s)	127.87 ± 39.27
180° turns toward paretic side (°/s)	127.16 ± 45.77
360° turns toward non-paretic side (°/s)	139.61 ± 50.72

Data are presented as mean ± standard deviation (min-max) and number (percentage).

Statistical Analysis

Statistical analyses were performed using SPSS version 19.0 (SPSS, Chicago, IL, USA). The significance level was set to $p < 0.05$. To analyze whether any correlation between participants' characteristics, cognitive function, and turning performance, the Spearman's rank correlation test and Mann-Whitney U test was used. Any significant correlations among cognition, participants' characteristics and turning tasks were found, linear regressions were conducted in three paths (between cognition and turning, between cognition and participants' characteristics, and between participants' characteristics and turning) in order to assess the potential mediator effect (participants' characteristics) on the association between cognition and turning.

RESULTS

In total, 90 patients with stroke were recruited for this study (**Table 1**). The mean age of participants are around 60 years old with the majority are men. The mean body mass index is borderline overweight, and more than half of them use assistive devices in their daily life. Nearly 70% of participants are ischemic stroke while 30% are hemorrhagic stroke. Participants are almost equally divided between right and left hemisphere damage. Their

TABLE 2 | Correlation analysis between cognitive function, turning performance and participants' characteristics in patients with stroke.

	180° turns		360° turns		Participants' characteristics								
	Toward P side	**Toward NP side**	**Toward P side**	**Toward NP side**	**Age**	**Sex**	**BMI**	**Lesion side**	**Post-stroke duration**	**Lesion type**	**Assistive devices**	**FTSTS**	**BBS**
Cognition													
MMSE score	**0.272**	**0.275**	**0.247**	0.194	−0.128	815.5	0.130	733.5	−0.165	826.5	919.0	**−0.281**	**−0.317**
Orientation	−0.130	−0.049	−0.097	−0.079	0.016	743.5	−0.038	908.0	−0.115	817.0	926.5	−0.125	0.090
Memory	0.019	0.099	−0.003	−0.053	0.008	816.5	0.240	777.5	−0.118	776.5	955.5	−0.034	**0.261**
Attention	−0.041	−0.083	−0.027	−0.065	−0.161	869.5	0.214	968.0	−0.119	655.5	934.5	−0.104	0.185
Language	**0.284**	**0.276**	**0.217**	0.164	−0.075	844.5	0.047	866.5	−0.085	753.5	954.0	**−0.245**	**0.350**
Visuospatial	**0.338**	**0.247**	**0.258**	**0.274**	−0.149	863.5	0.089	917.0	−0.019	797.5	961.5	**−0.299**	**0.209**
Characteristics													
Age	−0.191	−0.167	−0.181	−0.180									
Sex	774.5	811.0	756.0	738.0									
BMI	−0.057	−0.096	−0.099	−0.139									
Lesion side	943.0	928.0	966.5	888.0									
Duration	−0.009	0.022	0.029	0.066									
Type	759.5	802.0	794.0	706.0									
Devices	760.0	880.0	768.0	901.5									
FTSTS	**−0.589**	**−0.571**	**−0.617**	**−0.624**									
BBS	**0.621**	**0.560**	**0.663**	**0.539**									

Data are presented as r values except sex, lesion side, lesion type and assistive devices presented as U values. Bold font indicates statistical significance at $p < 0.05$. P, paretic; NP, non-paretic; BMI, body mass index; MMSE, mini mental state examination; FTSTS, five times sit-to-stand; BBS, berg balance scale.

TABLE 3 | Mediator effect of FTSTS and BBS on the association between cognition and turning in patients with stroke.

	180° turns				360° turns				Participants' characteristics			
	Toward P side		Toward NP side		Toward P side		Toward NP side		FTSTS		BBS	
	B (SE)	*p* value	B (SE)	*p* value	B (SE)	*p* value	B (SE)	*p* value	B (SE)	*p* value	B (SE)	*p* value
Cognition												
MMSE score	2.742	**0.041**	2.548	0.081	3.797	**0.029**	1.744	0.397	−0.796	**0.020**	0.739	**0.004**
Language	18.403	**0.033**	13.088	0.163	30.706	**0.004**	22.537	0.060	−8.883	**0.005**	6.094	**<0.001**
Visuospatial	10.890	**0.005**	10.903	**0.008**	9.574	**0.047**	9.342	0.072	−4.572	**0.001**	1.333	0.072
Participants' characteristics												
FTSTS	−2.006	**<0.001**	−2.050	**<0.001**	−2.767	**<0.001**	−2.505	**<0.001**				
BBS	3.106	**<0.001**	3.016	**<0.001**	4.226	**<0.001**	3.927	**<0.001**				

B, unstandardized parameter estimation; SE, standard error for B. Bold font indicates statistical significance at $p < 0.05$. P, paretic; NP, non-paretic; MMSE, mini mental state examination; FTSTS, five timed sit-to-stand; BBS, berg balance scale.

mean MMSE score is 26, indicating a normal cognition. In terms of physical function, their mean score of 45 on BBS represents good balance and mean time of 22s on FTSTS represents poor lower limbs strength.

The MMSE total score was significantly associated with all turning tasks except 360° turns to the non-paretic side (**Table 2**). In terms of cognitive domains, only visuospatial ability was significantly associated with all turning tasks while language was associated with all turning tasks except 360° turns to the non-paretic side. Orientation, memory, and attention were not associated with turns. On the top of that, MMSE score, language and visuospatial ability were significantly correlated with FTSTS and BBS. The FTSTS and BBS were also significantly correlated with all turning tasks. Due to significant correlations among cognition (MMSE, language and visuospatial ability), participants' characteristics (FTSTS and BBS) and turning tasks, further mediator analysis was conducted (**Table 3**). The results showed that FTSTS and BBS were mediators of the association between MMSE and turning tasks (180° and 360° turns to the paretic side). The FTSTS and BBS also mediated the association of language and turning tasks (180° and 360° turns to the paretic side). However, only FTSTS was found as a mediator of the association between visuospatial and all turning tasks except 360° turns to the non-paretic side.

DISCUSSION

This is the first study to analyze the association between turning mobility and cognitive function after stroke. Our findings indicate that turning mobility is significantly associated with global cognitive function and distinct cognitive domains, such as visuospatial ability and language, in patients with stroke. Mediator analysis revealed that balance function and lower limbs strength played a mediating role in the relationship between cognitive function and turning mobility.

The correlation between turning mobility and global cognition has been observed among patients with stroke in the current study, which was line with previous studies (13, 30, 31). Studies have indicated a negative effect of dual-tasking on turning performance (10, 11), and the detrimental effect was amplified in patients with poorer cognition (16, 17), which may be due to limited cognitive capacity (32). When a task is challenging, it imposes additional cognitive demands. For patients with stroke having a limited cognitive capacity because of brain injury, turning is a complex form of walking that is more cognitively demanding than straight walking. Such cognitive–motor interference or inappropriate use of limited cognitive resources causes an exacerbation of motor impairments. In fact, the role of cognition on turning has been supported by some studies, which have reported an association between higher prefrontal cortex activity and poorer turning performance in older people (30) and individuals with neurological disorders (14). Prefrontal cortex activity increased during the transition from straight walking to turning, indicating that the prefrontal cognitive control could compensate for motor deficits (33). Turning seems to be less autonomous than is walking in a

straight line because it involves more interlimb coordination, more coupling between posture and gait, and modifications of locomotor patterns, requiring a high cortical control that plays a crucial role in postural transitions.

Our study found that turning is associated with distinct cognitive domains. Visuospatial ability was observed to be associated with turning, which is in line with previous studies (34, 35). Turning might place excessive demands on visuospatial processing to enable the directional movements required for accomplishing a change in direction while walking. Several studies have proposed a visuospatial contribution to gait, particularly gait stability, in older adults (36) and patients with Parkinson's disease (37). Such individuals rely on visual information for control of balance and locomotion and adjust their limb and axial motor control through visual feedback, which are the elements for the successful completion of the turning task. We also found an association with language, which was not reported previously. In fact, research has demonstrated language to be associated with gait speed in studies on walking and cognition (38, 39). The cerebral region, such as Broca's area, is involved in sentence processing (40). An imaging study reported a correlation of gait disorder with activation of the contralateral inferior frontal cortex (Broca's area), contralateral sensory motor cortex, and homolateral cerebellum. Neuroanatomical evidence reveals a direct connection between Broca's area and the supplementary motor area (41). We posit that Broca's area facilitates walking during an alteration of gait control, such as turning. However, this explanation is speculative and should be empirically evaluated.

Such correlations were not found in the remaining distinct cognitive functions in the current study, although attention (12), processing speed (35), and executive function (12) have been reported to be correlated with turning in previous studies. This disparity may be attributed the attention domain of the MMSE focusing only on an item of serial subtraction, may not adequately represent the attention function to detect associations. Additionally, MMSE does not contain the cognitive domains of processing speed and executive function for analyzing their relevance to turning, and thus their correlations remain unclear.

One of the most widely used tools for cognition evaluation is the MMSE, which has been validated and extensively used in both clinical practice and research. Despite its widespread use, whether the scores on individual items and domains of the MMSE can represent the cognitive domain remains uncertain. Although some studies have concluded that subtests were domain specific (42, 43), a study indicated that a part of the subtests lack sufficient validity to warrant a conclusion of their domain specificity (44). Thus, a thorough neuropsychological assessment to provide a valid description of an individual's cognitive profile is required for future studies. For instance, the Digit Span Forward and Trail Making Test A are commonly used for attention and processing speed assessments; the Digit Span Backwards can be used to assess working memory, and the Trail Making Test B for executive function. Impairments in patients with stroke are most frequently found in memory and visuospatial and executive functions (15), which should be examined preferentially to justify their relationship to turning. Our findings should be considered preliminary.

Lower limbs strength and balance function were introduced as the mediators of the association between cognition and turning in the current study, suggesting that cognition affects muscle strength as well as balance and subsequently results in poor turning performance. Previous studies have shown that the lower limbs strength and balance control correlated with cognitive function (45, 46) and both also contributed to turning difficulties (18, 19). Motor and cognitive deficits commonly interact through cognitive–motor interference, and it is therefore to be expected that strength and balance played a mediating role in the relationship between cognition and turning.

It is also worth mentioning that MMSE score and language function were correlated with all turning tasks except 360° turns to the non-paretic side. The correlations were observed in specific turning situations only. Turning while walking may be more difficult to execute than turning on the spot because it is affected by impaired motor planning and patients with stroke have difficulty in changing from one motor program (walking) to another (turning). Also, turning to the paretic side was more challenging than turning to the other side (26) and associated with instability and falls (2). However, visuospatial ability was significantly correlated with all turning tasks. Steering is an essential component of goal-directed locomotion, allowing individuals to walk toward the desired direction while avoiding static or dynamic obstacles along the travel path (9). Stroke patients with poorer cognition or impairments in language or visuospatial ability may be more prone to instability when performing walking turns or turning to the paretic side, significantly elevated fall risks. Such findings provide insight into the effects of cognitive factors in falls risk for specific turning situations.

Once the association between cognition and turning after stroke is established, turning mobility can be used to further enhance the prediction of cognitive decline in the stroke population. Approximately 70% of patients with stroke have cognitive impairment in the first year after the stroke (47). The prevalence of cognitive impairment after a stroke is high and may progress to dementia, which affects secondary prevention, rehabilitation, prognosis, and quality of life (48). Studies have revealed that the BBS and 10-m walk test could predict cognitive impairment in a year after stroke (49), indicating that motor biomarkers such as balance and gait can be used for early detection of cognitive impairment. However, a balance test battery includes multiple test items, and a walking test applies to ambulatory poststroke only. Assessment of turning is comparatively simple and quick to administer, which may specifically be suitable for those who walk with difficulty or are unable to walk for a long distance.

Relative to studies that have investigated turning in patients with stroke, interventional studies aimed at improving turning performance remain scarce. Our findings of a significant association between turning and cognition indicate that interventional studies could possibly incorporate cognitive training into the turning exercise. The integration physical and cognitive exercise into training seems to render more

favorable results in both physical and cognitive performance than when either type of training is used alone in many populations, including those with stroke (50, 51), because of the enhancement of resting-state functional connectivity between the medial prefrontal cortex and medial temporal lobe regions (52). Turning performance could potentially be improved if turning training is combined with cognitive training, and such improvement may be related to the improvement of specific cognitive functions related to turning.

The strength of the current study is that 90 participants with poststroke from 4 hospitals were enrolled. Thus, problems associated with the use of a small sample size and heterogeneous sample were absent. Furthermore, 2 turning tasks, 180° walking turns and 360° turning on the spot, conducted in the present study eliminated bias caused by assessment of different turning tasks or different turning angles. Turning performance could vary in terms of turning tasks and turning angles. Various turning tasks may involve distinct motor programming, and turns at different angles are executed during daily activities.

A few limitations of this study can serve as guidance for follow-up studies. First, our participants obtained a mean MMSE score of 26.93 ± 2.91 (range: 16–30), they did not have dementia, and they were able to provide informed consent and follow instructions; thus, our sample may not be completely representative of this population. Our results can likely only be generalized to high-functioning patients with stroke. Studies with more participants with moderate or severe cognitive impairments should be conducted in future to improve the generalizability of the findings and strengthen the correlation of distinct cognition and turns. Second, a study revealed that natural turns in the home can be used to efficiently differentiate between those who fall recurrently from those who have not fallen; however, prescribed turns in the laboratory cannot differentiate between older adults with and without a history of falls (34). Thus, laboratory-based turning measurement may not adequately reflect real-life functioning. The laboratory environment is static, and the vigilance of the researcher reduces anxiety and fear of falling, which could temporarily enhance the participant's performance and unintentionally mask turning difficulty. The lack of significant associations of certain cognitive domains with turning mobility may be because these turns were all prescribed movements evaluated in a laboratory. Third, neither visual acuity nor use of corrective vision devices were measured and recorded in the study. Poor visual function could possibly influence visuospatial ability and execution of movement. However, all participants can read and sign the consent forms and they are encouraged to wear spectacles to get the better eyesight during the testing, which may reduce the impact. Finally, our findings indicated a significant relationship between turning parameters and cognitive function; however, the strength of the correlation was low. Thus, cognitive functions could be one of the several factors affecting turning performance.

CONCLUSIONS

This is the first study to analyze the association between turning mobility and cognitive function after stroke. Our findings showed that turning mobility was significantly associated with global cognitive function and distinct cognitive domains, such as visuospatial ability and language, in patients with stroke. The association between turning and cognition highlights the complexity of turning and the dynamic motor and cognitive coordination necessary to safely execute a turn. However, our findings should be regarded as preliminary, and a thorough neuropsychological assessment is essential to establish a robust association between turning mobility and distinct cognitive domains.

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 study was approved by the Institutional Review Board of Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (Reference No. 08-XD-051) and Taipei Medical University Joint Institutional Review Board (N201912127). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

S-CL was a major contributor in study design. Y-CK, L-FL, C-YW, C-CH, and P-JL have done the data collection. S-CL and Y-CK have done the manuscript writing and analyzed and interpreted data. All authors read and approved the final manuscript.

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Reliability and Validity of the Composite Activity-Related Fall Risk Scale

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Introduction: The newly developed Composite Activity-related Risk of Falls Scale (CARFS) is designed to measure composite activity-related risk of falls (CARF) in relation to the activity-specific fear of falling and physical behavior. This study tested the reliability and validity of the CARFS in older people with various health statuses and persons with stroke or spinal cord injury.

Methods: Participants included 70 older adults, 38 persons with stroke, and 18 with spinal cord injury. They were first surveyed using a combined questionnaire including the CARFS and activity-specific balance confidence (ABC) scale in addition to items asking for personal and disease-related information, fall history, walking independence levels for examining internal consistency, ceiling and floor effects, and convergent validity in each participant group. One week after the initial survey, 33 older participants were reexamined using the CARFS to analyze test-retest reliability, where a minimal detectable change was found. Significance was set at $\alpha = 0.05$ for all analyses.

Results: The CARFS showed excellent test-retest reliability in the dimensions of fear of falling, physical behavior, and CARF [ICC (3,1) = 0.972, 0.994, and 0.994, respectively for their overall score], with a minimal detectable change of 3.944 in the older population. The internal consistency of CARFS items was excellent in the older participants, good in participants with stroke or spinal cord injury (Cronbach's alpha = 0.945, 0.843, 0.831 in each participant group, respectively). No ceiling and floor effects were demonstrated in the wide range of people. For the convergent validity, overall CARF score was significantly correlated with the average ABC score in each participant group (rho = −0.824, −0.761, and −0.601, respectively; $p < 0.01$), and was significantly correlated with walking independence levels in each participant group (rho = −0.636, −0.423, and −0.522, respectively; $p < 0.01$). It showed weak correlation with the number of previous falls only in participants with stroke (rho = 0.291, $p = 0.076$).

Conclusion: The CARFS is a reliable and valid tool for measuring fall risk in older people and persons with stroke or spinal cord injury.

Keywords: composite activity-related fall risk scale, psychometrics, older people, stroke, spinal cord injury

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INTRODUCTION

Falls are the most common cause of accidental injury among inpatients. They not only increase pain and financial burdens for these individuals, but may also result in medical disputes (1, 2). Nearly half of all falls cause physical injuries, with many severe cases leading to brain injury, internal organ damage, fractures, and even death (2). Related fear and anxiety can also create psychological damage, which may lead to dependency, thus increasing the burden of family care and severely impacting living quality (1, 3). This emphasizes the need for fall prevention both at the individual level and to ensure the integrity of health and social care services.

Risk assessment is crucial in fall prevention. Fear of falling, physical behavior, and physical functioning are psychosocial, lifestyle, and intrinsic risk factors of falls in elderly people, respectively (4), which intercorrelate with each other (5, 6). Fear of falling and physical behavior play dual roles in preventing falls, which are initially protective by making the person more aware of surroundings or avoiding exposure to activities that may lead to falling. However, this may be detrimental in the long term due to physical deconditioning induced (7, 8). The Composite Activity-specific Risk of Falls Scale (CARFS) was developed by Wang et al. to compositely evaluate the risk of falls by linking fear of falling and physical behaviors (9). It has questions on the degree of fear of falling (FoF) and performance frequency comprising 14 items of daily activities, and a score of Composite Activity-specific Risk of Falls (CARF) of each item calculated *via* a formula with FoF degree and performance frequency. To the best of our knowledge, the CARF is the first to consider and quantify dual influences of activity restriction through interactions with FoF on risk of falls (9). The Survey of Activities and FoF in the Elderly (SAFE) is an existing relevant assessment tool (10), which contains dimensions of FoF and activity restriction as well. However, Non-linkage between the two dimensions impedes the examination of dual influences of activity restriction and FoF on risk of falls. Besides, regarding activity restriction in the SAFE, subjects are asked to compare to 5 years ago to determine if and how restriction exists. Recalling 5-year memory makes the SAFE not suitable as an outcome measure of activity restriction in long-term evaluations or evaluations before and after interventions.

The CARFS is expected to be applicable for a wide range of people with different health statuses or different disability levels, since between-populations comparison in fall risks and long-term monitoring of fall risks are important to optimize resource and augment effectiveness in fall prevention. The Fall Efficacy Scale (FES) (11) or the Activities-specific Balance Confidence Scale (ABC) (12), the most common tool of activities-specific FoF assessment, have either ceiling effect for persons with better mobility (11), or floor effect for those with poor mobility (12). Thus, they are not suitable to use in between-populations comparison of fall risks or in long-term monitoring of fall risks for persons whose mobility changes largely. In development of the CARFS, respective interview responses from people with different health statuses (older persons, persons with stroke and persons with spinal cord injury) who had different disability levels was considered.

The CARFS has been approved with strong content validity by an expert panel (9). This study further assessed the reliability and validity of the CARFS in target populations. We hypothesized that the CARFS is reliable enough, has no ceiling and floor effects, correlates other measures on risk of falls, and applicable for different target populations.

MATERIALS AND METHODS

Design

This study was designed to evaluate reliability and validity of the CARFS. Two questionnaire surveys were conducted with 1 week of rest in between. The first survey was performed in three target participant groups for examining internal consistency, checking ceiling and floor effects, and analyzing convergent validity (older adults, persons with stroke or with spinal cord injury). The second survey was performed only in the older participant group to explore test-retest reliability and calculate the minimal detectable change [$MDC_{(95)}$] in the population. Older participants living in the community, and those with stroke or spinal cord injury who were admitted for at least a month when took part in the first survey were invited to complete the second survey, ensuring similar lifestyle components between surveys. The study was approved by the Ethics Committee of Shanghai YangZhi Rehabilitation Hospital affiliated with Tongji University (YZ2019-005).

Participants

The participants consisted of three groups of individuals, particularly older persons over 60 years of age, persons with stroke, and persons with spinal cord injury. All participants were recruited from the Shanghai Yangzhi Rehabilitation Hospital affiliated with Tongji University and nearby resident communities using poster advertisements. For older participants, they were required to be aged 60 years and above and have adequate communication abilities to complete the survey. Individuals were excluded if they showed inadequate communication ability or had Mini-Mental State Examination scores of 23 or lesser (13). For participants with stroke or spinal cord injury, there was no criterion on age but rather on health status. For those who had suffered a stroke or spinal cord injury, other selection criteria were similar to those for the older participants in the first group. It must be noted that for older participants, no specific health status was required as a criterion. Older participants living in a community and those with stroke or spinal cord injury staying at a hospital were included into the older participant group in the evaluation of reliability and validity of the CARFS. All participants provided written informed consent prior to study engagement.

Measures

This study implemented a general questionnaire asking for personal and health-related information, fall history, walking independence level, and balance confidence in addition to the CARFS. Personal information included gender, age, and education level, while health-related information included health status (healthy, stroke, spinal cord injury, or others) and time

after disease onset. For falling history, participants were asked "Have you fallen within the past 6 months and how many times, if yes?" Here, a fall was defined as an event during which an individual came to rest on the ground or lower level, but not as the result of a major intrinsic event, such as a syncope, stroke, seizure, or overwhelming hazard (14). Walking independence levels were measured using the Functional Assessment Measure (FAM), including no disability (complete independence in a timely, safely manner), slight disability (modified independence with extra time or assistive devices), and severe disability (dependence with supervision or assistance) (15). Balance confidence was assessed using the ABC scale. It contains 16 items comprising different standing and walking activities. Participants rate their confidence in performing each activity without losing balance by selecting from values ranging from 0 (no confidence) to 100 (completely confident). Previous research has shown that the ABC has good psychometric properties for older people and patients with stroke (16, 17).

The CARFS contains 14 items and two activity-specific prompts on FoF and activity frequency, including "Think about the degree of FoF you feel when you perform the following activities" and "Think about how often you have performed the following activities over the last month". A Likert scale ranging from 0 to 4 was used to quantify both FoF and activity frequency. For FoF, 0 indicates no worry at all, 1 indicates slight worry, 2 indicates moderate worry, 3 indicates high worry, and 4 indicates extreme worry. For activity frequency, 0 indicates none (have not done the activity over the last month), 1 indicates occasionally (within the last month), 2 indicates sometimes (weekly), 3 indicates often (daily), and 4 indicates very often (daily, at a higher frequency than normal). CARF scores were calculated based on the degree of FoF (A) and activity frequency (B) using the following formula: C = A + (4–B) + A * B/2, where 4-B reflects the restriction of activity (9). The CARF scores for each item ranged from 0 to 12 (9). The overall scores of the 3 dimensions including FOF, activity frequency, and CARF are calculated by the sum of each item score, which ranged from 0–56, 0–56, and 0–168, respectively. The full version of the CARFS is accessible in a previously published paper (9).

Statistical Analysis

We conducted the statistical analyses using IBM SPSS version 21.0. First, we used descriptive statistics to describe all quantitative data. Subsequently, we analyzed test-retest reliability in the older participant group using intraclass correlation coefficient [ICC(3,1)] with two-way mixed model, single measure type (18). We further calculated the difference and mean of the overall CARF scores at the two assessments and employed Bland Altman plots to evaluate the degree of agreement between the test scores of the two assessments. Thereafter, with the ICC of the overall CARF score, we calculated the $MDC_{(95)}$ through the formula: $MDC_{(95)} = SEM^{*}1.96^{*}\sqrt{2}$, where SEM = $SDbaseline^{*}\sqrt{(1\text{-}ICC)}$. The SDbaseline was the standard deviation of the overall CARF score at the first time. The $\%MDC_{(95)}$ was further calculated by the formula: $\%MDC = MDC_{(95)}/168 \times 100\%$ (18).

Afterwards, we evaluated internal consistency of the CARFS items using Cronbach's alpha in each participant group. Subsequently, we checked the ceiling and floor effects through the frequency plot of the overall CARF score. Finally, for examining convergent validity, we used Spearman's correlation to explore the correlation of the CARFS with the ABC score, and independence level of walking measured by FAM, and number of previous falls.

We classified ICC and Cronbach's alpha values as poor (<0.50), moderate (0.50–0.75), good (0.75–0.90), and excellent (≥0.90) (19). For floor and ceiling effects, we set the proportion of the highest or lowest CARF score higher than 15% of target participants (20). For the correlation between the CARFS and other fall risk measures, we graded the rho values as very weak (<0.20), weak (0.20–0.39), moderate (0.40–0.59), strong (0.60–0.79), and very strong (0.80–1.00) (21). Significance was determined at $p \leq 0.05$. All p values were 2-tailed.

RESULTS

General Participant Characteristics

The first survey comprised 98 participants, including 70 older adults aged 60 years, 38 adults with stroke, and 18 adults with spinal cord injury.

Among older participants, there were 42 common older persons without neurological disorders, 22 with stroke and six with spinal cord injury. They showed a more equal sex ratio than persons with stroke or spinal cord injury. The mean disease duration was 7.6 ± 6.7 months for participants with stroke, and 10.9 ± 5.8 months for those with spinal cord injury.

The second survey comprised 33 older adults including 29 older persons living at the community without any neurological disorder, two having previously suffered a stroke, and two with spinal cord injuries who had been in the hospital for over 1 month during the first survey. Another 13 common older persons without neurological disorders failed to complete the second survey because they had no time or lost connection during the second week of the survey.

Detailed participant characteristics are shown in **Table 1**.

Test-Retest Reliability and Minimal Dateable Change

The three dimensions of the CARFS showed good to excellent repeatability for all items (ICC = 0.766–1.000) except for FoF of walking on wet ground which showed moderate reliability (ICC = 0.655). The ICC of the overall CARF score was 0.994, indicating excellent test-retest reliability. The results are shown in **Table 2**.

The mean difference of the overall CARF scores at the two assessments was −0.7 (95% CI: −5.70 to 4.25). From the Bland Altman plot, only one extreme change exceeded the 95% CI. The result implies excellent repeatability for the overall CARF score. For the extreme change, it occurred in an older person without a neurological disorder, and arose from the change of two items,

TABLE 1 | Participant characteristics.

Characteristics	Older ($n = 70$)	Stroke ($n = 38$)	SCI ($n = 18$)	Older ($n = 33$)[#]
Sex (Male:Female)	35:35	27:11	13:5	14:19
Age (year)^	68.0 ± 5.4	55.8 ± 18.3	48.4 ± 15.7	67.7 ± 5.6
Education (median)	Secondary	Higher	Secondary	Secondary
Health status				
Healthy w/o motor impairment	42	–	–	29
Hemiplegia (duration, month)^	22 (7.9 ± 7.3 m)	38 (7.6 ± 6.7 m)	–	2
Paraplegia (duration, month)^	3 (12.3 ± 2.3 m)	–	10 (9.0 ± 4.9 m)	1
Quadriplegia (duration, month)	3 (10.7 ± 6.7 m)	–	8 (13.0 ± 6.4 m)	1
Walking ability				
Complete independence	52	21	1	29
Modified independence	2	2	2	1
Dependence	16	15	15	3
Number of previous falls				
0	62	33	13	30
1	7	5	3	2
2	1	0	2	1
Average ABC^	81.9 ± 23.9	71.4 ± 19.9	27.5 ± 18.6	88.9 ± 21.8
Overall CARF score[@]	23.8(3.0–199.0) (3–119)	34.3(19.0–72.5)	89.3(53.5–121.5)	19.0(3.0–119.0)

[#]Older participants who completed two surveys; ^Data are presented with mean and standard deviation; [@]data are presented with median and range.
SCI, spinal cord injury.

TABLE 2 | Test-retest reliability of the CARFS.

Items	ICC (95% CI)		
	FOF	Frequency	CARF score
1. Sitting down & standing up	0.943 (0.889–0.972)	1.000 (1.000–1.000)	0.857 (0.731–0.927)
2. Bending down & straightening up	0.986 (0.972–0.993)	1.000 (1.000–1.000)	0.978 (0.956–0.989)
3. Standing activities	1.000 (1.000–1.000)	1.000 (1.000–1.000)	1.000 (1.000–1.000)
4. Squatting activities	0.974 (0.947–0.987)	0.987 (0.973–0.993)	0.977 (0.955–0.989)
5. Transferring while sitting	1.000 (1.000–1.000)	1.000 (1.000–1.000)	1.000 (1.000–1.000)
6. Walking short distances	1.000 (1.000–1.000)	1.000 (1.000–1.000)	1.000 (1.000–1.000)
7. Walking long distances	1.000 (1.000–1.000)	0.888 (0.785–0.943)	0.965 (0.931–0.983)
8. Walking on wet ground	0.655 (0.406–0.813)	0.982 (0.964–0.991)	0.766 (0.578–0.877)
9. Walking on uneven ground	0.915 (0.836–0.957)	1.000 (1.000–1.000)	0.876 (0.764–0.937)
10. Using transportation	0.972 (0.944–0.986)	0.961 (0.922–0.980)	0.959 (0.918–0.979)
11. Washing oneself	0.980 (0.961–0.990)	0.808 (0.647–0.901)	0.958 (0.916–0.979)
12. Toileting	0.982 (0.964–0.991)	1.000 (1.000–1.000)	0.975 (0.951–0.988)
13. Putting on/taking off trousers	1.000 (1.000–1.000)	1.000 (1.000–1.000)	1.000 (1.000–1.000)
14. Putting on/taking off footwear	1.000 (1.000–1.000)	1.000 (1.000–1.000)	1.000 (1.000–1.000)
Overall	0.972 (0.953–0.983)	0.994 (0.991–0.997)	0.994 (0.988–0.997)

ICC, Intraclass Correlation Coefficients.

that is, walking on wet ground and walking on uneven ground. The Bland Altman plot is shown in **Figure 1**.

Based on the ICC value of 0.994, the $MDC_{(95)}$ was calculated as 3.944 [% $MDC_{(95)}$: 2.35%].

Internal Consistency

For older participants, Cronbach's alpha for CARFS items was 0.945. A stepwise deletion of each of the 14 items did not alter the internal consistency for the CARFS (Cronbach's alpha if item deleted: 0.938–0.946). The item-total correlation was moderate to very strong, (coefficient: 0.523–0.850) for all items. The result indicated excellent internal consistency of the CARFS items in the elderly participants (**Table 3**).

In patient groups, the CARFS items showed good internal consistency with Cronbach's alpha of 0.843 and 0.831 in the stroke group and spinal cord injury group, respectively. The

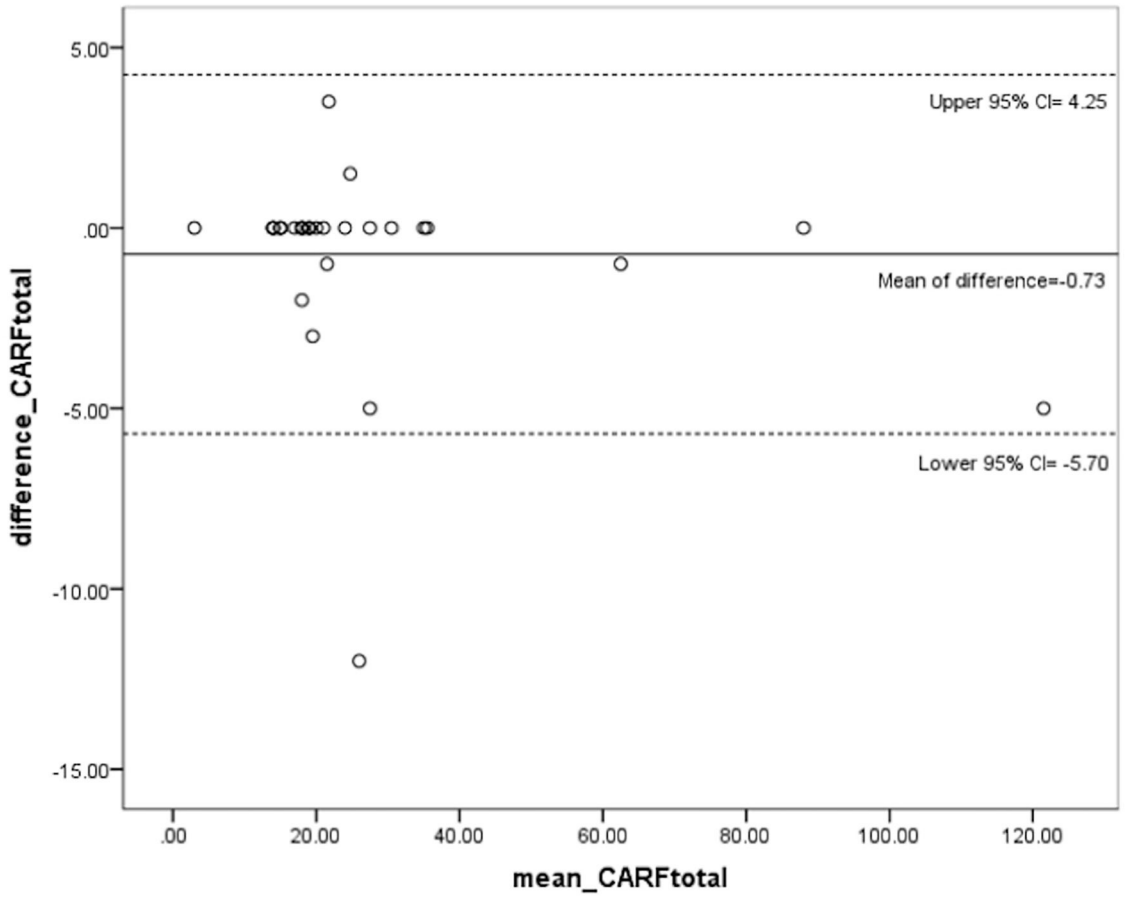

FIGURE 1 | The Bland Altman plot of the overall CARF score between two assessments of test-retest.

TABLE 3 | Internal consistency of the CARFS in the elderly, persons with stroke or with spinal cord injury respectively.

Items	Cronbach's alpha if item deleted			Corrected item-total correlation			Cronbach's alpha		
	Older	Stroke	SCI	Elderly	Stroke	SCI	Elderly	Stroke	SCI
1. Sitting down & standing up	0.941	0.836	0.819	0.698	0.441	0.485	0.945	0.843	0.831
2. Bending down & straightening up	0.940	0.825	0.807	0.754	0.603	0.674			
3. Standing activities	0.945	0.845	0.837	0.590	0.300	0.216			
4. Squatting activities	0.939	0.833	0.822	0.802	0.496	0.482			
5. Transferring while sitting	0.943	0.839	0.806	0.624	0.387	0.634			
6. Walking short distances	0.946	0.850	0.838	0.523	0.166	0.161			
7. Walking long distances	0.939	0.841	0.835	0.793	0.353	0.253			
8. Walking on wet ground	0.942	0.830	0.835	0.694	0.543	0.132			
9. Walking on uneven ground	0.940	0.836	0.841	0.754	0.438	−0.042			
10. Using transportation	0.938	0.825	0.823	0.850	0.687	0.439			
11. Washing oneself	0.939	0.827	0.796	0.780	0.571	0.762			
12. Toileting	0.938	0.821	0.805	0.809	0.653	0.659			
13. Putting on/taking off trousers	0.941	0.829	0.799	0.741	0.557	0.712			
14. Putting on/taking off footwear	0.941	0.823	0.797	0.722	0.622	0.726			

SCI, spinal cord injury.

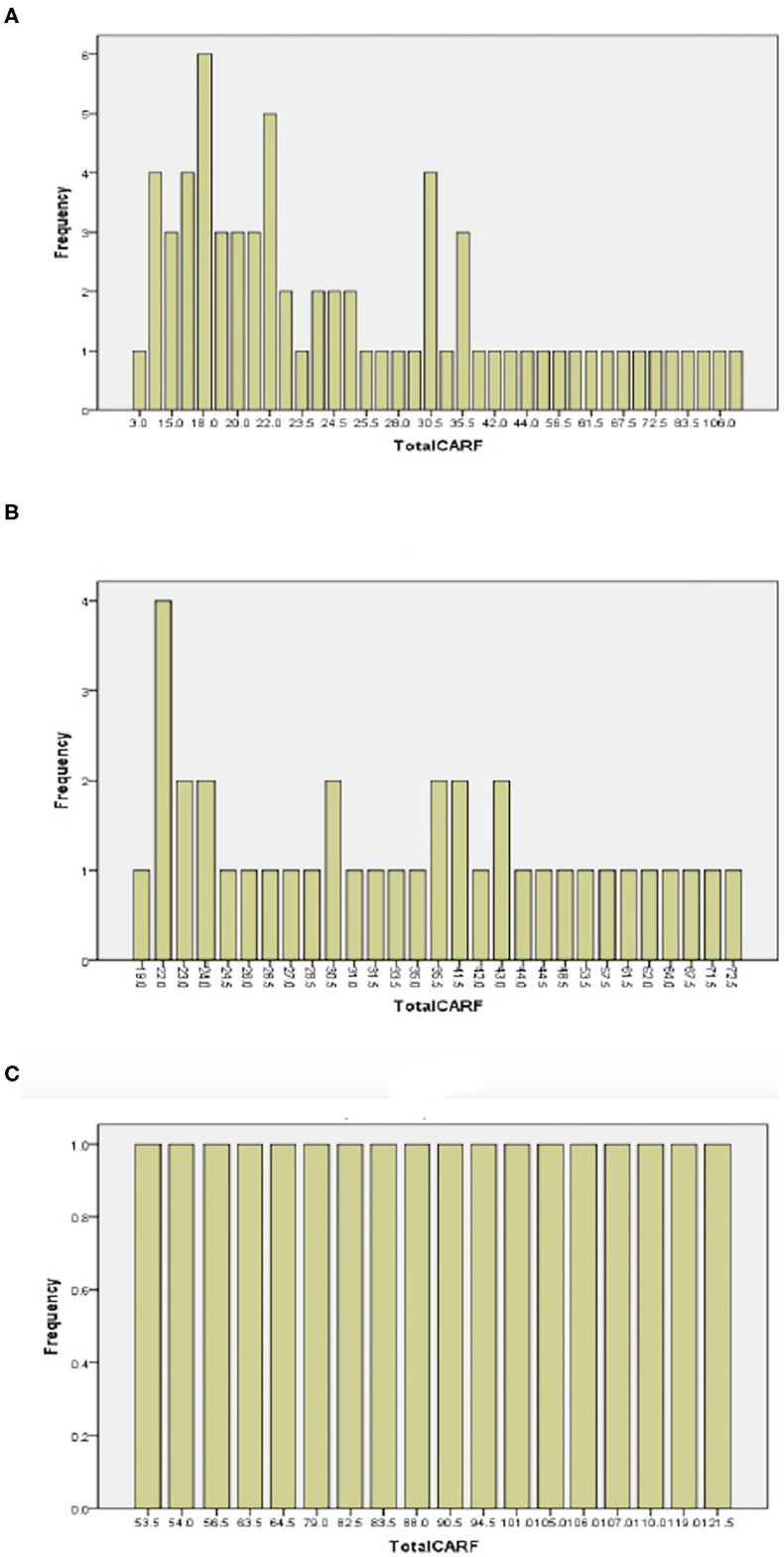

FIGURE 2 | Frequency plots of overall CARF score in older participants **(A)**, persons with stroke **(B)**, and persons with spinal cord injury **(C)**.

TABLE 4 | Convergent validity of the CARFS on relation with other fall risk measures.

	CARFS				
	Overall CARF score (0–168)	**Overall FOF score (0–56)**	**Overall performance frequency (0–56)**	**ABC (0–100)**	**Walking independence level (1/2/3)[#]**
Elderly (*N* = 70)					
ABC (0–100)	−0.824**	−0.856**	0.679**		
Walking independence level (1/2/3)	−0.636**	−0.614**	0.700**	0.603**	
No of falls	0.197	0.224!	0.067	−0.181	0.003
Stroke (*N* = 38)					
ABC (0–100)	−0.761**	−0.811**	0.456**		
Walking independence level (1/2/3)	−0.423**	−0.356**	0.480**	0.331*	
No of falls	0.291!	0.288!	0.104	−0.430*	−0.142
SCI (*N* = 18)					
ABC (0–100)	−0.601**	−0.694**	0.604**		
Walking independence level (1/2/3)	−0.522**	−0.532**	0.573**	0.325	
No of falls	0.039	0.154	−0.424!	−0.155	0.002

$^{**}P < 0.01$.
$^{*}p < 0.05$.
$^{!}p < 0.10$.
[#]Walking independence level:1: Dependence, 2: Modified independence, 3: Complete independence.
SCI, spinal cord injury.

internal consistency for the CARFS did not change much if any item was deleted in both patient groups. (Cronbach's alpha if item deleted: 0.821–0.850, and 0.797–0.841 in the stroke group and spinal cord injury group, respectively). The item-total correlation was moderate to strong for most items (coefficient: 0.438–0.687), weak for three items (coefficient: 0.300–0.387), and very weak for one item (coefficient: 0.166) in the stroke group. It was moderate to strong for 9 items (coefficient: 0.439–0.726), weak for two items (coefficient: 0.216–0.253), very weak for three items (coefficient: −0.042–0.161) in the spinal cord injury group (**Table 3**).

Ceiling and Floor Effects

More than 85% of older persons scored the CARF between 17.0–119.0. All persons with stroke scored between 19.0–72.5 and all persons with spinal cord injury scored between 53.5 and 12.5. The results indicate no ceiling or floor effects observed in any target participant group (**Figure 2**).

Convergent Validity

The overall CARF score was strongly to very strongly correlated with the average ABC score in each participant group (rho = −0.824, −0.761, and −0.601, respectively; $p < 0.01$), and was moderately to strongly correlated with the walking independence levels in each group (rho = −0.636, −0.423, and −0.522, respectively; $p < 0.01$). It showed weak correlation with number of previous falls only in the group with stroke (rho = 0.291, $p = 0.076$). The average ABC score showed weak to moderate correlation with the walking independence levels in each group [rho = 0.603, 0.331, and 0.325 for elderly ($p < 0.01$), stroke ($p < 0.05$), and spinal cord injury groups, respectively ($p > 0.05$)]. The average ABC showed moderate correlation with number of previous falls only in the group with stroke (rho = 0.430, $p < 0.05$) (**Table 4**).

DISCUSSION

The purpose of this study was to evaluate the reliability and validity of the newly developed CARFS in various target populations. Our results provide preliminary evidence for its reliability and validity in the assessment of fall risk among older persons, persons with stroke or with spinal cord injuries.

Reliability

The ICC values for overall CARF score, FoF degree, and performance frequency rank were 0.994, 0.972, and 0.994, respectively, all denoting excellent reliability. Most ICC values for the three dimensions of each activity item were over 0.700 indicating good to excellent reliability except for one FoF score of walking on wet ground that was 0.655 implying moderate reliability. Powell et al. have reported the exceptional items of ABC scale with poor reliability as well (test-retest $r < 0.40$, car transfer and walking at home), in spite of excellent reliability for the overall ABC score ($r > 0.90$) (12). Although exact reasons of the exceptions were difficult to track, for questionnaires on FoF like ABC and FES, making hypothetical responses for activities which subjects have not experienced for a long time or have restricted totally, is a common manner which may lead to inaccurate FoF score and thereby affect test-retest reliability (11, 12). The data of activity frequency,

although by recalling memories, could be more accurate than the psychological estimation of FoF. The concept is supported by our results that the activity frequency demonstrated higher test-retest reliability than FoF in most items of CARFS. Linking FoF with activity frequency, the CARF scores showed good to excellent reliability in all items. Observing the Bland Altman plot of difference of the overall CARF scores at the two assessments, the difference value of all persons located within the 95% CI except for one person's data. Thus, we can conclude that the CARFS has good to excellent test-retest reliability.

The MDC(95) of the CARF was 3.944, which implied that 95% of older adults showed random variation of fewer than 3.944 points in the CARFS. Thus, when the CARFS is adopted to monitor fall risk change for a certain period, a change of 3.944 or more is considered to be a true change. The % MDC of the CARFS was 2.35%, which is much lower than that of common survey tools, such as ABC scale (13%), Berg balance scale (9%), and 36-Item Short Form Survey (28%) used in people with Parkinson's disease (22). Lower % MDC could indicate greater competence to detect the change of fall risk in target population.

The Cronbach's alpha of the CARFS used in older adults was 0.945, implying excellent internal consistency of the CARFS. The item-total correlation of each CARFS items ranged from 0.523 to 0.850, which is superior than the result found in the ABC and SAFE scales used with older persons (10, 12). However, the Cronbach's alpha of the CARFS in patient groups was lower than that in older participants. Smaller sample size in patient groups than the older group could be an important factor contributing to the result. Because based on the formula of Cronbach's alpha, larger sample size produces larger Cronbach's alpha if other variables are kept the same (23). Generally, the value of 0.843 and 0.831 of Cronbach's alpha can still indicate good internal consistency of the CARFS in participants with stroke or with spinal cord injury.

Validity

The overall CARF score ranged from 3.0–119.0 in older persons, from 19.0 to 72.5 in persons with stroke, and from 53.5 to 121.5 in persons with spinal cord injury. The maximum range of overall CARF score is 0–168. Therefore, ceiling effects did not occur in all participants. Observing the frequency chart, more than 85% of older persons scored over 17.0, indicating no floor effect in older persons, as well as in persons with stroke or spinal cord injury. Hence, we can conclude that there is no ceiling and floor effects in various ranges of population, including the older population, and people with either stroke or spinal cord injury.

For convergent validity, the overall CARF scores had a strong to very strong correlation with the ABC score (rho $= -0.824$, -0.761, and -0.601, respectively; $p < 0.01$) and had a moderate to strong correlation with the walking independence level in each participant group (rho $= -0.824$, -0.761, and -0.601, respectively; $p < 0.01$) (rho $= -0.636$, -0.423, and -0.522, respectively; $p < 0.01$). However, only a weak correlation was found with the number of previous falls in stroke participants (rho $= 0.291$, p $= 0.076$). The ABC scale has been found sensitive to discriminate individuals who are likely to suffer a fall in the elderly population with a cut-off value of 67 (24). In our study, the ABC scale had a weak, Non-significant correlation with the number of previous falls in older participants. We noticed that the rate of falling was only 11% in older participants, which is much lower than 36%, as found in previous studies (24, 25). Additionally, in our study, only one participant had recurrent falls in the previous 6 months, much <40% of recurrent fallers rate reported by the World Health Organization (26). Inadequate representativeness regarding falls features of our sample could be an important factor resulting in both ABC and CARFS providing a Non-significant correlation with the number of falls. The same situation about falls characteristics existed in the samples of participants with stroke or spinal cord injury. In stroke participants, although lacking representativeness, the CARFS showed near-to-significant weak correlation with the number of falls (rho $= 0.291$, $p < 0.1$), whilst the ABC had higher correlation with the number of falls (rho $= -0.430$, $p < 0.1$). The validity of the CARFS on correlating with fall history needs further examination in representative samples. The recruitment strategy should be modified to include greater frail elderly individuals, such as patients from nursing homes. Generally, CARFS showed moderate to strong convergent validity on correlating with the psychological and physical intrinsic risk factors of falls.

This study produced evidence suggesting that the CARFS is reliable and valid for use among populations with different health statuses. However, there were some limitations as well. First, although the sample size was much larger than that implemented in the pilot study (9), the representativeness of the target population is still not sufficient in terms of the demographic features and falls characteristics. Thus, a larger sample size is needed to improve representativeness. Second, this study did not explore a series of psychometric properties within the CARFS, including predictive validity to falls, and sensitivity to change. Additional research is needed to investigate these elements. Third, the CARFS is expected to be useful to provide guidance on designing fall prevention programs based on dual effects of activity restrictions on fall risk reflected in the CARF score. Hence, further studies are needed to assess the applicability and effectiveness of recommended fall prevention programs.

In conclusion, the CARFS is a reliable and valid tool for quantifying the composite activity-specific risk of falls in older people and persons with stroke or spinal cord injury. Future studies with representative samples are needed to explore the predictive validity of falls, sensitivity to change, and to testify applicability and effectiveness of guiding fall prevention in different target populations.

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 Ethics Committee of Yangzhi Affiliated Rehabilitation Hospital of Tongji University (YZ2019–005). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XS conceived and designed the study. YJ, JW, LC, JY, LN, and JS performed data acquisition and analysis. YJ interpreted the data and drafted the manuscript. All authors read, revised the paper, and approved the final manuscript.

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Locomotor Adaptation Deficits in Older Individuals With Cognitive Impairments: A Pilot Study

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Gait dysfunction and fall risk have been well documented in people with Alzheimer's Disease (AD) and individuals with mild cognitive impairment (MCI). Normal locomotor adaptation may be an important prerequisite for normal and safe community walking function, especially in older adults with age-related neural, musculoskeletal, or cardiovascular changes and cognitive impairments. The split-belt walking task is a well-studied and robust method to evaluate locomotor adaptation (e.g., the ability to adjust stepping movements to changing environmental demands). Here, we capitalized on the split-belt adaptation task to test our hypothesis that a decreased capacity for locomotor adaptation may be an important contributing factor and indicator of increased fall risk and cognitive decline in older individuals with MCI and AD. The objectives of this study were to (1) compare locomotor adaptation capacity in MCI and AD compared to healthy older adults (HOA) during split-belt treadmill walking, and (2) evaluate associations between locomotor adaptation and cognitive impairments. Our results demonstrated a significant decrease in split-belt locomotor adaptation magnitude in older individuals with MCI and AD compared to HOA. In addition, we found significant correlations between the magnitude of early adaptation and de-adaptation vs. cognitive test scores, demonstrating that individuals with greater cognitive impairment also display a reduced capacity to adapt their walking in response to the split-belt perturbation. Our study takes an important step toward understanding mechanisms underlying locomotor dysfunction in older individuals with cognitive impairment.

Keywords: split-belt, Alzheimer's Disease, mild cognitive impairment, locomotion, walking, aging, adaptation

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INTRODUCTION

The ability to walk without the risk of falling is a defining feature of independent community function for elderly individuals. Individuals with cognitive impairment, such as Alzheimer's Disease (AD), are reported to experience falls and loss of independence twice as often as age-matched healthy older adults (HOA) (1, 2). Many individuals who fall will experience a serious injury and have an increased likelihood of recurrent falls (3, 4). Medical costs of fall-related injuries are a large financial burden for both fall victims and the economy. In 2015 alone, medical costs for non-fatal falls reached nearly $50.0 billion and are projected to reach $100.0 billion annually by 2030 (5, 6). The average cost of hospitalization for non-fatal falls is approximately $30,000 per patient,

thus causing a financial burden in addition to disrupted daily function (7). The loss of independence, risk of injury, and financial burden caused by falls necessitate an investigation of why individuals, especially those with cognitive impairments, are prone to falling.

The unimpaired nervous system enables us to ambulate in the community while smoothly navigating environmental demands such as varying terrain, obstacles, visual cues, and multi-tasking. When presented with changes or perturbations in the environment, neural circuits controlling locomotion recalibrate their output *via* sensorimotor adaptation—a process through which sensorimotor mappings update in response to errors caused by environmental perturbations or demands. Over the course of multiple exposures to such environmental perturbations, adaptation processes can aid the formation of new motor memories, contributing to flexible and robust motor behaviors (8, 9). The capacity for locomotor adaptation enables us to flexibly transition between different environments and maintain our balance in the face of perturbations, slips, and trips.

Normal locomotor adaptation may therefore be an important prerequisite for normal and safe community walking function, especially in HOA who have age-related cardiovascular or muscular deconditioning, frailty, and balance dysfunction (10). A decline in sensorimotor adaptation may explain the increased risk of falling in individuals with cognitive decline and gait disturbances. Walking is a complex motor task that integrates inter-joint and inter-limb coordination, sensory feedback, dynamic balance, and adaptation to constantly changing environmental stimuli or perturbations (11). Poor adaptation can lead to gait disturbances and subsequent increased fall risk. After-effects from the new adaptation occur if the environment reverts to the previous or baseline state, and gait must be de-adapted for disturbance-free movement (8, 9). Gait disturbances and variability have been shown to precede cognitive decline (12, 13). Individuals with mild cognitive impairment (MCI) and AD often have decreased gait speed, stride length, stride symmetry, and step regularity (14–17). However, the relationships between cognition, locomotor adaptation capacity, and gait dysfunction are poorly understood, warranting further study.

The split-belt walking task is a well-studied and robust method to evaluate locomotor adaptation, the ability to adjust stepping movements to changing environmental demands *via* trial-and-error processing. Here, we capitalized on the split-belt adaptation task to study the relationship between walking flexibility and cognitive decline. Locomotor adaptation can be systematically assessed by using a split-belt treadmill, where the speed of each leg can be controlled independently. During the split-belt adaptation task, one belt and the corresponding leg run at a different speed (e.g., twice as fast or a 2:1 speed ratio) than the other. When exposed to this 2:1 split-belt treadmill condition, the participant initially "limps" (i.e., shows inter-limb temporal and spatial asymmetry of leg motion), and within 10–15 min of split-belt walking, gait symmetry is restored (9, 18–20). The modified or recalibrated walking pattern is retained for a short period even when treadmill belt speeds are returned to normal (i.e., when the belts move at the same speed or tied-belt condition), which results in the participant limping in the opposite direction (measured as a characteristic after-effect) (8, 9, 18). In previous work, both the magnitude and rate of adaptation as well as de-adaptation (during the after-effect) provided objective measures of an individual's locomotor adaptation capacity. Despite a large body of literature on split-belt adaptation in individuals of multiple ages and neuropathologies, surprisingly, split-belt adaptation has not been assessed in AD participants. We hypothesize that decreased capacity for split-belt adaptation may be an important contributing factor and a potential indicator of increased fall risk and cognitive decline in older individuals with MCI and AD. There is a need to understand how the split-belt adaptation task relates to cognitive deficits and walking function in individuals with a high risk of falls.

Herein, we utilized the split-belt adaptation task to compare the capacity for motor adaptation between a group of older adults with cognitive impairment (MCI, AD) and age-matched healthy controls. We also evaluated the hypothesis that locomotor adaptation capacity would be associated with cognitive function. To our knowledge, this is the first analysis of locomotor adaptation and its relationships with cognition in MCI and AD individuals.

MATERIALS AND METHODS

All study procedures were approved by the Emory Institutional Review Board, and all participants provided informed written consent.

Subjects

All subjects were recruited from the Emory Alzheimer's Disease Research Center Registry. These subjects had undergone standard evaluations including measures that comprise the Uniform Data Set of the National Alzheimer's Coordinating Center. HOA subjects had received a diagnosis of normal cognition within 6 months before completing the study, while MCI and AD subjects received a diagnosis of MCI or AD, respectively, within 6 months before completing the study protocol. The MCI and AD subjects were grouped together as MCI/AD for data analysis. All subjects had no history of psychiatric (Axis I) disorders, alcohol/substance-related abuse, and neurologic conditions such as stroke or Parkinson's disease. Additionally, the subjects had no current significant alcohol use, were not taking hypoglycemic agents, no newly diagnosed neurologic conditions, and no orthopedic problems in the lower limbs or spine that limit walking.

Lab Equipment

A 7-camera motion capture system (Vicon Inc., Colorado, USA) and an instrumented split-belt treadmill (Bertec Corporation, Ohio, USA) were used to collect marker and ground reaction force data during the walking assessment. Retro-reflective markers were attached to the subjects' upper back, pelvis, bilateral hip, knee, and ankle joints with adhesive skin tape, as detailed in our previous publications (21). The split-belt treadmill allows the two belt speeds to be operated independently, enabling different belt speeds for each leg. While walking on the treadmill, the subjects wore a safety harness without body weight support

suspended from a roof-mounted support rail. The subjects had access to a front handrail during treadmill walking and were allowed to hold on to the handrail as needed during data-collection. When using the handrail, subjects were instructed to maintain a consistent handrail grip throughout the session.

Walking Assessment

The walking assessment consisted of three phases: a baseline phase in which the belts operated at the same speed (Pre-tied), a phase in which the belts operated at different speeds (Split-belt), and a final phase in which the belts operated at the same speed (Post-tied) (**Figure 1**). At the start of the session, the subject's self-selected walking speed was assessed by slowly increasing the treadmill belt speed to ascertain the subject's self-selected comfortable gait speed. This self-selected speed was designated as the "fast" speed and 50% of the self-selected speed was designated as the "slow" speed. Additionally, subjects were asked which leg was their dominant leg, by asking which leg they would use to kick a ball. Throughout the different phases of the split-belt walking session, the subjects were informed when the treadmill was going to start speeding up, slowing down, or going to be split. Subjects were instructed to look straight ahead and refrain from looking down at their feet to avoid any visual feedback regarding belt speeds.

Pre-Tied Phase

After assessing the subject's self-selected speed, data were collected during the pre-tied phase, with the subject walking on the treadmill with belt speeds tied for 1 min at the fast speed, followed by 1 min at the slow speed.

Split-Belt Phase

Following the pre-tied phase, the belt underneath the subject's dominant leg was increased to the fast speed, while the belt underneath the non-dominant leg remained at the slow speed. Thus, the treadmill belt speeds were split to a 2:1 speed ratio. This change in speed induced an initial asymmetry or limp in the subject's gait pattern. The subject continued to walk with this split-belt adaptation condition for 15 min. Gait data collected during this period were used to evaluate each individual's locomotor adaptation capacity by assessing the difference in inter-limb step symmetry that the split-belt induced, and the number of steps required to reach a plateau in step symmetry.

Post-Tied Phase

After the conclusion of the split-belt phase, during the post-adaptation period, the belt moving at the fast speed was returned to the slow speed. The subject walked at this tied-belt slow speed for 2 min. Then, both belts increased to the fast speed, and the subject walked for an additional 2 min. After 2 min of fast walking, both belts slowed to a stop. Gait data from this phase were used to evaluate aftereffects or the locomotor system's ability to de-adapt following the split-belt adaptation.

Cognitive Assessment

Following the treadmill assessment, the experimenters administered the Montreal Cognitive Assessment (MoCA) and the n-back subtests of the NIH EXAMINER (Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research).

Data Processing

Marker data were labeled using Vicon Nexus software and then transferred to Visual 3D software (C-Motion, Inc., Maryland, USA) for further processing. Bilateral step lengths were calculated as the antero-posterior distance between the heel markers of the leading foot and the trailing foot at heel strike. Step length was defined with reference to the leading leg (i.e., 'fast step length' corresponds to the step length when the foot on the fast belt is the leading foot). To compare the fast and slow steps, step length symmetry was calculated for each step as follows (22):

$$Step\ symmetry = \frac{(Fast\ step\ length\ -\ slow\ step\ length)}{(Fast\ step\ length\ +\ slow\ step\ length)} \quad (1)$$

Using this formula, a step symmetry of zero would correspond to equal step lengths for both the fast and slow steps.

Step symmetry data for the split-belt and post-tied periods were normalized for each individual by subtracting with respect to the average of the last 5 steps of the pre-tied period. Therefore, a step symmetry equal to zero for each individual corresponds to that individual's baseline step symmetry.

Four periods were primarily used to assess the magnitude of adaptation and de-adaptation (19):

- Early adaptation: mean of first five steps of the split-belt period.
- Late adaptation: mean of last five steps of the split-belt period.
- Early aftereffects: mean of first five steps of the post-tied period.
- Late aftereffects: mean of last five steps of the post-tied period.

The early adaptation step symmetry is also referred to as the **magnitude of adaptation** since it is the initial magnitude of change induced at the beginning of the split-belt adaptation period.

The **rate of adaptation** was defined as the number of steps taken after the split-belt period begins for the subject to reach the adaptation plateau, defined as the average step symmetry of the last 30 steps of the split-belt period. A custom MatLab (The MathWorks, Inc., Massachusetts, USA) program was used to compare the average step symmetry of every five steps with the step symmetry in the plateau window, defined as the adaptation plateau $\pm$ the standard deviation of the step symmetry of the last 30 steps. The plateau was considered to be reached when five consecutive 5-step averages were within the plateau window. The rate of adaptation was then defined as the step number of the first of those five consecutive 5-step averages.

The **rate of de-adaptation** was calculated in the same manner, with the exception that the plateau was calculated as the mean of the last five steps (instead of the last 30 steps) because the de-adaptation period did not contain as many steps as the split-belt period.

Statistical Analysis

The primary dependent variables for analysis were **step symmetry, magnitude of adaptation, and rate of adaptation**. A

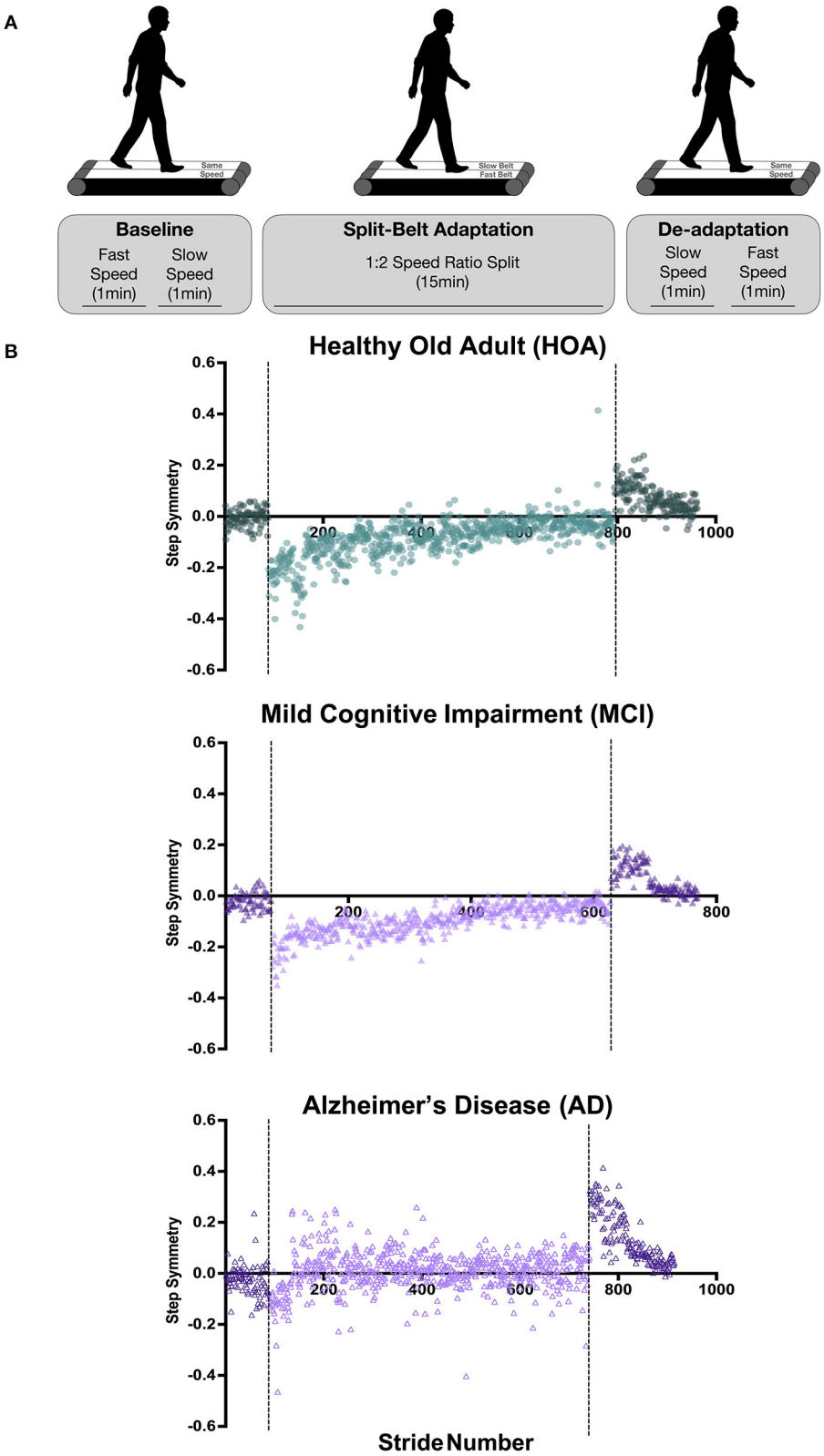

FIGURE 1 | Split-belt walking adaptation protocol and individual participant step symmetry data. **(A)** During baseline (tied-belt) walking, participants walked at their self-selected "fast" speed for 1 min followed by 1-min walking at 50% of the self-selected speed, deemed the "slow" speed. During the split-belt adaptation period, the treadmill belt under the participant's dominant leg was set to the fast speed, whereas the non-dominant leg was set to slow speed for 15 min. The de-adaptation

(Continued)

FIGURE 1 | period involved 1-min walking with belts tied at the slow speed, followed by 1 min tied at the fast speed. **(B)** Step symmetry for individual participants throughout the duration of the experiment. Strides that occurred during tied belt walking are depicted as a darker color than the lighter-colored split-belt walking strides. Baseline walking is shown prior to the first dotted line, split-belt walking adaptation period is shown between the dotted lines, and de-adaptation walking trials can be found after the second dotted line. Note that the HOA participant data are shown in green circles, MCI participant data in purple filled triangles, AD participant in purple unfilled triangles.

TABLE 1 | Participant demographics.

Variables	Healthy Old Adults (HOA) $n = 8$	Mild Cognitive Impairment (MCI) $n = 5$	Alzheimer's Disease (AD) $n = 2$
Age (yr)	69.6 ± 1.5	70.2 ± 7.3	63.0 ± 5.7
Height (cm)	155.6 ± 5.7	151.9 ± 6.8	159.2 ± 8.9
Weight (kg)	59.9 ± 9.7	54.9 ± 7.8	52.1 ± 12.9
Education level (yr)	12.4 ± 2.7	11.0 ± 1.9	12.0 ± 1.0
Female: Male	5: 4	3: 2	1: 1
MOCA (score)	28.75 ± 1.58	21.5 ± 3.35	14.0 ± 7.07
Slow belt speed (mps)	0.41 ± 0.07	0.36 ± 0.08	0.40 ± 0
Fast belt speed (mps)	0.82 ± 0.14	0.72 ± 0.15	0.80 ± 0

2-way ANOVA was used to evaluate the effect of group (HOA, MCI/AD) and time (early adaptation, late adaptation, early aftereffects, late aftereffects) on step symmetry. A 1-way ANOVA was used to evaluate the effect of group (HOA, MCI/AD) on the magnitude of adaptation (signed values and not absolute values) and the rate of adaptation. *Post-hoc t*-tests were used for specific comparisons that showed differences after completing the ANOVAs. Secondary variables included MOCA and n-back scores. *T*-tests were performed to evaluate the difference in MOCA scores and n-back scores between the HOA and MCI/AD groups. Pearson correlations were computed to detect correlations between the primary (locomotor) and secondary (cognitive) variables. SPSS version 24 (IBM) was used for all statistical analyses. We also similarly included analysis on belt speeds to evaluate whether group differences in belt speeds influence adaptation. Alpha level was set as 0.05.

RESULTS

Participant demographics are listed in **Table 1**. A total of 15 subjects completed the study protocol: 8 healthy old adults (HOA; age: 69.6 ± 1.5 years), and 7 subjects in the MCI/AD group−5 older adults with mild cognitive impairment (MCI; age: 70.2 ± 7.3 years), and 2 older adults with Alzheimer's disease (AD; age: 63.0 ± 5.7 years).

Belt Speeds

A two-way ANOVA found no significant difference in belt speeds (slow or fast) between HOA and MCI/AD groups (**Tables 1**, **2**). A Pearson's correlation analysis also did not detect any correlations between belt speed and adaptation magnitude, adaptation rate, de-adaptation magnitude, or de-adaptation rate (**Table 2**).

Pre-Tied Step Symmetry

The average baseline or pre-tied step symmetry for HOA (0.001 ± 0.080) and MCI/AD (−0.022 ± 0.049) revealed no difference between groups (**Figures 2A,B**, **Table 2**).

Magnitude and Rate of Adaptation and Aftereffects

The one-way ANOVA revealed a larger magnitude of adaptation for HOA (−0.267 ± 0.102) compared to MCI/AD (−0.140 ± 0.048) (**Table 2**). The ANOVA revealed no difference in the rate of adaptation for HOA (258.6 ± 171.6 steps) compared to MCI/AD (286.7 ± 138.0 steps) (**Table 2**).

The one-way ANOVA revealed no significant difference in magnitude of de-adaptation for HOA compared to MCI/AD (**Table 2**). Similarly, the ANOVA revealed no difference in the rate of de-adaptation for HOA compared to MCI/AD (**Table 2**).

Comparison of Step Symmetry During Adaptation and Aftereffects

The 2-way ANOVA evaluating the effect of group (HOA, MCI/AD) and time (early adaptation, late adaptation, early aftereffects, late aftereffects) on step symmetry revealed a significant main effect of group and time. There was no interaction effect (**Figure 2A**, **Table 2**).

Planned, pairwise comparisons revealed a significant difference between each time point pooled across groups (**Table 2**). Planned, pairwise comparisons pooled across groups revealed a significant difference between early adaptation (−0.208 ± 0.102) vs. late adaptation (−0.011 ± 0.096), early aftereffects (0.189 ± 0.077), and late aftereffects (0.096 ± 0.069) (**Table 2**). Additionally, there were differences between late adaptation vs. early aftereffects, late adaptation vs. late aftereffects, and early aftereffects vs. late aftereffects (**Table 2**).

Planned, pairwise comparisons between groups revealed a significant difference between HOA and MCI/AD at early adaptation (**Figure 2A**, **Table 2**). There was no significant difference between HOA and MCI/AD at late adaptation (HOA = −0.036 ± 0.116, MCI/AD = 0.018 ± 0.064), early

TABLE 2 | Statistical results.

	Analysis	Figure	*p*-value
Two-Way ANOVA	Belt speeds in HOA vs. MCI/AD	**Table 1**	slow belt: 0.909 fast belt: 0.550
Pearson's correlation analysis	Belt speed vs. adaptation magnitude		0.979
Pearson's correlation analysis	Belt speed vs. adaptation rate		0.950
Pearson's correlation analysis	Belt speed vs. de-adaptation magnitude		0.692
Pearson's correlation analysis	Belt speed vs. de-adaptation rate		0.144
One-Way ANOVA	Average baseline for HOA vs. MCI/AD	**Figures 2A,B**	0.532
One-way ANOVA	Magnitude of adaptation for HOA vs. MCI/AD		0.0098*
One-Way ANOVA	Rate of adaptation for HOA vs. MCI/AD		0.943
One-Way ANOVA	De-adaptation magnitude for HOA vs. MCI/AD		0.289
One-Way ANOVA	Rate of deadaptation for HOA and MCI/AD		0.140
Two-Way ANOVA	Group (HOA, MCI/AD) and time (early adaptation, late adaptation, early aftereffects, late aftereffects) on step symmetry	**Figure 2A**	Group: 0.009* Time: <0.001* Interaction: 0.324
Planned, pairwise comparison	Each time point (early adaptation, late adaptation, early aftereffects, late aftereffects) pooled across groups		all <0.003*
Planned, pairwise comparison	Early adaptation vs. late adaptation, early aftereffects and late aftereffects.		all <0.001*
Planned, pairwise comparison	Late adaptation vs. early aftereffects		<0.001*
Planned, pairwise comparison	Late adaptation vs. late aftereffects		0.001*
Planned, pairwise comparison	Early aftereffects vs. late aftereffects		0.002*
Planned, pairwise comparison	HOA vs. MCI/AD at early adaptation	**Figure 2A**	0.010*
Planned, pairwise comparison	HOA vs. MCI/AD at late adaptation		0.299
Planned, pairwise comparison	HOA vs. MCI/AD at early aftereffects		0.139
Planned, pairwise comparison	HOA vs. MCI/AD at late aftereffects		0.289
One-Way ANOVA	HOA vs. MCI/AD MOCA scores		<0.001*
One-Way ANOVA	HOA vs. MCI/AD n-back scores		0.005*
Pearson's correlation analysis	MOCA score vs. early adaptation magnitude	**Figure 3A**	$p = 0.024$, $R^2 = 0.335$
Pearson's correlation analysis	N-back score vs. early adaptation magnitude	**Figure 3B**	$p = 0.012$, $R^2 = 0.398$
Pearson's correlation analysis	MOCA score vs. early de-adaptation magnitude	**Figure 3C**	$p = 0.028$, $R^2 = 0.319$,
Pearson's correlation analysis	N-back score vs. early de-adaptation magnitude	**Figure 3D**	$p = 0.008$, $R^2 = 0.428$
Pearson's correlation analysis	MOCA score and adaptation plateau	**Figure 3E**	$p = 0.087$, $R^2 = 0.209$

*$p < 0.05$.

aftereffects (HOA = 0.161 ± 0.0.075, MCI/AD = 0.221 ± 0.070), or late aftereffects (HOA = 0.078 ± 0.071, MCI/AD = 0.117 ± 0.066) (**Table 2**).

Cognitive Outcome Variables and Their Relationship With Adaptation

A significant difference was observed in the MOCA scores between HOA (28.8 ± 1.6) and MCI/AD (18.9 ± 5.2), as well as the n-back scores between HOA (0.84 ± 0.07) and MCI/AD (0.63 ± 0.16) (**Table 2**). For both MOCA and n-back tests, a higher score relates to better cognitive status.

Pearson correlation analyses revealed a significant relationship between MOCA score and early adaptation magnitude, with a higher MOCA score (better cognitive status) correlating to a greater magnitude of adaptation (**Figure 3A**, **Table 2**). Similarly, Pearson correlation analyses revealed a significant correlation between n-back score and early adaptation magnitude, with a higher n-back score (better cognitive status) correlating to a greater magnitude of adaptation (**Figure 3B**, **Table 2**). Pearson correlation analyses also revealed a significant correlation between MOCA score and early de-adaptation magnitude, with a higher MOCA score (better cognitive status) correlating to a lesser magnitude of de-adaptation (**Figure 3C**, **Table 2**). Similarly, Pearson correlation analyses revealed a significant correlation between n-back score and early de-adaptation magnitude, with a higher n-back score (better cognitive status) correlating to a lesser magnitude of de-adaptation (**Figure 3D**, **Table 2**). A trend toward a significant correlation between MOCA score and adaptation plateau was found, with a higher MOCA score (better cognitive status)

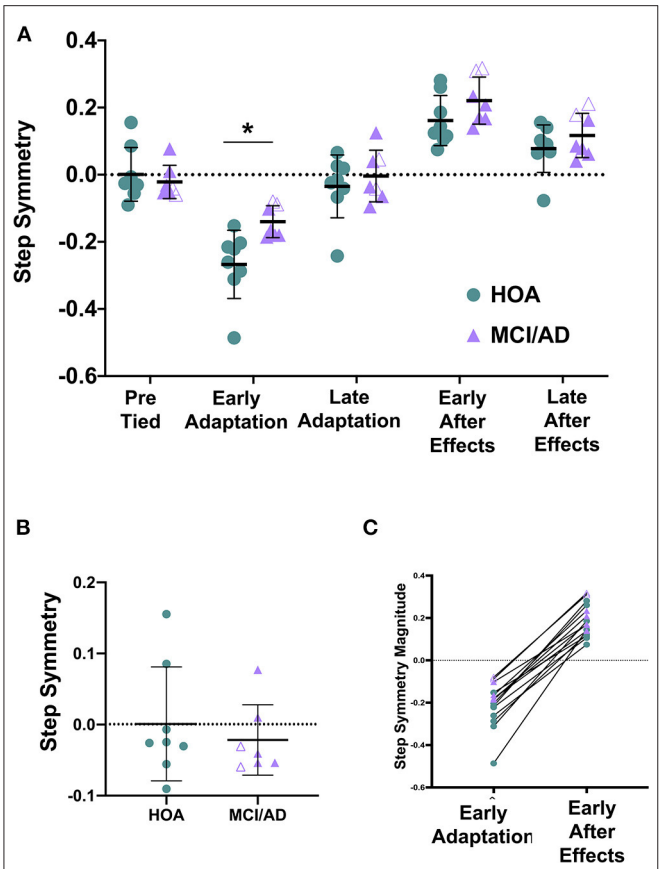

FIGURE 2 | The magnitude of Early Adaptation is significantly reduced in MCI/AD compared to HOA. **(A)** Two-way ANOVA revealed a significant main effect of group ($p = 0.009$) and time ($p < 0.0001$) on step symmetry. Pairwise comparisons between groups revealed a significant difference between HOA and MCI/AD at early adaptation (*$p = 0.0098$). **(B)** Unpaired *t*-tests depicted no significant difference in step symmetry during baseline or tied-belt walking between HOA and MCI/AD ($p = 0.532$). **(C)** Comparison of step symmetry (magnitude) during early adaptation and early de-adaptation. Note that the HOA participant data are shown in green circles, MCI participant data in purple filled triangles, AD participant in purple unfilled triangles.

correlating with a more symmetrical step symmetry plateau during the adaptation period (**Figure 3E**, **Table 2**).

DISCUSSION

We found a significant difference in split-belt locomotor adaptation between healthy older adults (HOA) and older individuals with mild cognitive impairments and Alzheimer's disease (MCI/AD). Individuals with MCI/AD showed a significantly reduced magnitude of locomotor adaptation (i.e., magnitude of step symmetry during the early adaptation phase of split-belt walking). We found no between-group differences in baseline (i.e., pre-tied) step length symmetry or in the magnitudes and rate of de-adaptation. While our small sample preliminary study did not reveal differences in the rate of adaptation between HOA and MCI/AD, we observed much higher inter-individual variability in the time course and patterns of adaptation in individuals with MCI/AD. Furthermore, our correlation analyses revealed that individuals who showed smaller magnitudes of adaptation also demonstrated greater cognitive impairment (i.e., poorer MOCA and n-back scores). Interestingly, although there were no between-group differences during the de-adaptation phase of split-belt walking, we also found significant correlations between the magnitude of de-adaptation and cognitive impairment. Our study takes the first step toward our long-term goal of elucidating mechanisms underlying locomotor adaptation dysfunction and fall risk in older individuals with cognitive impairment.

Revealing a significant effect of group (HOA, MCI/AD), our results depicted a significantly reduced adaptation ability in cognitively impaired participants during early adaptation compared to healthy age-matched controls. We did not find significant differences during de-adaptation. Additionally, based on lack of significant differences in and correlations with belt speed, we infer that belt speed was not a major contributing factor for our observed effects on adaptation. Step-symmetry differences observed in HOA during early adaptation are somewhat consistent with previous literature on changes in gait with aging (22). Bruijn et al. (22) showed that HOA adapt less and more slowly, showing fewer aftereffects compared to young adults. Under the premise that cognition tends to decline with age, our study agrees somewhat with Bruijn et al. (22) in that our more cognitively impaired group (i.e., MCI/AD) showed a lesser magnitude of adaptation. Bruijn et al. (22) also noted a small sample size as a limitation of their work. In another previous study, Wolpea et al. (23) found a smaller magnitude of adaptation in HOA than young adults during visuomotor rotation learning tasks. The observed changes in locomotor adaptation with cognitive decline are also supported by longitudinal studies showing a decline in gait speed with AD progression, exacerbated by the performance of dual-task paradigms (15, 17). Studies observing changes in gait with cognitive decline during natural aging suggest that HOA demonstrate alterations in the locomotor system and adaptation strategies to maintain stability (24–26). Further cognitive decline, in the case of MCI/AD, may induce additional changes in the locomotor system and adaptation, which merit deeper investigation in future studies.

Walking in the real-world environment places high demands on the interplay between cognitive (i.e., executive function, working memory, and attention) and motor functions to adapt walking to rapidly evolving situations, terrains, and weather conditions. A well-functioning ability to sustain, shift, and divide attention between environmental and body function factors is essential for safe ambulation in everyday life. Unfortunately, cognitive dysfunction, the hallmark of MCI and AD, directly impacts the cognitive-motor neural resources available to carry out such activities of daily living (1, 2). Therefore, in addition to the hallmark cognitive features of MCI and AD, loss of independent mobility induced by balance and gait dysfunction is becoming increasingly recognized (27–29). This is consistent with our findings of significant correlations between the magnitude of adaptation and level of cognitive impairment. Importantly, our results show that individuals who

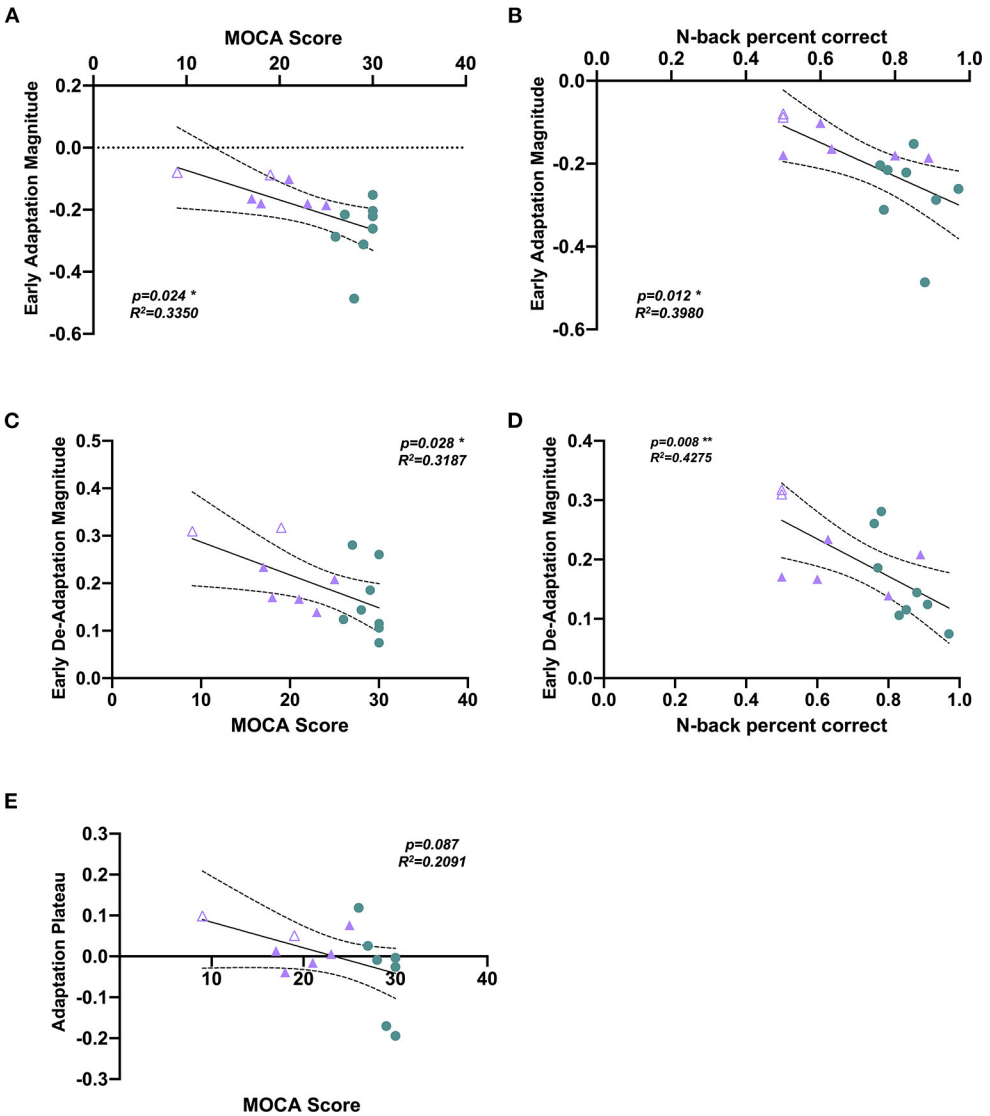

FIGURE 3 | Scatterplots showing correlations between cognitive impairment measures and split-belt walking adaptation measures. A significant Pearson's correlation was observed between **(A)** MOCA score and early adaptation magnitude ($p = 0.024$, $R^2 = 0.3350$), with a higher MOCA score correlating to a greater magnitude of adaptation. **(B)** n-back correction rate and early adaptation magnitude ($p = 0.012$, $R^2 = 0.3980$), with a higher n-back accuracy correlating to a greater magnitude of adaptation. **(C)** MOCA score and early de-adaptation magnitude ($p = 0.024$, $R^2 = 0.3350$), with a higher MOCA score correlating to a lesser magnitude of de-adaptation. **(D)** n-back correction rate and early de-adaptation magnitude ($p = 0.008$, $R^2 = 0.4275$), with a higher n-back accuracy correlating to a lesser magnitude of de-adaptation. **(E)** Correlation analysis between MOCA score and adaptation plateau ($p = 0.087$, $R^2 = 0.2091$). Note that the HOA participant data are shown in green circles, MCI participant data in purple filled triangles, AD participant in purple unfilled triangles. $^*p < 0.05$, $^{**}p < 0.005$.

have cognitive impairments may also demonstrate impairments in locomotor adaptation.

Split-belt walking, a unique adaptation task that induces complex asymmetries in the spatial and temporal coordination of walking patterns, has been used to investigate locomotor adaptation in various populations (18, 30–32). The split-belt method provides an advantage because it involves a standardized, robust, and well-studied locomotor task with potential implications for walking function, community participation, as well as fall prevention. Previously, split-belt has provided a robust measure of motor adaptation in children (33), young adults (34), elderly individuals (9, 22, 35, 36), stroke survivors (19, 20), people with Parkinson's disease (37, 38), and individuals with hemispherectomy (39). Furthermore, Malone and Bastian (31) showed a reduction in the rate of split-belt adaptation when able-bodied participants were distracted by a cognitive task during split-belt walking (31). Although we did not find a reduced rate of adaptation in MCI/AD, our finding of reduced adaptation magnitude in MCI/AD may suggest that cognitive impairments, somewhat similar to cognitive

distraction, adversely affect the locomotor adaptation processes. These research questions need more in-depth study because to maintain stability and prevent falls during locomotion, human gait must be readily adapted in response to changes in internal and external environments. Similarly, and as noted, deficits in dual-tasking abilities have been shown to be related to increased gait variability and greater risk of falls (40). Individuals with MCI and AD, especially those with notable deficits in executive function, have difficulty with cognitive-motor dual-tasking, which may contribute to their fall risk (14, 16, 28, 40). Future studies could evaluate the effect of cognitive-motor dual-tasks during split-belt walking in people with MCI and AD.

Despite finding a significant difference in magnitude of adaptation, we observed no significant difference between HOA and MCI/AD for the magnitude of de-adaptation nor the rates of adaptation and de-adaptation. The lack of significant difference for the magnitude of de-adaptation may be due to a small sample size. Due to the small sample, MCI and AD were grouped together to represent cognitively impaired individuals; however, our individual subject data suggested that AD participants showed greater average de-adaptation magnitude compared to those with MCI, both of which were greater than HOA. Both MOCA and n-back scores showed significant relationships with the magnitude of adaptation, suggesting that individuals with greater cognitive impairment also demonstrate a reduced capacity to adapt their walking in response to the split-belt perturbation. These relationships suggest that cognitive status may be an important contributor to walking function and the risk of falls in older individuals with cognitive impairments. Furthermore, given the absence of between-group differences in de-adaptation, we were surprised to find significant associations between de-adaptation magnitude and cognition, such that individuals who showed a larger magnitude of de-adaptation also showed greater cognitive impairment. Notably, we found considerable inter-individual variability in the time course of adaptation and de-adaptation in people with greater cognitive impairment in our cohort. Additionally, individual participant data revealed several examples wherein a small magnitude of early adaptation was accompanied by a relatively large magnitude of de-adaptation (**Figure 2c**). The mechanisms underlying the somewhat disparate effects of MCI/AD on adaptation vs. de-adaptation processes merit further investigation in larger sample studies. Potentially, impairments in higher-order executive functions contribute to greater stride-to-stride variability during walking and adaptation, as well as a variable time course of response to the split-belt task. While correlation does not prove causation, future studies should probe potential factors causing locomotor adaptation deficits by implementing walking training comprising multiple sessions of split-belt walking, to evaluate whether improvements in locomotor adaptation are accompanied by improved cognitive function in people with MCI and AD.

Our findings have implications and provide a foundation for future inquiry aimed at understanding locomotor dysfunction in MCI and AD. However, this study is not without limitations. The most notable limitation of our study is the small sample size. Despite having a small sample size, our correlation results and differences between MCI and AD participants warrant further larger-sample investigations. With a larger sample size, sex differences in locomotion and adaptation could also be analyzed. Previous literature proposes that individuals may cope with gait disturbances *via* a "risky" adaptation (e.g., increased gait speed), as seen in dementia patients, or a "secure" adaptation (e.g., slowed gait speed and shortened stride length), common in HOA (17). Previous literature shows that repeated exposure to the split-belt adaptation task may improve locomotion in stroke survivors (9, 19, 41, 42). Despite these promising previous results, it is unknown if multiple sessions of split-belt adaptation could be successfully applied as a potential exercise-based treatment for enhancing walking function in MCI and/or AD, necessitating further study.

CONCLUSIONS

Understandably, to date, the neural underpinnings and the related cognitive outcomes in MCI and AD are the primary focus of evaluation, treatment, and research aimed at lessening the disease progression and burden. However, considering the known importance of locomotion in maintaining the quality of life and the benefits of non-pharmacological exercise-based interventions for enhancing physical and cognitive function, our study aimed to understand the effects of MCI and AD on locomotor adaptation using a robust, standardized split-belt walking task. Our results showed a significant reduction in locomotor adaptation in MCI/AD compared to HOA and significant relationships between locomotor adaptation and cognitive function impairments. Future research is needed to better understand neuromechanical factors contributing to gait dysfunction in people with MCI and AD, the relationships between locomotor and cognitive impairments, and their association with disability, falls, and quality of life in individuals with MCI and AD.

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 Emory University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TK and JN conceived and designed research. TK, JN, and SE performed experiments and analyzed data. TP, TK, JN, and SE interpreted results of experiments. TP, TK, and SE prepared figures. TP, TK, and JN drafted, prepared, edited, revised, and edited the final versions of the manuscript. All authors approved the final version of manuscript.

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Principal Component Analysis of Oxford Cognitive Screen in Patients With Stroke

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Cognitive deficits occur in most patients with stroke and are the important predictors of adverse long-term outcome. Early identification is fundamental to plan the most appropriate care, including rehabilitation and discharge decisions. The Oxford Cognitive Screen (OCS) is a simple, valid, and reliable tool for the assessment of cognitive deficits in patients with stroke. It contains 10 subtests, providing 14 scores referring to 5 theoretically derived cognitive domains: attention, language, number, praxis, and memory. However, an empirical verification of the domain composition of the OCS subtests in stroke data is still lacking in the literature. A principal component analysis (PCA) was performed on 1,973 patients with stroke who were enrolled in OCS studies in the UK and in Italy. A number of six main components were identified relating to the domains of language and arithmetic, memory, visuomotor ability, orientation, spatial exploration, and executive functions. Bootstrapped split-half reliability analysis on patients and comparison between patients and 498 healthy participants, as that between patients with left and right hemisphere damage, confirmed the results obtained by the principal component analysis. A clarification about the contribution of each score to the theoretical original domains and to the components identified by the PCA is provided with the aim to foster the usability of OCS for both clinicians and researchers.

Keywords: cognition, stroke, rehabilitation, psychometrics, assessment

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INTRODUCTION

Cognitive deficits occur in 50–78% of patients with stroke (1), and their early identification is fundamental to plan the most appropriate neurorehabilitation program (2). The Oxford Cognitive Screen (OCS) is a screening tool providing a "snapshot" of the patient's cognitive profile helpful for designing the rehabilitation program according to the patient's needs (3). The OCS entails 10 subtests: picture naming, semantics, orientation, visual field, sentence reading, number writing and calculation, broken hearts, imitation, recall and recognition, and trails. It is easy to administer and score, takes a relatively short time, can be delivered at the bedside, and can be administered in the acute phase (3, 4).

The Oxford Cognitive Screen was initially tested on 140 neurologically healthy English participants and 208 acute patients with stroke demonstrating its reliability, convergent and divergent validity, and sensitivity in differentiating between patients with right vs. left brain damage (4). In a successive study (5) on 200 patients with stroke, the OCS was shown to be more sensitive than the Montreal Cognitive Assessment (MoCA) in highlighting cognitive impairments in this type of patients. In addition, OCS was found to be more inclusive for participants with aphasia and not dominated (as MoCA) by left hemisphere impairments, instead of giving differentiated profiles across the contrasting domains. Similar results on patients with stroke were obtained by the comparison of OCS with the Mini-Mental State Examination (6). Overall, the OCS detects important cognitive deficits after stroke not assessed in standard cognitive screening developed for dementia, it is inclusive for patients with aphasia and neglect, and it is less confounded by co-occurring difficulties in these domains.

The OCS has been validated and standardized in many other languages, including Italian (4), Spanish (7), Brazilian Portuguese (8), Chinese (9), Dutch (10), Russian (11), and Danish (12).

The original study classified the OCS subtests under five different theoretical domains: attention (divided into the subdomains of executive functions and visual attention), memory, language, praxis, and number (**Figure 1**) (4).

A Chinese study tested the reliability of OCS with 5 domains, but the first one was named as "attention and executive function," and the others were language, memory, number processing, and praxis. The authors found a nearly acceptable level of data-to-model fit, with an improvement in the fitting model obtained when the two subtests related to numerical cognition and praxis were dropped from the model. This yielded an acceptable fit in a model including only three domains:(1) attention and executive function; (2) memory; and (3) language (9). The internal consistency of each of these three domains was tested using Cronbach's alpha coefficient, finding values of 0.3, 0.52, and 0.44 for attention, memory, and language, respectively. These values were lower than the Cronbach's alpha equal to 0.907 evaluated for assessing internal consistency among all the items in a Spanish study (7). This difference could be due to the fact that, in the Chinese study, the Cronbach's alpha was computed on each one of the identified three dimensions on the patients' sample, whereas in the Spanish study, it was computed on all the subtests and collapsing patients and healthy elderly. The Chinese study (9) investigated the structural validity of OCS, but it was done by a confirmatory (and not by an exploratory) factor analysis in which the hypothesis of five and three domains was *a priori* formulated and tested in a sample of 100 patients and 120 controls. Given the known heterogeneity in the cognitive consequences of stroke, it would be important to also carry out exploratory factorial analyses of the OCS on large samples of patients with stroke and healthy controls. Information on this is still limited in the literature.

A recent study conducted on 237 patients with stroke identified only three main components of cognitive functions impaired 1 week after stroke assessed by OCS and the National Institutes of Health Stroke Scale (13). Authors interpreted their results suggesting that neurological deficits following stroke are correlated in a low-dimensional structure of impairment, related neither to the damage of a specific area nor to a vascular territory, but rather reflecting widespread network impairments caused by focal lesions. The first component resulted linked to language, calculation, memory, praxis, and right-sided neglect and was found to be mainly related to left hemisphere damage. The second component was linked to left visuomotor deficits and spatial neglect and mainly related to damage of right cortico-subcortical regions. The third component was linked to right motor deficits and damage in the left subcortical regions. However, the proposed model explained only 50% of the variance, and it was dominated by left hemisphere impairments, similar to other cognitive assessment tools (5, 6). It would appear that while clinicians highlight a high clinical variability among patients with stroke, psychometric tests reveal a limited set of dimensions accounting for a large proportion of variance in performance of the patient with stroke. This could be due to the fact that the large-scale physiological abnormalities following a stroke reduce the variety of neural states visited during task processing and at rest, resulting in a limited repertoire of behavioral states (14).

Overall, a large variability of results and related interpretations emerges from the previous studies on OCS. Presumably, this is due to methodological differences such as whether healthy subjects have been included into the analyses with patients or not, and whether psychometric properties were measured on the OCS in general or on its specific domains.

Despite the general utility of OCS as a cognitive screening tool, the lack in the scientific literature of an exploratory psychometric analysis of OCS domains has led to some critical issues related to its use in clinical routine. A first issue is that in the original OCS under the umbrella domain of attention, executive functions and visuospatial attention are merged, putting together two conceptually different cognitive functions. Even if attention plays a central role in both these functions, neither executive functions nor visuospatial attention can be used to define the impairment of the attention function. This problem also implies that the original OCS does not allow the spatial inattention to emerge as a possible deficit distinct from the attentive component, despite three scores of original OCS could be used to assess unilateral spatial neglect (cancelation, space symmetry, and object asymmetry). Because of the role played by spatial inattention in affecting neurorehabilitative outcomes in patients with stroke (15–17), it would be fundamental to detect and hence to treat this syndrome in a very early phase of stroke. Another critical issue concerns the separation between the "number" and "language" domains in the original OCS; indeed, more recent literature has shown that number writing and calculation should be considered as associated with the language domain (18, 19), indicating the importance of checking the factorial composition of subtests related to linguistic and number processing. These problems may have contributed to the gap between clinicians claiming a high clinical variability among patients with stroke and scientific psychometric tests revealing a limited set of dimensions accounting for a large proportion of variance in the cognitive functions of patients with stroke.

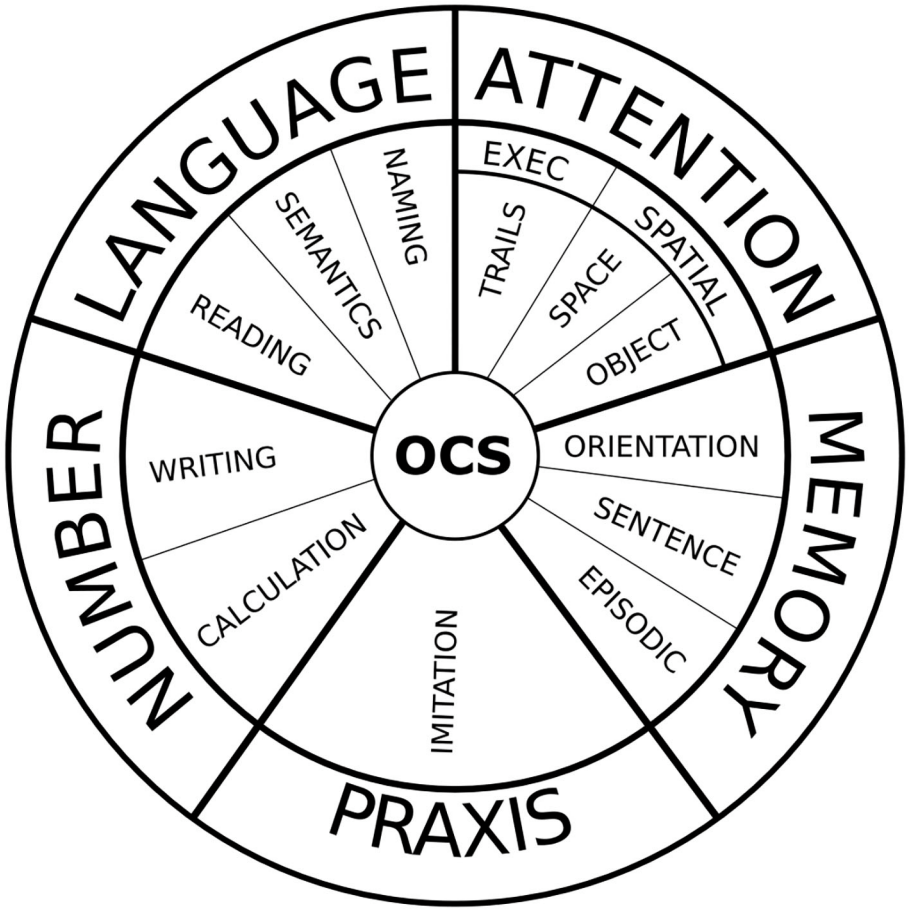

FIGURE 1 | The visual snapshot of the OCS is a compact modality of OCS scoring, in which compromised domains are colored. It provides a quick but informative overview of the cognitive profile of the patient.

Therefore, the aim of this study was to carry out a factor analysis on a large number of patients with stroke to identify the main OCS domains to solve some scientific and clinical issues related to this useful and valid screening tool.

MATERIALS AND METHODS

Participants

This project represents a secondary analysis of data collected within the UK and Italy. Overall, the OCS was administered to 1,973 patients and 498 healthy participants. In the UK, the data of patients were study data from the Oxford Cognitive Screen (OCS) screening project (n = 416) (4, 5) and the OCS-Care study (n = 873) (20) from 2015 to 2019. In Italy, both already collected patients' data (3) and original data were analyzed (n = 684). The UK study protocols were reviewed and approved by the National Research Ethics Committee (UK) (references: 11/WM/0299, 14/LO/0648, and 12/WM/00335), and the Italian study protocols were approved by the regional ethics board (Comitato Etico Regione Toscana-Area Vasta Sud Est prot. n.376CEAVSE del 17 12 2015).

The age of patients ranged between 18 and 98 years (mean: 71.91 ± 3.3 years), with mean schooling years of 10.43 ± .9 and 54.8% men. According to the prevalence of stroke, 80.9% of diagnosed cases were of an ischemic origin, 18.8% of hemorrhagic, and 0.3% of other origins. Side of cerebral stroke was the right hemisphere in 51% of cases, left hemisphere in 44%, and the remaining 5% cases were bilateral (extending past the midline or brainstem). A total of 15 patients had a cerebellar stroke (0.08%). The median time from stroke was 6 days (interquartile range: 16 days). Not all the clinical data or OCS items were recorded for all patients, those with a complete dataset being 1,444 (74%). For each analysis, all the available data were used. The age of healthy participants ranged between 18 and 89 years (mean: 53.51 ± 8.4 years); the education years were 12.24 ± .4; for all subjects, there was a complete dataset. Both these values were significantly different from those of patients ($p < 0.001$), presumably because of inclusion or exclusion criteria. Exclusion criteria for healthy subjects were as follows: the presence of previous or ongoing neurological and/or psychiatric disorders, the presence of cognitive decline (as indicated by a Mini-Mental State Examination score lower than (22), the presence of visual

field defect as revealed by clinical examination, the presence of visual impairment uncorrected by glasses (3). Given the purpose of the study, it was important that the responses of the healthy group to the tests were not affected by any cognitive or visual impairment, but the above criteria affected the sampling shifting it toward younger and more schooled people. Participants with age <30 years old were the 3% of the full sample, and those with schooling <3 years only the 0.4%.

OCS Subtests

The OCS is divided into domains and subdomains assessed with specific subtests (for a complete description refer to (3, 4)). The subtests for the language domain are as follows: picture naming (min–max possible range: 0–4), sentence reading (range: 0–15), and semantics (assessed by a picture pointing task; range: 0–3). The subtests for numerical cognition include a subtest of number writing and calculation with two separate subscores: number writing (range: 0–3) and calculation (range: 0–4). The subtest for praxis is imitation (range: 0–12), a task involving meaningless gestures. The subtests of memory include orientation (range: 0–4) and recall and recognition; in this latter subtest, there are separate subscores for sentence recall (range: 0–4) and episodic memory (range: 0–4). Trails (range: −13 /+ 12) is the subtest for attention related to executive functions. Visuospatial attention is assessed by a visual field test (for assessing hemianopia; range: 0–4) and the broken heart cancelation subtest which provides three different subscores: cancelation (i.e., the total number of complete hearts canceled within the time limit as a measure of selective visual attention; range: 0–50), space asymmetry (the difference between complete hearts canceled in the left and right portions of the page as a measure of egocentric neglect; range: −20/+20), and object asymmetry (the difference between left- and right-broken hearts as a measure of allocentric neglect; range: −50/+50). Most of the subtests are formed by 4 items, but semantics (three items) and the trails (two items). Raw data of space and object asymmetry were corrected considering their absolute values, to avoid directionality effects. No scaling corrections were applied to raw data. The total number of obtained subscores is 14.

Statistical Analyses

The OCS subscores were examined in terms of means and standard deviations according to the previous studies. Data of patients and healthy participants were compared by Mann–Whitney U-test; then, the data of patients with stroke in the left hemisphere were compared with those of the right hemisphere. The alpha level of significance was set at 5%, but it was reduced for multiple comparisons applying Bonferroni correction. A heatmap correlation matrix was computed among all the subtests of OCS using the Pearson correlation coefficient and also partial correlation corrected for demographical factors (age and education). Factor analysis was conducted to identify the main domain in which OCS item scores resulted aggregated by means of principal component analysis (PCA). Being the factors potentially correlated with each other and not totally independent, an obliquity rotation method (direct oblimin method with delta = 0 with Kaiser normalization) was preferred to an orthogonal one. However, because varimax rotation method was often associated with an orthogonal solution often more easily interpretable, we performed a secondary analysis using varimax rotation.

Principal component analysis was conducted on the sample of patients using 14 OCS scores (using absolute values for the space and object asymmetry tasks instead of raw scores to capture both left-sided and right-sided neglect). The selection of the components was performed according to the following criteria suggested by Schonrock-Adema et al. (21): (1) the point of inflection displayed by the scree plot (determined as the maximum or minimum of the derivate of the curve); (2) eigenvalues >1; or (3) eigenvalues with an additional variance of at least 5%. Based on this approach, the choice among the above criteria also depends upon the following criteria about interpretability: (4a) each component should contain variables with a loading $\geq$ 0.4; (4b) variables loading on the same component should share the same conceptual meaning; (4c) variables loading on different components should appear to measure different constructs; and (4d) most variables should load relatively high on only one component and low on the others. The reliability of PCA results was assessed performing a bootstrapped split-half reliability analysis: patients' data were randomly split into a subsample of 986 individuals, on which a new PCA was conducted; then, a new random split was performed and analyzed. The reliability was assessed computing the Pearson's correlation coefficient (R) on the subtest loadings on corresponding components between the two PCAs and computing the 95% confidence intervals of subtest loadings with respect to their main components.

Being the OCS a screening tool developed for identifying the presence of cognitive deficits in patients with stroke with respect to healthy subjects (more than assessing the level of severity of these deficits within patients' population), we also performed a secondary PCA collapsing data of patients and healthy subjects into a single group for increasing the data variability. At the same time, one may note that this data merging might affect the covariance structure of data, introducing unmatched covariates, and reducing the robustness of the results of PCA calling for caution in its interpretation. These results are reported in the **Supplementary Materials**.

RESULTS

Comparison of Patients With Healthy Subjects

The comparison of scores between healthy participants and patients with stroke confirmed statistically significant differences for all OCS subscores with patients showing higher absolute scores for space and object asymmetry tasks and significantly lower scores in all the other tasks (**Table 1**). Significant differences were also found among patients with respect to the side of stroke (left hemisphere, right hemisphere, or bilateral, **Table 2**). The heatmap correlation matrix among the OCS scores showed higher correlations (i) of picture naming with

TABLE 1 | Average scores (mean ± standard deviation) for each group and their comparison carried out with the Mann–Whitney U test (better performances are related to higher values for all the tasks, but trails, object and space asymmetry; for these last two tasks absolute values are reported).

OCS Domains	OCS Tasks	Patients	Healthy subjects	*p*-value
Language	Picture naming	2.81 ± 1.28	3.63 ± 0.62	<0.001
	Semantics	2.84 ± 0.54	3.00 ± 0.00	<0.001
	Sentence reading	12.41 ± 4.36	14.85 ± 0.55	<0.001
Number Cognition	Number writing	2.32 ± 1.0	2.97 ± 0.24	<0.001
	Calculation	3.16 ± 1.10	3.78 ± 0.47	<0.001
Memory	Orientation	3.60 ± 0.90	3.98 ± 0.22	<0.001
	Sentence Recall	2.81 ± 1.61	3.41 ± 0.76	<0.001
	Episodic Memory	3.12 ±1.14	3.87 ± 0.42	<0.001
Attention	Trails	1.82 ± 3.54	−0.43 ± 1.81	<0.001
	Visual Field	3.73 ± 0.70	4.00 ± 0.04	<0.001
	Cancelation	34.44 ± 14.79	47.05 ± 4.0	<0.001
	Object Asymmetry	1.39 ± 2.71	0.15 ± 0.62	0.003
	Space Asymmetry	3.61 ± .67	0.99 ± 1.15	<0.001
Praxis	Imitation	9.07 ± .318	11.40 ± 1.16	<0.001

TABLE 2 | Average scores (means ± standard deviation) for each subgroup of patients with respect to side of stroke (the significantly worst performance is highlighted in bold). The *p*-values were computed using Mann–Whitney U-test (in bold if <0.016, based on Bonferroni correction on alpha level of significance).

OCS Domains	OCS Tasks	Stroke in left hemisphere	Stroke in right hemisphere	Bilateral Stroke	L vs R	L vs B	R vs B	Cerebellar Stroke
Language	Picture naming	**2.50 ± 1.43**	2.91 ± 1.15	2.93 ± 1.29	**<0.001**	**0.015**	0.562	2.67 ± 1.29
	Semantics	**2.76 ± 0.66**	2.86 ± 0.51	2.93 ± 0.31	**0.004**	0.048	0.316	3.00 ± 0.00
	Sentence reading	**11.32 ± 5.19**	12.81 ± 3.88	12.57 ± 4.0	**<0.001**	0.211	0.190	13.07 ± 3.71
Number cognition	Number writing	**2.11 ± 1.16**	2.42 ± 0.90	2.27 ± 1.03	**<0.001**	0.434	0.244	2.47 ± 0.99
	Calculation	**2.95 ± 1.25**	3.27 ± 0.99	2.97 ± 1.23	**<0.001**	0.873	0.066	3.47 ± 0.64
Memory	Orientation	3.56 ± 0.91	3.60 ± 0.95	3.41 ± 1.04	0.531	0.407	0.271	3.87 ± 0.35
	Sentence Recall	**2.29 ± 164**	3.01 ± 1.54	2.82 ± 1.40	**<0.001**	**0.003**	0.565	2.67 ± 1.34
	Episodic Memory	**2.91 ± 1.22**	3.22 ± 1.09	3.07 ± 1.20	**<0.001**	0.213	0.324	3.20 ± 0.86
Attention	Trails	**1.49 ± 3.53**	2.32 ± 3.56	2.14 ± 3.87	**<0.001**	0.329	0.434	2.36 ± 4.18
	Visual Field	3.77 ± 0.69	**3.65 ± 0.75**	3.68 ± 0.78	**<0.001**	0.154	0.697	3.71 ± 0.61
	Cancelation	36.82 ± 13.51	**31.04 ± 15.55**	33.10 ± 15.47	**<0.001**	0.117	0.255	36.60 ± 15.73
	Object Asymmetry	−0.29 ± 2.13	**1.18 ± 3.66**	−0.30 ± 2.45	**<0.001**	0.854	**<0.001**	0.87 ± 7.04
	Space Asymmetry	−1.24 ± 4.89	**2.62 ± 6.08**	0.63 ± 5.38	**<0.001**	**0.006**	0.026	2.47 ± 4.55
Praxis	Imitation	**8.58 ± 3.40**	9.21 ± 3.06	9.12 ± 2.62	**0.001**	0.589	0.324	9.21 ± 2.42

sentence reading, number writing, episodic memory, (ii) of sentence reading with number writing and calculation, (iii) of number writing with calculation, and (iv) of cancelation with imitation, visual field, and space asymmetry (**Table 3**). The overall Cronbach's alpha (obtained reversing the scores of trails and absolute values of space and object asymmetry) for internal consistency was 0.615. Similar results were found also when correlations were corrected for age and education (**Table 3**). In general, all the correlations between age or schooling and the patients' scores of OCS subtests had an R <0.25 (the average absolute value of R was 0.10 and 0.15 for age and schooling, respectively), with the only exception of an R = 0.27 between the sentence recalling score and schooling.

Principal Component Analysis

Performing the PCA on the patients' sample, the scree plot of **Figure 2** was obtained. The components with an eigenvalue >1 were three, but they seemed quite different from the three proposed by the three-component proposed model of OCS (9) that were language, memory, attention, and executive functions. Our PCA identified a 1st component that seemed to put together language and memory, being formed by picture naming (0.685), sentence reading (0.612), number writing (0.642), calculation (0.624), imitation (0.404), sentence recall (0.766), episodic memory (0.680), and orientation (0.500). The 2nd component was formed by cancelation (-0.623), object asymmetry (0.691), and space asymmetry (0.734) and seemed related to the unilateral spatial neglect. The 3rd component was formed by semantics

TABLE 3 | Heatmap correlation matrix for the OCS scores (Pic Nam, picture naming; Sem, semantics; Read, reading; Num. Wr., number writing; Calc, calculation; Ori, orientation; SR, sentence recall; EM, episodic memory; IM, imitation; VF, visual field; Canc., cancelation; O AS, object asymmetry; S AS, space asymmetry; TR, trails).

	Language			Number Cognition		Memory			Pra-xis	Attention				
	Pic Nam	Sem	Read	NumWr	Calc	Ori	SR	EM	IM	VF	Canc	O As	S As	TR
Pic Nam	1	0.30	0.43	0.37	0.29	0.23	0.36	0.35	0.33	0.19	0.28	−0.05	−0.09	−0.10
Sem	0.28	1	0.35	0.28	0.27	0.17	0.16	0.24	0.28	0.26	0.23	0.01	−0.08	−0.05
Read	0.45	0.32	1	0.47	0.41	0.25	0.33	0.31	0.26	0.28	0.29	−0.02	−0.08	−0.08
NumWr	0.42	0.26	0.50	1	0.42	0.27	0.26	0.29	0.30	0.24	0.31	−0.08	−0.13	−0.14
Calc	0.36	0.24	0.43	0.47	1	0.32	0.28	0.25	0.25	0.17	0.29	−0.07	−0.14	−0.14
Ori	0.27	0.18	0.24	0.31	0.33	1	0.29	0.28	0.25	0.20	0.29	−0.12	−0.15	−0.09
SR	0.38	0.15	0.31	0.30	0.32	0.29	1	0.40	0.18	0.06	0.12	0.01	−0.02	−0.11
EM	0.41	0.25	0.33	0.36	0.31	0.31	0.42	1	0.25	0.14	0.24	−0.04	−0.03	−0.05
IM	0.39	0.27	0.29	0.37	0.30	0.26	0.22	0.32	1	0.27	0.38	−0.10	−0.16	−0.14
VF	0.20	0.25	0.30	0.24	0.18	0.20	0.08	0.17	0.28	1	0.40	−0.14	−0.22	−0.03
Canc	0.38	0.23	0.33	0.39	0.37	0.32	0.19	0.34	0.44	0.40	1	−0.21	−0.42	−0.20
O As.	−0.12	−0.01	−0.08	−0.16	−0.12	−0.12	−0.02	−0.11	−0.16	−0.16	−0.29	1	0.25	0.16
S As.	−0.17	−0.11	−0.15	−0.19	−0.21	−0.17	−0.07	−0.13	−0.22	−0.25	−0.49	0.31	1	0.09
Trails	−0.21	−0.06	−0.15	−0.23	−0.24	−0.15	−0.19	−0.17	−0.24	−0.08	−0.31	0.22	0.18	1

Above the diagonal, partial correlations corrected for demographical factors (age and education), below the diagonal, not corrected correlations.

(0.553), visual field (0.620), and trails (0.512), with an unclear clinical meaning. The trails subtest also loaded 0.395 on the 2nd component. This model explained less than 50% of variance (48%), keeping out six components with a variance >5% (three with a variance >5.5%).

Analyzing the scree plot a first inflection point was found at the 5th component (a local minimum into the derivate of the scree plot), and a second one at the 6th component (a local maximum). The model with five components maintained the second component related to unilateral spatial neglect as the model with three components, formed by: cancelation (−0.568), object asymmetry (0.678), space asymmetry (0.758). The first component of the three-component model was mainly divided into two components in this new model: one formed by episodic memory (0.757), sentence recall (0.719), and orientation (0.649) and another formed by sentence reading (0.798), number writing (0.732), and calculation (0.766). Semantics (0.670), imitation (0.646), and visual field (0.532) formed another component. The last component was formed by the trails subtest only (0.875). This model explained 60.5% of variance, keeping out only one component with a variance >5.5% (5.6%); however, it violated the criteria 4a and 4d, because picture naming did not achieve the threshold of a loading >0.4, and its loadings were divided between the component related to language (0.306) and that related to memory (0.351), with a low communality (0.511).

The model with six components differed from that with five only because orientation formed a single component, as shown in **Table 4**, but allowed including all the subtests with an additional variance >5.5%, with each component containing variables with a loading ≥0.4 only on one component. In fact, with respect to the previous model, here, picture naming had a loading >0.4 (0.514) only in the component also formed by sentence recall and episodic memory but not on any other one. The explained variance by this six-component model was 66.1%. All the other eigenvalues showed a variance lower than 5.5%. **Table 4** shows the pattern matrix obtained with the PCA for the identified six components. A total of two of these components were mainly formed by a single task: orientation and executive functions (trails).

Reliability Analysis

We tested the bootstrapped split-half reliability by randomly splitting the data of patients into two subgroups, running the PCA, and comparing the results obtained for the two subsamples. We obtained results similar to those obtained for the entire sample. The scree plots of these two analyses are reported in **Figure 3**, with the first inflection point observed at the 5th component for one PCA, and at the 6th component for the other one. Similar to the main PCA performed on the whole sample of patient, these two PCAs explained the 67 and 68% of variance, respectively. The six-component model satisfied the above-reported criteria in both cases (21). The correlations between the loadings of the subtests in the two subgroups were all statistically significant. Referring to the order of components reported in **Table 4**, the absolute values of R were highly significant ($p < 0.001$); for four components, R was >0.9 ($p < 0.001$), for the 4th component (related to memory) R = 0.86 ($p < 0.001$) and for the 6th component (orientation) R = 0.66 ($p = 0.011$). This reliability analysis allowed also identifying the 95% confidence intervals of the loadings of each subtest with respect to its main component. Only the cancelation and picture naming subtests had an interval crossing the threshold of 0.4 (criterion 4a and 4d), despite achieving in both the subsamples a main loading >0.4.

Then, we performed a PCA on all the data combining patients' and healthy subjects' data: the results did not change with six components overcoming the cutoff, formed by the same

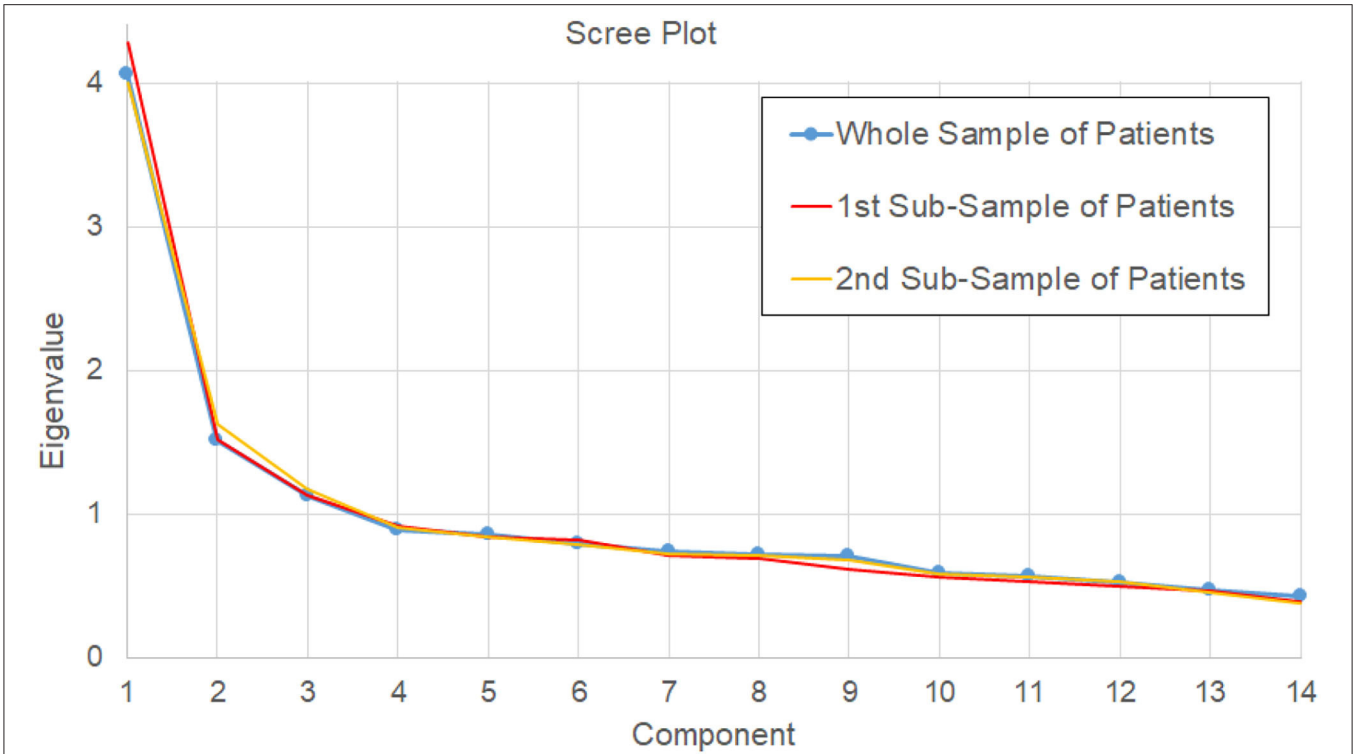

FIGURE 2 | Scree plot of eigenvalues determined by PCA on the 14 scores for the whole sample of patients (main analysis, blue line), and for the two bootstrapped samples of the reliability analysis (red and orange lines).

TABLE 4 | The pattern matrix from the principal component analysis on the patients' sample (in bold the higher value for each task, forming clear aggregation of subtasks with absolute values > 0.4).

OCS Subtask	Components						Communality	95% CI main load
	1	2	3	4	5	6		
Sentence Reading	**0.771**	0.006	0.123	0.093	0.128	−0.159	0.699	0.66–0.76
Number Writing	**0.713**	−0.051	−0.083	0.074	0.032	0.010	0.611	0.64–0.78
Calculation	**0.761**	0.013	−0.129	−0.055	−0.102	0.250	0.678	0.78-0.85
Cancelation	0.115	**−0.430**	−0.166	0.019	0.383	0.241	0.642	0.34-0.64
Object Asymmetry	0.004	**0.852**	0.055	−0.132	0.178	0.211	0.723	0.46–1.00
Space Asymmetry	−0.024	**0.676**	−0.021	0.101	−0.121	−0.201	0.592	0.60–0.96
Trails	−0.083	0.053	**0.921**	0.082	0.000	0.035	0.860	0.91–0.91
Sentence Recall	0.137	0.060	−0.043	**0.721**	−0.161	0.148	0.640	0.65–0.86
Episodic Memory	−0.061	−0.080	0.088	**0.808**	0.111	0.090	0.681	0.80–0.82
Picture naming	0.278	−0.077	−0.056	**0.514**	0.214	−0.155	0.590	0.31–0.73
Semantics	0.175	0.166	0.048	0.078	**0.666**	−0.135	0.556	0.63–0.74
Visual Field	0.107	−0.228	0.202	−0.151	**0.609**	0.149	0.581	0.49–0.70
Imitation	−0.110	0.016	−0.342	0.214	**0.629**	0.076	0.615	0.54–0.68
Orientation	0.092	0.035	0.024	0.230	−0.006	**0.813**	0.792	0.69–0.93

The last two columns report the results of the communality table on the whole sample of patients and the 95% confidence interval of the main load for each subtest obtained by the reliability analysis of the two subsamples of patients.

tasks identified by the main analysis (details are reported in the **Supplementary Materials**). The explained variance of the PCA performed on patients and healthy subjects was slightly increased (67.5 vs. 66.1%), and the number of required rotations was reduced (9 vs. 19). Finally, we repeated this last analysis changing the rotation method using the varimax rotation instead of obliquity rotation and results did not change (for details refer to **Supplementary Materials**).

FIGURE 3 | On the left the original structure of OCS with five domains and on the right the six components identified by the principal component analysis, with arrows reported for values >0.25 according to the legend.

DISCUSSION

Our results showed alterations in all the OCS subtests in patients with stroke with respect to healthy subjects also with high levels of statistical significance, confirming the sensitivity of the tasks into detecting cognitive alterations (5). Also, specificity was confirmed by the significant differences found between patients with left versus right stroke (20).

The PCA identified components quite different from those originally proposed. Hong et al. (9) already proposed a revision of the OCS with three main domains, but simply removing the domain of number and that of praxis. It is important to note that their study was conducted only on patients without unilateral spatial neglect. Indeed, they highlighted the need of studies reviewing the existing five-dimensional domains for improving the structural validity and internal consistency of OCS also for patients with neglect. In our study, which includes also patients with unilateral spatial neglect, one of the domains, independently by the chosen number of components (three, five, or six), was formed by cancelation, object asymmetry, and space asymmetry, which is conceivably related to unilateral spatial neglect. In the original version of OCS, these subtests were associated also with the trails subtest and referred to the domain of attention (subdivided into spatial attention and executive functions). Also in our study, a model based on three components showed the additional loading of the trails subtest in this last domain. However, this model explained only 50% of variance, had a large component including eight subtasks, and excluded three components with an additional variance higher than 5.5%. The models with 5 and 6 components differed from each other only for the orientation subtest that, in the former, was aggregated to the memory domain as in conventional OCS, while, in the latter model, was defined as an independent component. With respect to the five-component model, that with six components had three advantages: (a) it included all the subtests with an additional variance >5.5% (criterion three of (21)); (b) each component contained variables with a loading ≥0.4 (criterion 4d of (21)); and (c) variables loaded relatively high on only one component and low on the others (criterion 4d of (21)).

The bootstrap split-half analysis confirmed the reliability of the model with six components, with statistically significant correlations between the results of the two PCAs performed on patients' subsamples. Furthermore, the 95% confidence intervals showed high values of loadings for each subtest only on one of the six components, in keeping with the above-defined criteria for interpreting PCA results (21). The robustness of our results was also confirmed by the fact that they did not change by varying the rotation method of the PCA. Finally, when patients'

data were analyzed together with those of healthy subjects, the PCA identified the same six components of the main analysis (as detailed in the **Supplementary Materials**).

Differences With Original OCS Structure

Independently of the number of components, our study also highlighted some differences with respect to the original classification, and, in particular, the existence of a domain related to unilateral spatial neglect, the aggregation of arithmetic subtaskswith that of sentence reading subtest, and the unexpected aggregation of semantics subtest with the visual field subtest. First of all, our PCA identified a first component mainly formed by the sentence reading, number writing, and calculation subtests. Associations between some aspects of reading and arithmetic, two cognitive skills learned during schooling, have long been supported by behavioral, brain lesion, and functional brain imaging studies (18, 19). The relationships that exist between some specific aspects of arithmetic and left hemisphere language were also reported by cognitive development research. These studies have showed that children's reading and mathematics activity converged in prefrontal cortex across multiple tasks, but dissociated in temporal and parietal cortices, showing similarities to the adult pattern of dissociation (18). As posited by the "triple-code model" of number processing (22–24), of the three systems of representations of numerical information (quantitative, verbal, and visual), the quantitative system is unique to numerical processing, whereas the verbal and visual systems share aspects with language processing. We note here that picture naming and semantics did not directly contribute to this component. This first latent component, therefore, was considered to relate to "Language and arithmetic."

In our study, the semantics subtest was found to be mainly involved in another component together with visual field (already in the 3-component model) and praxis (in the models with five and 6 components). Though this may seem surprising, it should be noted that the semantics subtest in the OCS is assessed by asking the patient to point with the hand to the drawing representing a word read by the researcher. This means that the task in essence is a picture pointing task. Some evidence suggests an interaction between the ventral visual-perceptual and the dorsal visuomotor brain systems during the course of object recognition (25). In the praxis task, the patient is required to mimic the gestures performed by the researcher. Furthermore, in the visual field subtest, the patient is asked to look at the examiner's nose and point to the moving hand. Since all these tasks could be hence related to visual attention and motor responses, this third component can be considered as related to "Visuomotor control."

The domain of memory was quite preserved in our models, with a component including sentence recall and episodic memory, but also the picture naming subtest (that in the original OCS was associated with language domain). The differences between our five- and six-component models are mainly related to this domain. In the five-component model, the picture naming subtest had a low loading (0.351, <0.4) and this component also included the orientation subtask (loading: 0.649). In the 6-component model, the picture naming subtest had a high loading (0.514) whereas the orientation subtest formed a single sub-test component (loading: 0.813). Hence, picture naming resulted related to semantic memory. As highlighted by a recent study, not all putative tests of semantic and episodic memory may necessarily measure the hypothesized construct, and there is a conceivable overlapping between these cognitive functions (26). The orientation subtask could be associated with memory domain or resulting in a separate domain factor instead of forming a part of a wider memory classification. For basic orientation to time and place to be impaired, patients usually present a severe cognitive impairment (even delirium or related to pre-existing dementia). Similarly, other cognitive scales consider orientation as a stand-alone cognitive domain, such as the Mini-Mental State Examination (based on five different domains: orientation, working memory, memory recall, language, visuospatial motor functions and a fifth domain related to attention, concentration, and calculation) and the Montreal Cognitive Assessment (based on ten domains) (27).

The main difference in our analyses with respect to the domains of the original version of OCS was the presence of a component clearly related to the presence of "Unilateral spatial neglect," being formed by the cancelation, object asymmetry, and space asymmetry measures of the broken heart subtest. This component is therefore referred to as "Spatial exploration function." As shown by the comparison of patients with left and right stroke, the latter ones had a more severe neglect, whereas the former had a score with the opposite sign. Visual field partially contributed to this component, but mainly to the visuomotor control domain. On the other hand, cancelation had a slight contribution also to visuomotor control domain, probably in terms of visuomotor attention. The presence of unilateral spatial neglect also reduces the motor skills re-acquired by patients with stroke during neurorehabilitation (15). It should be noted that in the OCS, peripersonal, but not personal, neglect is considered, and these two deficits may recover independently (28).

Finally, the trails subtest marked another component which may be interpreted as related to "Executive functions," a domain considered as independent also in the Montreal Cognitive Assessment (27).

Importantly, neither the model with three components nor that with six components defined attention as a separate domain. This could be due to different intertwined reasons. Attention can be seen as a control function with a cross-test influence. At the same time, many different types of attention exist (selective attention, divided attention, sustained attention, and so on) and their impairment could lead to different cognitive deficits, and in turn, they can influence the performance of other cognitive functions.

Our results could be summarized as follows. Our PCA showed that some differences in how sub-tests should be aggregated into domains, with respect to the original version of OCS. The model with three principal components matched the criterion of eigenvalues >1, which was in line with previous results (9, 13), had a clear meaning, but it could be only poorly useful because too simple (explaining only the 50% of variance). The model with

five components matched the criterion of the first inflection point to determine the number of components, but the picture naming subtest had loadings on two components instead of only one. The model with 6 components matched the criterion of including components with an additional variance higher than 5.5%, and it was associated with a second inflection point. With respect to the five-component model, this one just associated a specific component to the orientation subtest, and it solved the problem of loadings on more components, facilitating the interpretability of results (criterion 4d).

Implications of the Present Analyses for the Clinical Use of OCS

Our results highlighted some important warnings that could be helpful for clinicians using the OCS. First of all, the domain called "Number" was found to be only related to that of language. Then, the subtest called semantics and hence referred to language includes a picture pointing subtask and may be related to visuomotor deficits even more than language deficits. Similarly, praxis is evaluated using the imitation subtest that requires visuomotor abilities. The picture naming subtest also includes the involvement of memory function in terms of semantic memory and loaded on this domain. Orientation proved very important and was found as a separate factor, suggested to be related to severe cognitive impairment. Finally, attention was already divided in the original OCS partly into executive functions and partly into visuospatial attention: the measures of cancelation task, space, and object asymmetry of the broken heart sub-test were clearly related to spatial exploration and hence to the possible presence of unilateral spatial neglect, whereas the visual field subtest was more related to visuomotor control.

Though the theoretical model of OCS can mainly be considered preserved, a more complex distribution of the weights of each subtest into different domains emerged from our analyses. Clinicians could effectively continue to use the OCS for the early assessment of cognitive deficits in patients with stroke, adopting the classical version of the visual snapshot. However, we propose here a slightly different version with the aim to take into account the results of our analyses. This new snapshot of OCS maintains the same subtests, subscores, and materials (test booklet and patient pack) but is redefined based on the alternative approach related to the six domains found in the present PCA (**Figure 4**): language and arithmetic, memory, visuomotor control, orientation, spatial exploration, and executive functions. In clinical practice, the new snapshot may be more useful for rehabilitation treatment compared to the original one, as it allows the team immediately focusing on the impaired cognitive domain such as attention (cancelation results in selective attention), spatial orientation (egocentric versus allocentric neglect), and executive functions. The impairment of these cognitive abilities plays a central role in rehabilitative recovery.

Study Limitations

The findings of our study should be considered in the light of some limitations. The main limit is that being focused on a principal component analysis of OCS, we did not use other cognitive assessment scales. Another limit of our study is the absence of information about lesion size that is an important factor related to stroke severity. However, previous studies already compared OCS scores with other cognitive assessment tools, proving the validity and reliability of OCS. Furthermore, we did not correct the data for the age or schooling of participants to simplify an already complex analysis (these corrections were limited to the correlation heatmap). This choice was due to two main reasons: (1) previous results showed that demographic variables had quantitatively small effects on the scores of OCS tasks (3),(2) a previous study showed that these effects could be modeled with different equations among tasks (3), (3) we were more interested in within-subject clusterization of items into domains than in between-subject comparisons.

It is important to note that the healthy group enrolled in our study was significantly younger and more schooled than the patients. This could be considered as a sampling bias of our study, related to the difficulties of finding subjects without any neurological or visual deficits over 70 years old (that was the mean age of patients). On one hand, according to the aim of this study, it was more important that the answers of healthy group were not affected by any deficits than matching age and schooling, as done in the original study about OCS, in which the same sampling bias was already present (4). On the other hand, the literature lacks a matched case–control study conducted resampling the groups by pairing age and schooling, despite it will probably reduce the width of samples. Then, the cognitive functions of patients widely vary among acute, subacute, and chronic phases of stroke. In our study, the median time from the acute event and the cognitive screening was 6 days (with an interquartile range of 15 days); so, our sample is mainly the representative of acute and subacute population, when the OCS is mainly used to define a personalized rehabilitation program.

So, the OCS is a helpful screening tool for cognitive functions, but its meaning and utility may depend on its interpretation that is left to the clinicians and it may depend on the stroke phase in which the patient is, especially in some domains. In particular, the assessment of orientation could be fundamental in the acute phase and less in the chronic one. On the other hand, an orientation deficit could also be detected in the chronic phase, being clinically relevant because attributable to different specific processes (e.g., degenerative processes). The results of our study could be helpful for helping clinicians in this interpretation because improved the definition of the cognitive domains covered by OCS subtests.

CONCLUSION

Overall, the Oxford Cognitive Screen has already been validated as a useful tool for an easy and early screening of cognitive deficits in patients with stroke (4, 5). With the analyses reported in our study, we provided important further information

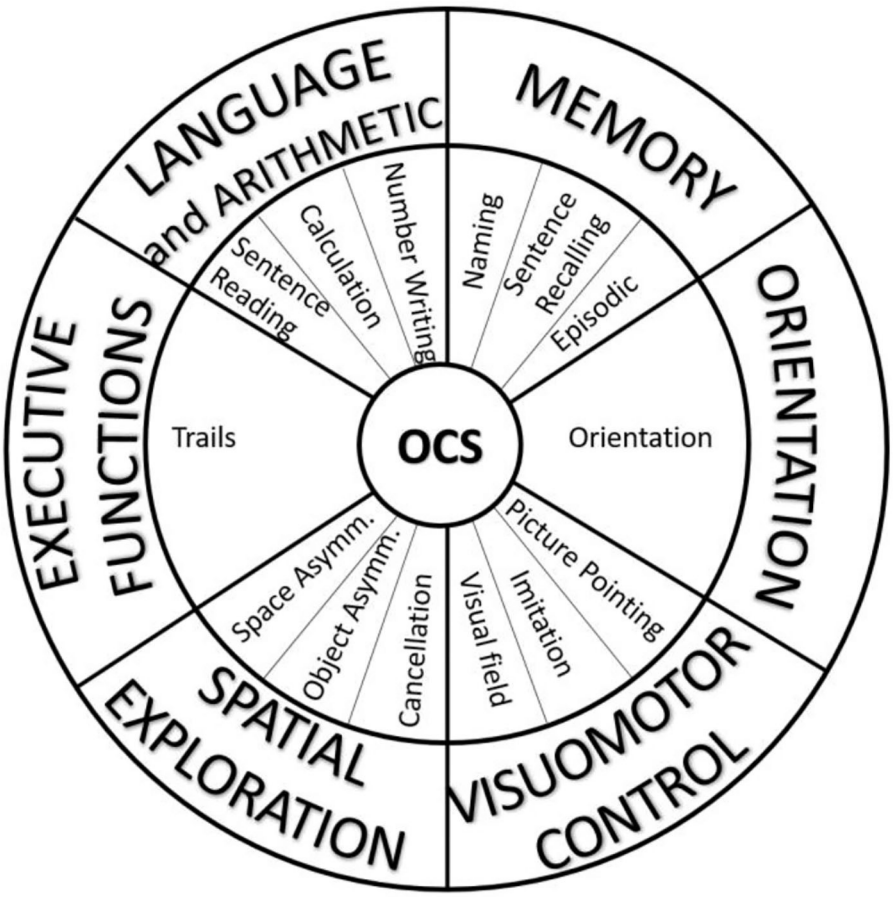

FIGURE 4 | The alternative visual snapshot of OCS developed in accordance with the results of principal component analysis. The subtasks (middle ring) remain the same, but the domains (external ring) are different from the original version.

about the meaning of the OCS subtests and their weights on specific cognitive domains. Even though the subtests of OCS are relatively simple, and each aims to measure a particular domain, nevertheless, a wider set of functions is involved in their execution. This pertains most clearly to the required motor responses and visuomotor coordination in some of the tasks. Based on these analyses, we proposed a new visual snapshot expressing the OCS subtests as a function of the six domains found: language and arithmetic, memory, visuomotor control, orientation, spatial exploration, and executive functions. We hope that this further information and caution about the OCS domains and/or the refinement of a new snapshot for the OCS may favor its clinical use by improving the tuning in the description of the patient's cognitive impairments.

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 National Research Ethics Committee (UK). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MM, and ND conceptualized the study. LA supervised the data collection. MI analyzed the data and wrote the first draft of this manuscript. MM, ND, and PZ supervised the study and provided important contributions to the draft. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Challenging the Vestibular System Affects Gait Speed and Cognitive Workload in Chronic Mild Traumatic Brain Injury and Healthy Adults

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People with persistent symptoms after mild traumatic brain injury (mTBI) report imbalance during walking with head movements. The purpose of this study was (1) to compare usual walk gait speed to walking with head turns (HT) between people with mTBI and controls, (2) to compare the cognitive workload from usual walk to HT walk between groups, and (3) to examine if gaze stability deficits and mTBI symptoms influence gait speed. Twenty-three individuals (mean age 55.7 ± 9.3 years) with persistent symptoms after mTBI (between 3 months to 2 years post-injury) were compared with 23 age and sex-matched controls. Participants walked a 12-inch wide, 60-foot walkway when looking ahead and when walking with HT to identify letters and their colors. Gait speed during usual walk and HT walk were calculated. Pupillary responses during both walks were converted to the Index of Cognitive Activity (ICA) as a measure of cognitive workload. Gaze stability was examined by the dynamic visual acuity (DVA) test in the yaw plane. The post-concussion symptom scale (PCSS) was used to collect symptom severity. Within group analysis showed that gait speed was lower during HT walk compared to usual walk in the people with mTBI ($p < 0.001$) as well as in controls ($p < 0.001$). ICA was higher with HT compared to usual walk in the mTBI group in the right eye ($p = 0.01$) and left eye ($p = 0.001$), and in controls in the right eye ($p = 0.01$) and left eye ($p = 0.01$). Participants in the mTBI group had slower usual ($p < 0.001$), and HT gait speed ($p < 0.001$) compared to controls. No differences were noted in ICA in the right or left eye during usual walk and HT walk between groups ($p > 0.05$). DVA loss in the yaw plane to the right and left was not different between groups ($p > 0.05$) and were not correlated with gait speed. PCSS scores were correlated with usual walk ($r = -0.50$, $p < 0.001$) and HT gait speed ($r = -0.44$, $p = 0.002$). Slower gait speed, poorer stability, and higher cognitive workload during walking with head turns may reduce community participation in people with mTBI and persistent symptoms.

Keywords: mild traumatic brain injury, persistent symptoms, dynamic visual acuity, cognitive workload, gait speed, usual walk, walking with head turns

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INTRODUCTION

Mild traumatic brain injury (mTBI) is defined as a "complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces" typically operationalized by a Glasgow Coma Scale of 13–15 (1, 2). Symptoms after a mTBI include dizziness, blurry vision, and imbalance, often due to injury to the vestibular system and its extensive connections with the visual system (3, 4). The number of people with persistent symptoms, including symptoms that evolve or emerge beyond the 3-month period since injury has been reported to be from 15% and up to 82% in the mTBI literature (5–8).

Of the various symptoms noted after chronic mTBI, head turning during walking is shown to have a destabilizing effect on dynamic balance (9). Individuals with vestibular dysfunction have significantly worse postural control, which is evident in dual task conditions where balance and cognitive tasks are combined (10–12). Gait speed and balance control are reported to be poorer in people with mTBI during dual task activities involving balance and cognitive tasks (13–16). A recent study by Gagne et al. had young adults with mTBI who were between 4 and 15 weeks post-injury participate in various locomotor tasks such as level walking, stepping over obstacles, and tandem walking with various cognitive conditions. They report slower gait speed in the mTBI group under dual task conditions (15). However, no studies have included a task such as head turns, which challenges the vestibular system, in combination with a cognitive task such as identifying letters while walking. A dual task of this nature is frequently encountered in daily life while grocery shopping or crossing the street. A lab-based test that mimics activities of daily life may allow us to explore the impact of head turns and consequent influence on balance control.

The vestibular system with calibration from the visual system, is also responsible for maintaining a stable gaze when the head or surrounding environment are moving (17). In people with persistent symptoms after mTBI, reports of blurred vision while driving have been reported by 30% of people (18). Wright et al. examined 14 young adults in the post-acute stage of concussion (within 6 months) and report that visual motion resulted in significantly poorer dynamic balance control compared to controls (19). In young adults with a previous history of concussion (>2 years), greater loss of visual acuity with head movements have been noted as compared to heathy controls (20, 21). However, the effect of gaze instability on balance control during walking has not been explored. The impact of persistent symptoms, gaze instability, and the destabilizing effect of head turns on dynamic balance can increase the mental effort needed to complete daily walking activities.

Cognitive workload is defined as the mental effort that is needed to execute a task (22). When task demand is lower than the cognitive resources, the task is executed accurately. When task performance requires increased cognitive processing, performance is shown to decline (22). Pupillary response has shown to be a reliable and valid measure of cognitive workload in healthy individuals as well as in people with neurological conditions and is responsive to change from single task to dual task postural balance conditions (23–26). Three studies have assessed pupillary changes following brain injury during performance of a cognitive task (27–29). Koelewijn et al. found no changes in task-evoked pupillary response (TEPR) in a speech perception task between individuals with brain injury and controls. However, higher accuracy in the performance of the speech perception task was associated with greater pupil dilation (28). Ayala and Heath revealed larger TEPR during anti-saccade movements in patients with a history of concussion compared to controls (27). Tapper et al. extended the findings of the previous studies by comparing mean pupillary diameter during dual-tasking between individuals without and with concussion. They found that individuals with a history of concussion exerted larger mean pupillary size during tasks of lower cognitive demand, compared to controls (29). Although there is encouraging evidence that pupil dilation can be used as a sensitive measure of cognitive workload in mTBI, no studies have evaluated pupillary responses in dual task walking conditions.

Therefore, the purpose of this study was (1) to compare the gait speed during usual walk and walking with head turns (HT) while performing a cognitive task between people with mTBI and controls; (2) to examine the associated cognitive workload measured by pupillary response during the usual walk and walk with HT, and (3) to examine the relationship between vestibular function (measured by gaze stability), symptom severity [measured by the post-concussion symptom scale (PCSS)], and gait speed. Our hypotheses were that because of symptoms experienced and gaze instability (1) people with mTBI will have decreased gait speed during usual walk which will further decrease during walk with HT and the cognitive task compared to controls, (2) people with mTBI will show increased cognitive workload, indexed by pupillary response, during usual walk which will further increase during walk with HT and cognitive task compared to controls, and (3) PCSS scores and gaze instability will correlate with usual and HT gait speed.

MATERIALS AND METHODS

Study Design

This was a cross-sectional, comparative study conducted at the University of Kansas Medical Center. The study protocol was approved by the University's Institutional Review Board.

Participants

Most participants with mTBI were recruited from the Neurology clinic, with the assistance of a neurologist (MR) (n = 21). Additionally, the Healthcare Enterprise Repository for Ontological Narration (HERON) (30, 31) search discovery tool was used to identify persons with mTBI who were seen at the university hospital and who met inclusion and exclusion criteria (n = 2). Participants were included if they were: (1) Between 40 and 80 years of age, (2) Had a diagnosis of mTBI coded by ICD-10 (S06.0X0A- S06.0X9S) criteria, which include a history of traumatic brain injury and the presence of 3 or more of the following 8 symptoms: (1) headache, (2) dizziness, (3) fatigue, (4) irritability, (5) insomnia, (6) concentration or (7) memory difficulty, and (8) intolerance of stress, emotion, or alcohol. (3) Had persistent symptoms from their injury (determined with the

FIGURE 1 | Experimental setup of the walking path which was 60 feet long and 12-inches wide. Photograph used with permission.

PCSS, a subjective self-report), (4) Were between 3 months to 2 years since their injury. The time since injury was determined with feedback from the neurologist based on patient population seen in the clinic.

Participants with mTBI were excluded if they (1) Had a diagnosed neurological problem such as stroke, Parkinson's disease, Multiple Sclerosis; (2) History of a visual disorder prior to the injury such as cataracts; (3) History of vestibular disorder such as vestibular neuritis, Meniere's disease prior to the mTBI, (4) Had lower extremity injury, recent surgery or pain that would impact the walking tests, (5) Had a history of cancer and received chemotherapy, or (6) If they were involved in litigation due to the injury. Exclusion criteria 5 was based on the independent effect of chemotherapy on the vestibular system (32, 33), and 6 was based on increased stress levels in people involved in litigation which may affect performance (8).

Healthy controls with no history of mTBI were recruited through word-of-mouth from the campus, and from the community, and were individually matched for sex and age (±5 years). Like participants with mTBI, healthy controls were excluded if they had prior neurological disease, visual dysfunction, or pre-existing vestibular disease such as vestibular neuritis or Meniere's disease; if they had lower extremity pain or recent surgery; and had a history of cancer and received chemotherapy.

Study Procedure

Participant eligibility was verified using a phone screen and eligible participants were scheduled for a testing session. All participants were informed to wear comfortable shoes and bring their corrective eyewear to the testing session. After completing informed consent, demographic information, medical history such as height, and weight; manual muscle test and sensory testing were completed. For people with mTBI, the date of injury was collected.

Walking Tests

The walking tests were conducted in a quiet hallway with no windows and consistent lighting where participants had to walk a 60-foot walkway that was 12-inches wide and marked by tape (**Figure 1**). Before initiating the tests, participants were informed of the two walking conditions and asked to identify letters and colors to assure that they did not have color blindness. First, they performed 3 trials while looking ahead with instructions to stay within the 12-inch path to the best of their ability. Next, participants performed 3 trials of walking with head turns from side to side to identify letters that were 1.5 inches in size and their colors. In this motor-cognitive dual task activity, there were 12 letters that were affixed ∼5 feet apart from each other on the walls of the hallway. Participants were instructed to turn their head to identify the letters and colors instead of reading the letters from a distance. The first trial started at one end of the walkway while the second trial started from the other end, hence they could not memorize the letters by the third trial. Time to walk the path, steps outside the path, and number of missed letters were collected for each trial and the average is reported. The entire foot had to be outside of the taped path to be considered "outside the path." Gait speed was calculated for usual walk and HT walk as (18.28 meters/time to walk the path) in meters/second.

Index of Cognitive Activity (ICA)

Participants wore the Tobii Pro 2 glasses (Tobii Technology AB Sweden.) to capture pupillary responses during the walking tests. Before each walking test, the glasses were calibrated with the participant focusing on the center of the calibration target which was affixed to the wall at eye level. Participants stood between 3 and 4 feet from the wall during the calibration and had to focus on the target until the calibration process was completed. After completing the walking tests, the pupillary response was extracted at 60 Hz using EyeWorks Analyze™ (Eye Tracking LLC, California, USA) software to calculate the Index of Cognitive Activity (ICA). Conventional measures of pupillary response that compare the averaged raw pupillary diameter after stimulus onset to the averaged baseline pupillary diameter (i.e., TEPR), pose some challenges. First, the light reflex may confound extraction of the TEPR, especially in experimental conditions where ambient lighting or luminosity of the screen settings cannot be entirely controlled (34). Second, changes in camera angle and eye movements may interfere with raw pupillary recording (35, 36). The Index of Cognitive Activity (ICA) is calculated from the number of rapid changes in pupillary diameter rather than the difference between averaged pupillary diameter before and after stimulus onset (37, 38). The ICA computes the average number of abrupt discontinuities in pupil size per second and transforms these values into a continuous scale ranging between 0 (no cognitive workload) and 1 (maximum workload). The average ICA of the 3 walking trials for each walking condition has been reported.

Dynamic Visual Acuity

The Bertec® Vision Advantage™ (Bertec® Corporation, Columbus, Ohio, USA) was used to administer the Dynamic Visual Acuity Test (DVAT). It includes a wireless inertial

measurement unit mounted in the center of the participant's forehead using an elastic headband with a 3-axis integrating gyro (Yost 3-Space Wireless Sensor, Yost Labs, Portsmouth, Ohio, USA) to determine rotational head velocity in the yaw and pitch planes (39). Details of testing have been described in a previous paper (9). In brief, visual acuity was determined in a static head position followed by perception time testing. Based on these parameters, dynamic visual acuity testing was individualized for each participant where they had to generate active rotational head movements to 20 degrees from midline in each direction at a target velocity of 100 degrees per second (with a range from 85 to 120 degrees/s). The outcome variable for the DVAT was loss of lines in logMAR, calculated as the difference between dynamic and static visual acuity, to the right and left in the yaw plane. Higher logMAR values indicate poorer dynamic visual acuity, with loss of more than 0.2 logMAR (>2 lines of loss) considered as clinically significant (40, 41).

Symptom Severity

The post-concussion symptom scale (PCSS) is a 22-item self-report measure of symptoms experienced. The severity of symptoms experienced is rated on a Likert scale from 0-indicating "no" symptom to 6-indicating "severe" complaint. The maximum PCSS score is 132 with higher scores reflecting either more symptoms or higher severity of symptoms (42, 43). The PCSS has 4 subgroups; somatic, emotional, cognitive, and sleep.

Statistical Analysis

Data were inspected for normality using histograms and the Kolmogorov-Smirnov test of normality. Independent sample *t*-tests were used to compare variables that were normally distributed between groups (age, BMI, DVA loss right, and left in LogMAR, gait speed), while data that was not normally distributed were compared using Mann-Whitney U test (ICA for each eye during usual walk, HT walk, and PCSS). Differences in ICA were assessed between the mTBI and control groups adjusting for gait speed using multiple linear regression analysis. Log transformation was used on ICA to satisfy the normality assumption. The analyses were carried out for both usual walk and HT walk and for the right and left eye separately. Paired samples *t*-tests were used to compare usual and HT gait speed within groups while Wilcoxon signed rank tests were used to compare usual and HT walk ICA values within groups. Pearson's correlations were used to examine the relationship between DVA loss and gait speed in both conditions where the data satisfied normality assumptions, while Spearman's rank correlations were used to examine the relationship between PCSS and gait speed in both conditions where data did not satisfy normality assumptions. Correlations were interpreted as fair (0.25–0.50), moderate (0.5–0.75), and good (>0.75) (44). All statistical analyses were conducted using SPSS for Windows version 25.0 (SPSS Inc., Chicago, USA) and *p*-value <0.05 were considered statistically significant.

RESULTS

Participant Characteristics

Forty-six individuals completed the study: 23 in the mTBI group (19 females and 4 males) and 23 age and sex-matched controls. The mean duration since injury was 33.2 ± 5.1 weeks (range: 12–92 weeks). There were no differences in demographics between the groups, participants with mTBI had higher PCSS scores ($p < 0.001$) compared to controls. Three control subjects had diagnosed hearing loss (two were genetic) and three had a prior history of migraines. In the mTBI group, two participants complained of tinnitus since the injury, two had a prior history of migraines, and three were wearing prescription glasses with prisms. No strength deficits were noted with manual muscle testing, sensation in the feet was impaired in one control and two persons with mTBI (**Table 1**).

Single and Dual-Task Gait and ICA Characteristics

Within group comparisons show that HT gait speed was lower compared to usual gait speed in the control ($p < 0.001$) and the mTBI group ($p < 0.001$) (**Figure 2**). The ICA was higher with HT compared to usual walk for controls in the right eye ($p = 0.01$) and left eye ($p = 0.01$) and for people with mTBI in the right eye ($p = 0.01$) and left eye ($p = 0.001$) (**Figure 3**).

Between group comparisons show that participants with mTBI had slower usual gait speed ($p < 0.001$), slower HT gait speed ($p < 0.001$) (**Table 2**, **Figure 2**) and took more steps off the path during usual walk and HT walk compared to controls (**Figure 4**). Participants with mTBI missed more letters (range: 0–5) compared to controls (range: 0–1.3), $p = 0.48$. The ICA for the right and left eye were not different between groups (**Figure 3**). After adjusting for differences in usual walk gait speed, ICA was not different between the mTBI and control groups for the right eye ($p = 0.7$) or left eye ($p = 0.51$). Likewise, no differences were seen in ICA after adjusting for baseline HT gait speed for the right ($p = 0.9$) or left eye ($p = 0.7$). Dynamic visual acuity in the yaw plane was not different between groups ($p > 0.05$). Correlations between right DVA loss and usual walk gait speed ($r = 0.16$, $p = 0.29$), left DVA loss and usual walk gait speed ($r = -0.05$, $p = 0.75$), right DVA loss and HT gait speed ($r = 0.26$, $p = 0.08$), and left DVA loss and HT gait speed ($r = 0.22$, $p = 0.14$) were not significant. Correlations between right eye ICA and usual walk speed ($r = -0.08$, $p = 0.59$), left eye ICA and usual walk speed ($r = -0.03$, $p = 0.87$), right eye ICA and HT gait speed ($r = 0.07$, $p = 0.66$) and left eye ICA and HT gait speed ($r = 0.12$, $p = 0.44$) were not significant, however, PCSS score was moderately correlated with usual gait speed ($r = -0.5$, $p = 0.001$) and HT gait speed ($r = -0.44$, $p = 0.002$) (**Figure 5**). All subgroups of the PCSS were correlated with gait speed ($p < 0.05$). The somatic subgroup showed moderate correlations with usual walk ($r = -0.57$, $p < 0.001$) and HT gait speed ($r = -0.55$, $p < 0.001$), and the remaining subgroups showed fair correlations.

TABLE 1 | Participant characteristics between mTBI and control groups.

	mTBI group ($n = 23$)	Control group ($n = 23$)	*p*-value
Age (years)[a] (mean ± SD)	55.70 ± 9.3	55.13 ± 9.1	$p = 0.84$
Sex (female/male)	19/4	19/4	
BMI (kg/m^2)[a] (mean ± SD)	31.4 ± 7.9	28.77 ± 6.5	$p = 0.22$
Weeks since injury	33.23 ± 5.1	NA	
Right DVA loss (LogMAR)[a] (mean, SD)	0.21 ± 0.11	0.20 ± 0.09	$p = 0.78$
Left DVA loss (LogMAR)[a] (mean, SD)	0.21 ± 0.09	0.21 ± 0.11	p = 0.98
Post-concussion Symptom Scale[b] (median, range)	58.50 (9–110)	2 (0–37)	$p < 0.001$*

mTBI, mild traumatic brain injury; DVA, dynamic visual acuity.
[a]Indicates comparisons using independent sample t-tests.
[b]Indicates comparisons using Mann–Whitney U test.
**Indicates significant differences between groups.*

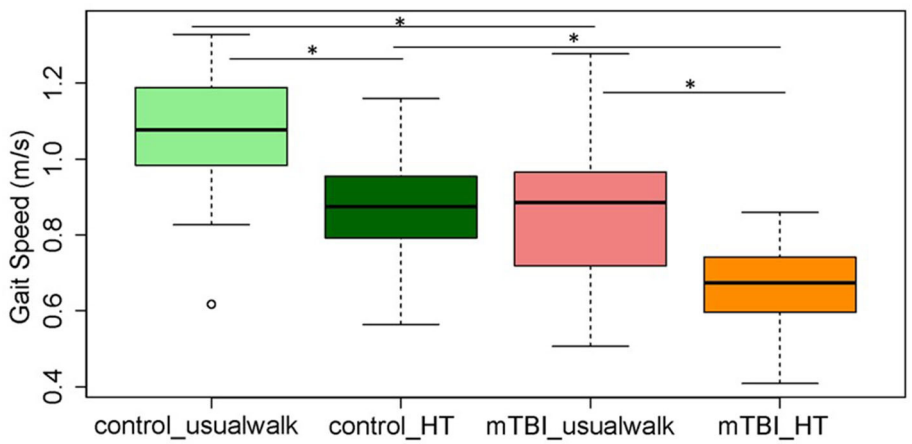

FIGURE 2 | Comparisons of average gait speed between and within the mTBI and control groups during usual walk and walking with head turns. *Indicates significant differences between and within groups. mTBI, mild traumatic brain injury; HT, head turns.

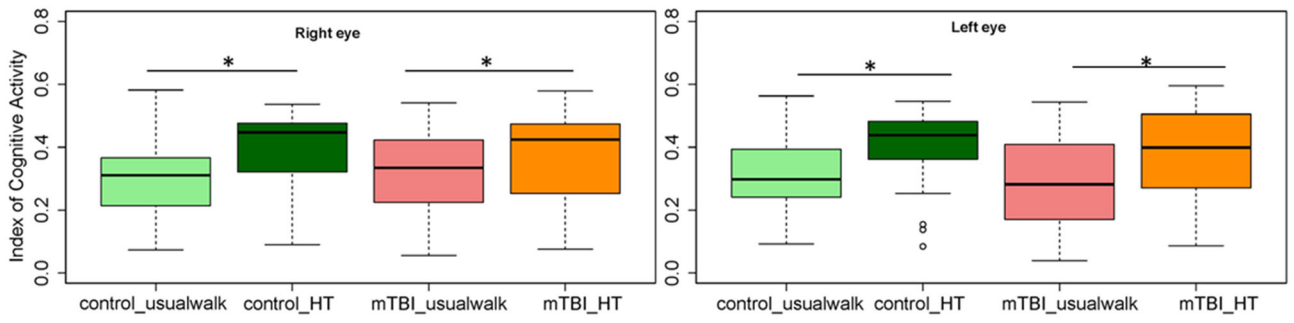

FIGURE 3 | Comparisons of the Index of Cognitive Activity of the right and left eye within groups and between groups in the usual walk and head turn walk conditions. mTBI, mild traumatic brain injury; HT, head turn. *Indicates significant differences within groups.

DISCUSSION

In this study we examined gait speed in usual walk and walking with head turns while performing a cognitive task and explored the associated cognitive workload in each condition, the effect of gaze instability, and symptom severity on gait speed in people with persistent symptoms after mTBI. Results of this study show that during the performance of a challenging walking task where people had to walk within a specified narrow path, those with mTBI and higher symptom severity had significantly slower gait speed compared to age matched controls. The walking with head turns that included a cognitive task of naming letters and colors

TABLE 2 | Differences in gait speed and cognitive workload between participants with mTBI and controls.

	mTBI group ($n = 23$)	Control group ($n = 23$)	p-value
Usual walk gait speed (m/s)[a]	0.86 ± 0.21	1.08 ± 0.17	$p < 0.001$*
Head turn gait speed (m/s)[a]	0.67 ± 0.11	0.86 ± 0.16	$p < 0.001$*
ICA- right eye-usual walk[b] (median, IQR, 95% CI)	0.33 (0.24) (0.26, 0.38)	0.31 (0.16) (0.25, 0.36)	$p = 0.59$
ICA- right eye-HT walk[b] (median, IQR, 95% CI)	0.42 (0.22) (0.29, 0.43)	0.45 (0.16) (0.33, 0.45)	$p = 0.56$
ICA- Left eye-usual walk[b] (median, IQR, 95% CI)	0.28 (0.26) (0.22, 0.35)	0.29 (0.17) (0.26, 0.36)	$p = 0.68$
ICA- Left eye-HT walk[b] (median, IQR, 95% CI)	0.39 (0.27) (0.31, 0.44)	0.44 (0.14) (0.33, 0.45)	$p = 0.96$

[a]*Indicates comparisons using independent sample t-tests and is expressed as mean ± standard deviation.*
[b]*Indicates comparisons between groups based on Mann–Whitney U test and is expressed as median, interquartile range, and 95% CI.*
**Indicates significant differences between groups. One person in the control group had missing ICA data.*

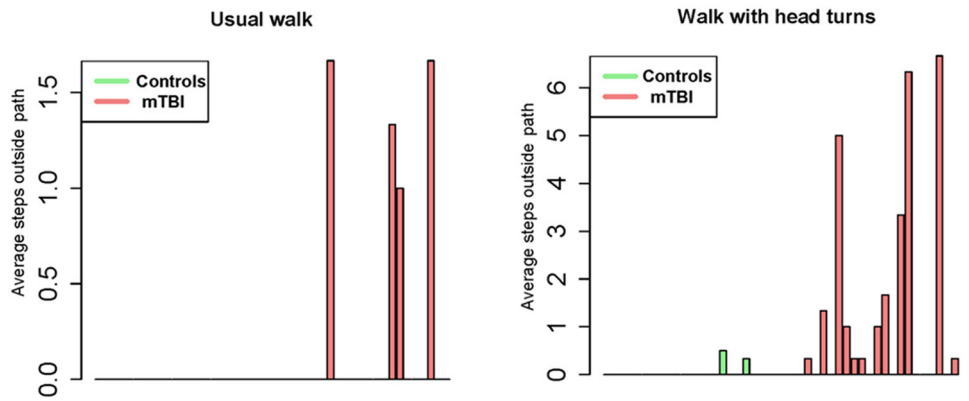

FIGURE 4 | Bar graph representation of steps taken outside the 12-inch pathway during usual walk and walking with head turns between controls and participants with mTBI.

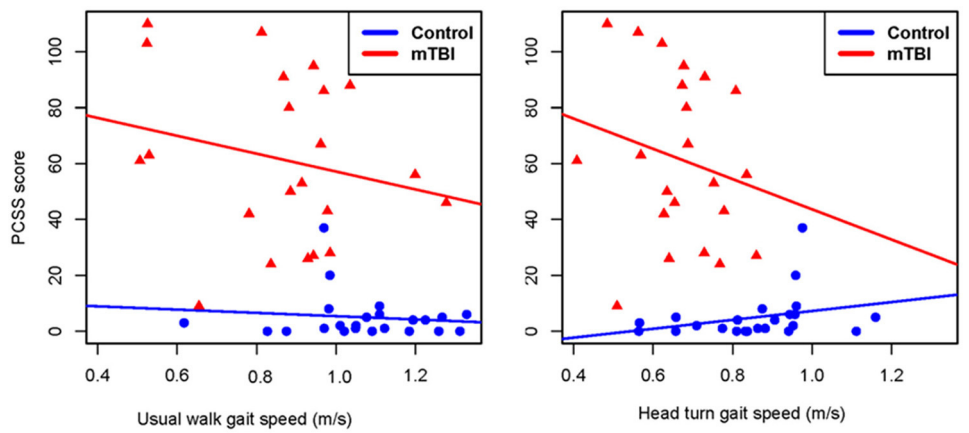

FIGURE 5 | Correlation plots showing the relationship between gait speed during usual walk and head turn walk and post-concussion symptom severity in people with mild traumatic brain injury and controls. PCSS, post-concussion symptom scale; mTBI, mild traumatic brain injury.

resulted in both groups reducing their gait speed, however, the mTBI group continued to have significantly lower gait speed compared to the control group. Pupillary response, reported by the Index of Cognitive Activity (ICA) increased from usual walk to the walk with HT condition in both groups, however, did not differ between groups. Gaze stability did not correlate with gait speed in either walking condition, however higher severity of post-concussion symptoms was associated with slower gait speed in both walking conditions.

Gait speed is an important measure of function and a powerful predictor of quality of life, disability, survival, cognitive decline and falls (45). However, walking as an activity is usually combined with cognitive tasks in daily life such as grocery shopping, walking across the street, or in a park where head turns are necessary. Studies in the younger mTBI population due to sports related injury have shown that motor-cognitive dual tasks result in slower gait speed immediately after injury (46, 47), as well as in the chronic stage of injury (14, 15, 48–50). Gagne et al. found slower gait speed in young adults (average age 22 years) compared to age matched controls, during various walking and cognitive dual tasks, although their subjects had normal cognitive test results and were considered "recovered" with no persistent symptoms (15). Likewise, Fino et al. found that concussed athletes (18–20 years of age, $n = 4$) had larger dual task costs in turning speed and stride time compared to controls when they were examined within 6 weeks of injury (46).

Studies in the middle-age and older adult population are limited but nonetheless very important as these age groups face different challenges after injury. Results of this study show that gait speed (age: 45–65 years) was significantly slower in the mTBI population and it decreased further with head turns and the cognitive task, compared to controls. On average, the gait speed in the mTBI group with HT walking was 0.67 m/s compared to 0.86 m/s during usual walk, which reflects the task difficulty of staying in a narrow path while scanning and walking. Fino et al. examined gait speed and turning dynamics in 14 adults (average age 38 years) with persistent symptoms after mTBI (>3 months post-injury) while walking laps. They report that participants with chronic mTBI had slower gait speed and impaired head stabilization during turning compared with controls which was correlated with higher symptom severity (47). The association between post-concussion symptoms, gait speed, and dynamic balance has been studied. Our group has shown that higher symptom severity is associated with poorer performance on the functional gait assessment, a test of dynamic balance in chronic mTBI (9). Kleffelgaard et al. report higher symptom severity (measured by the Rivermead post-concussion questionnaire) was associated with persistent gait and balance deficits measured by gait speed, the dynamic gait index and the 6-min walk test, 4 years after injury (51), and people with mTBI (3 months post-injury) who experienced more dizziness related disability had poorer performance on balance (Balance Error Scoring System) and mobility (HiMAT) tests (52). Results of this study confirm previous study findings, showing that higher symptom severity is associated with slower gait speed.

Our second objective was to examine the cognitive workload during usual and HT walking conditions. Our hypothesis was that walking with HT and a dual task would require more cognitive workload, indexed by the ICA, compared to the usual walk condition. Study results showed that cognitive workload increased from the usual walk to the HT condition within each group. Our results are similar to Kahya et al. who examined ICA during standing with eyes open and occluded and with dual tasking. They reported increased cognitive workload with eyes occluded and with dual tasking which was correlated with higher postural sway (24). However, our results differ from Tapper et al. who report that with increasing task difficulty, asymptomatic athletes with a sports-related concussion had poorer behavioral responses but did not demonstrate an increase in pupil dilation when compared to the easier single task and to control subjects. They suggest that individuals with concussion reach their cognitive capacity limits earlier and with easier tasks with an inability to recruit more cognitive resources leading to deterioration in task performance as demand increases (29). Likewise, Koelewijn et al. found no differences in pupil dilation with increasing task difficulty in the acute stage of mTBI suggesting that depleted resources due to increased distractibility and higher fatigue levels result in cognitive overload relatively early (28). A reason for the difference between our results and the studies mentioned above is that we examined ICA as a moment-to-moment change in pupillary response whereas Tapper et al. and Koelewijn et al. looked at mean pupillary size and baseline corrected pupillary size, respectively. Vogels et al. found that ICA and baseline corrected pupillary size respond differently to changes in task demand and dual tasking in healthy individuals. They report that although pupil dilation increases with task difficulty and dual tasks, the ICA showed a decrease during dual tasks (53). This collective information suggests that we are comparing different constructs of cognitive workload which may explain the discrepancy.

No differences in pupillary responses were found between mTBI and controls in usual walk or HT walk conditions, even after adjusting for baseline differences in gait speed. We hypothesized that symptom burden and gaze instability in the mTBI group would require more cognitive workload to perform the HT motor-cognitive dual task. We examined gaze stability using the dynamic visual acuity (DVA) test, which is a functional measure of the vestibulo-ocular reflex (VOR). A difference of more than 0.2 LogMAR on the dynamic visual acuity test is indicative of gaze instability, with previous research reporting persistent gaze stability deficits in chronic mTBI (20, 21, 47, 52). However, we did not find differences in DVA loss between the mTBI and control groups, because the control group exhibited gaze stability deficits, resulting in non-significant differences between groups. This may be one reason why cognitive workload was not different between the groups. Symptom burden was significantly higher in the mTBI group and may be reflected in the ICA variability seen in the mTBI group. Ultimately, our study results did not show a difference in ICA between the mTBI and control groups, indicating that either ICA is not sensitive enough to differentiate between mTBI and healthy controls or the task was not complex enough to result in a significant change in ICA values. Future studies that include a moving platform that requires participants to maintain a certain speed along with

randomly presented visual tasks may increase task complexity enough to detect larger changes in ICA.

Although cognitive workload was similar between groups, participants with mTBI had slower gait speed, poorer balance indicated by steps off the path, and more missed letters during HT walking compared to controls, indicating poorer performance. Devos et al. have reported that people with multiple sclerosis and impaired cognitive function did not increase their cognitive workload but showed a deterioration in functional performance compared to those without cognitive impairment and healthy controls (54). It is possible that people with mTBI are unable to effectively allocate cognitive resources to compensate for decreased performance in walking tests.

Our third objective was to examine if vestibular function, measured by gaze stability, was associated with gait speed. Vestibulo-ocular dysfunction is common after mTBI (19, 55, 56), therefore we expected to see greater DVA loss in the mTBI group compared to controls. We found DVA loss of >0.2 logMAR in 56% of controls and 65% of mTBI participants. We did not find correlations between DVA loss and gait speed and DVA loss and symptom severity. One reason for these results may be the exclusion criteria. We did not exclude control participants with neck pain and did not assess for neck range of motion. Fino et al. examined turning dynamics in 14 individuals (average age 38 years) with chronic mTBI. They found that participants with mTBI had slower gait speed, and impaired turning dynamics compared to controls. Thirty percent of their mTBI participants had impaired gaze stability measured by the video head impulse test, however, their control group was younger (mean age 25.6 years) and had no vestibular dysfunction (47). Kleffelgaard et al. found that 62% of their mTBI subjects had positive findings during oculomotor tests and 29% had DVA loss, however the relationship between vestibular function and performance measures of balance and mobility were not examined (52). Future studies with stringent inclusion/exclusion criteria are necessary to examine how vestibular dysfunction may affect gait speed, cognitive workload, and eventually recovery with training.

This study has several limitations. The main goal was to use an ecologically valid test that included walking with head turns, however, to encourage participants to turn their head we also included a cognitive task of identifying letters and their colors. We tested participants for color blindness before the walking test, however, we did not assess cognitive skills such as working memory, processing speed or executive function that may be affected after mTBI. Cognitive deficits in these domains are common after mTBI and can impact gait speed and dynamic balance. Likewise, mood profiles such as depression and anxiety can affect gait speed and these data were not collected. The walking tests were not randomized; hence participants may have slowed down during the head turn walking tests due to tiredness. In order to track steps outside the path, we taped the narrow walkway, however, the taped path may have resulted in participants slowing down to stay within the path. We emphasized and demonstrated to each participant that head turns were required when they were close to the letter and to avoid looking at the letters ahead of time with eye movements only. However, some subjects may have not turned their head as much which may have influenced gait speed. In this study, neck range of motion was not captured, hence future studies need to examine the extent to which people with mTBI move and/or restrict head movement, and the effect on gait speed. Several subjects in the study wore glasses and the TOBII glasses used to measure pupil dilation had the capability to be fitted according to the subject's needs, but we were not able to match the prescription accurately since some participants with mTBI wore prisms. We did not assess eye movements such as smooth pursuit, and saccades and did not examine visual function for tropias and phorias which could impact the ability to see clearly. We examined vestibular function using the dynamic visual acuity test, which is a functional measure of gaze instability and is dependent not only on the effort the subject puts forth but also on factors such as neck pain. We did not assess vestibular function physiologically, hence future studies that examine vestibular evoked potentials, the video head impulse test, and videonystagmography to quantify otolith, semicircular, and visual function are necessary. Retrospective sample size analysis showed that we had adequate sample size to detect usual walk (91% power) and HT gait speed (97% power) differences between the mTBI and controls, however, ICA was not adequately powered. Future studies with greater task complexity will allow for a closer analysis of the relationship between the visual-vestibular interaction, symptom presentation, cognitive workload, and gait.

CONCLUSION

People with persistent symptoms after a mild traumatic brain injury have slower usual gait speed compared to age-matched controls months after the injury. With head turns and an added cognitive task, their gait speed decreased further and continued to be significantly slower than healthy controls. Gait speed which is a marker of health and disability was associated with higher symptoms experienced. These results have important implications for people with mTBI as they return to work, leisure, and community activities.

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 IRB at the University of Kansas Medical Center. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LD'S: conception of study, data collection, data analysis, writing, reviewing, and revising of manuscript. PC and HD: conception of study, data analysis, writing,

reviewing, and revising of manuscript. MR: recruitment for study, reviewing, and revising of manuscript. All authors contributed to the article and approved the submitted version.

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Effects of the CarFreeMe Traumatic Injuries, a Community Mobility Group Intervention, to Increase Community Participation for People With Traumatic Injuries: A Randomized Controlled Trial With Crossover

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Introduction: After traumatic injuries community participation is a common goal, promoting wellbeing and independence. Community mobility and transportation influence an individual's independence in community participation. With the ability to drive safely often compromised after traumatic injuries, the adverse consequences of driving cessation include a loss of identity and reduced participation in chosen activities. In rehabilitation, individualized community mobility intervention is not routinely provided. The primary aim of this trial was to evaluate whether a group-based intervention, the CarFreeMe TI program was more effective than standard intervention, an information sheet of alternative transport, in improving community mobility for people following traumatic injuries. The secondary aim of this study was to evaluate the effect: types of transport used, transport satisfaction, community mobility self-efficacy, quality of life, goal satisfaction and performance, for people following traumatic injuries; and to undertake a preliminary assessment of the potential resource use associated with the intervention, and lessons for implementation.

Design: Prospective, pilot, randomized, blind observer, controlled trial with crossover.

Participants: Twenty individuals with traumatic injuries.

Intervention: Six-week group-based support and education program, the CarFreeMe TI delivered in community settings (intervention) and standard information related to transport options available (control).

Primary Outcome Measures: Community participation using a Global Positioning System device to record the location and number of outings from home.

Secondary Outcome Measures: CarFreeMe TI Transport Questionnaire, Community Mobility Self-efficacy Scale, quality of life measures, Modified Canadian Occupational Performance Measure for goals (importance and satisfaction), participant satisfaction survey results and researcher logs.

Results: Those who received the intervention were more likely to use public transport and transport services and had an improved quality of life, when compared to the control group. The intervention group also reported high levels of improvement in goal performance and satisfaction. Global Positioning System data collection was incomplete, with geolocation data unusable. There was no significant change in number/type of visits away from home.

Conclusions: A group-based community mobility education program promoted modes of active independent transport but did not impact on outings from home. Future research could include passive collection methods using a smartphone to record community participation.

Clinical Trial Registration: https://www.anzctr.org.au/, identifier: ACTRN12616001254482.

Keywords: trauma injuries, traumatic brain injury, spinal cord injuries, group-based intervention, community mobility, participation, community participation

INTRODUCTION

Injuries caused through trauma, including traumatic brain injuries (TBI) and spinal cord injuries (SCI) are a leading cause of disability (1, 2), internationally. In rehabilitation, community participation is a common goal for people with traumatic injuries (TI), aiding engagement in meaningful and chosen activities (3, 4). Community participation can be considered within the International Classification of Functioning and Disability (ICF) (5). In the ICF framework: Activities are the execution of a task or action by an individual; Participation is the performance of people in activities across social life domains, through interaction with others; and community participation is the performance in activities across the domains of: (1) domestic life; (2) interpersonal life (entailing formal and informal social, family and intimate relationships); (3) major life activities including education (informal, vocational training and higher education) and employment (remunerative and non-remunerative, excluding domestic work); and (4) community, civic and social life (including religion, politics, recreation and leisure, hobbies, socializing, sports, arts and culture); of an individual in the context of the community in which they live.

Success of community participation is markedly influenced by community mobility and transportation, enabling access to healthcare services, independence and participation in daily activities (6–8). Following TBI and SCI, driving, a form of transportation, has been identified as a key activity to maximizing community participation (7, 9). Generally driving is the most accessible and highly valued transport option, particularly so for the generally younger and male demographic of people acquiring a TBI or SCI injury in developed countries (10).

However, the capacity to drive safely can be compromised after traumatic injuries, as driving is a complex task involving a high level of physical, sensory, perceptual and cognitive functions integrated in an unpredictable and challenging environment. This reduced safety in driving for individuals after traumatic injuries, can be related to changes in physical functions, visual abilities (11), judgment and attention in TBI (12), and sensory awareness and muscle strength in SCI. Research indicates that a proportion of people return to driving at some stage post-traumatic injury, with rates of between 36 (13)−50% (14) following TBI and 36.5% (7) following SCI. Thus, at least half of the population who sustain severe TBI and 63% of people following SCI are unable to return to driving.

Driving cessation after having a complex traumatic injury is associated with emotional, identity, transport and participation related needs (9), and leads to a reduced quality of life for the individual (9). Furthermore, following a traumatic injury, such as TBI and SCI, much adjustment to returning to valued life roles is required by the individual (15). As such the actual adjustment to driving cessation has been found to be an important component to successful community participation, and a unique and continuing experience for individuals with traumatic injuries (9).

Returning to valued life roles, like being a driver, are important for life satisfaction after injuries, such as TBI and SCI (16). Research is required to examine participation in life roles, after traumatic injuries, specifically the personal importance and changes in these life roles (including driving and community mobility). Additionally, it is critically important to develop education and intervention programs to address these specific life roles to maximize life satisfaction after traumatic injuries (16). Research demonstrates that intervention to facilitate community

mobility in the context of driving cessation following traumatic injuries needs to target the emotional, social and practical issues in a personalized way (9), specifically in relation to the life role of driving and community mobility.

Following traumatic injuries, including TBI and SCI, community rehabilitation in developing countries is often provided through government supported insurance schemes. Presently, individualized community mobility intervention is not routinely provided in these rehabilitation services (17). Rehabilitation programs in developed countries offer community mobility interventions comprising of: driving assessment, information describing alternative forms of transport options, and the coordination of multidisciplinary support (9, 17). With successful intervention to maximize community mobility for people following traumatic injuries, being required to be individualized, ongoing and include: 1. information provision; 2. support to facilitate adjustment and decision-making; 3. goal setting and; 4. practical support to use alternative transport; in order to maximize participation in valued roles. Explorations of the experiences of key stakeholders, has identified that the needs related to driving cessation were affected by the processes of formal driving requirements, rehabilitation, adjustment and support available (9). A flexible, individualized approach that considered emotional and practical needs was indicated (9).

The CarFreeMe intervention (http://carfreeme.com.au/) is a community-based education and support program, developed in Queensland, Australia which has been demonstrated in a randomized controlled trial to increase community mobility and transport satisfaction in older adults following driving cessation (18). CarFreeMe TI, where the TI refers to Traumatic Injuries (TI), a modified version of the program, thereby enhancing the ecological validity, that is the real world application to the specific needs of people who are unable to drive, resulting from traumatic injuries, was developed through expert clinical input and a review of relevant research. Modifications included introduction of an optional family module, adaptation of language, examples and images to ensure relevance to this group, and inclusion of traumatic injury specific content (including licensing/fitness to drive requirements, impact of symptoms on driving and alternative transport use, and reference to rehabilitation pathways) and specific traumatic injury related organizations/resources. Modifications to the program were made in consultation with experienced clinicians, researchers, service providers, and advocacy organizations in the area.

The CarFreeMe TI intervention program consists of seven modules run over 6 weeks, with sessions on: adjusting to losses and changes (including mindfulness and relaxation techniques, cognitive behavior therapy approaches); experiences of stopping driving; alternative transport; lifestyle planning (how to stay involved without driving, planning for the future); and advocacy and support. An additional family caregiver module was added in recognition of the important and challenging role of family members of people after traumatic injuries in driving cessation support. Group activities took the form of information sharing, group discussion, speakers, practical sessions and outings facilitated by an occupational therapist and a peer leader (a person living with a TBI or SCI and no longer driving, mentored by the occupational therapist). The approach and rationale to engaging peer leaders in the driving cessation program has been described elsewhere (19). The order and focus within modules were also adapted depending on individual goals, which are set before the first session. For example, if group members had priority goals on finding alternative transport, or advocating for change within the local area, the relevant modules (numbers 5 and 7) would form part of early sessions. In addition, the nature of goals (e.g., organizing transport to a future study location, to feel okay discussing not driving) were reflected in planned guest speakers, outings and worked examples. Individual sessions, homework and individual transport plans also reflected individual goals. **Table 1** contains an overview of the modules and example content and activities. In terms of implementation of the program, the factors considered included the length of sessions and frequency of breaks to consider mental fatigue, and individual sessions for practical training in actual contexts (i.e., catching the bus from own home to University or gym), in addition to a group based outing that provided more generalized exposure to public transport use.

Currently no intervention programs, specifically targeting community mobility such as CarFreeMe TI regarding driving cessation and community mobility are available for people with complex traumatic injuries in Australia within standard practice. There are high costs to the community for providing rehabilitation, community support (20, 21), and also non-travel and non-participation to people following TBI and SCI. Moreover, there are no published studies evaluating the clinical effectiveness or efficiency in terms of cost effectiveness of interventions targeting enhanced community mobility in people following traumatic injuries (22, 23). There are also relatively few economic evaluations of rehabilitation strategies following severe traumatic injuries (24–27), with those that are published predominantly focusing on cost-analysis or cost-benefit analysis.

When considering targeting intervention at community participation, the use of outcome measurements to evaluate effectiveness needs to be considered. A recent scoping review recommends a mixed method approach including Global Positioning Systems (GPS) for quantitative data (distance and location), and qualitative data including self-reported participation diaries to provide insight into where and why individuals chose to complete certain community activities (28). GPS has been used effectively in older community dwelling adults (29) and people with lower limb amputations (30) to measure community participation in observational cross-sectional studies. Other research investigating community participation uses the construct of lifespace, the geographic area where an individual lives and carries out their life. Lifespace measurement has been used mostly in relation to older people including those with mild cognitive impairment and dementia (31) and is measured more recently through the passive collection of the recording of outdoor locations using GPS on a smartphone. The data are then converted to metrics including areas, percentage of time at home and number of times leaving the home.

The primary aim of this trial was to establish whether a 6-week CarFreeMe TI intervention focused on improving community

TABLE 1 | Modules and example content and activities of the CarFreeMe-TI program.

Module	Example content and activities
1. Traumatic injury	Nature of experiences and changes Challenging myths, perceptions of those in society Activities: Discussing experiences, perceptions; Guest speaker from related services;
2. Balancing safety and independence	Formal requirements and processes for licensing Impact of symptoms on driving safety Activities: Presentation on local requirements and driving assessment experiences Discussion (including unlicensed driving)
3. Adjusting to losses and changes	Grief, loss and coping styles Activities: Worked examples (cognitive behavioral/challenging thinking; problem solving) Relaxation exercises-Meditation guest speaker
4. Experiences of giving up driving	Sharing experiences, expectations, concerns about driving cessation Activities: guest speaker (peer leader or other), sharing experiences, discussion, workbook activities
5. Alternative transport	Information about local options (ticketing, concessions, getting information, planning trips) Practical experience with relevant options Activities: group and individual outings and reflection; Individual Transport Plan, Guest speaker from public transport service, Peer support in a targeted guest speaker role in relation to using alternate transport
6. Lifestyle planning	Reflecting on personally optimal lifestyle Occupational balance, pacing/energy conservation Activities: workbook led reflection on current time use patterns, reflection and discussion of goals/ future planning
7. Advocacy and support	What is advocacy Current and future opportunities for transport, support Activities: Supported feedback of local area audit, connection with advocacy groups; Guest speaker: local council member
8. Family member (optional)	Conversations during driving disruption Support for carers/family members Activities: Discussion about experiences, Guest speaker from carer support organization or peer

mobility is more effective than standard intervention, in people following traumatic injuries, vs. a standard intervention on: types of transport used, transport satisfaction, community mobility self-efficacy, quality of life, goal performance and satisfaction, participant satisfaction, for people following traumatic injuries; Carer's self-efficacy and strain; and to undertake a preliminary assessment of the potential resource use associated with the intervention, and lessons for implementation.

MATERIALS AND METHODS

Study Design

This study was a prospective, randomized, blind observer, controlled trial with crossover, following the guidelines of the Consolidated Standards of Reporting Trials (32). The protocol has previously been published (33).

Participants

Fifty seven individuals with traumatic injuries recruited from rehabilitation facilities and the community, in Adelaide South Australia, were screened for eligibility between July 10, 2016 and July 25, 2017 by a research Occupational Therapist. Of these, 32 were ineligible, with reasons detailed in the Flow Diagram (**Figure 1**) of those who were deemed eligible three declined and two were not contactable. Twenty participants were included in the study. The inclusion criteria were as follows: (a) had a traumatic injury, that is a TBI and/or a SCI, which precludes returning to full driving; (b) aged over 18 years old; (c) adequate cognition/behavioral abilities to participate in sessions; (d) mobile, either walking or in a wheelchair independently or with carer assistance. The research assistant who made the assessment of suitability to participate, was an Occupational Therapist with experience working with people with traumatic brain injury, and their clinical judgment, and knowledge of the CarFreeMe program and options for adaptation, and information from referees which included Occupational Therapists providing intervention, informed the assessment of suitability to participate. If there was concern about the participant's ability to make decisions, capacity to consent was confirmed from the treating doctor, with permission from the client. Exclusion criteria were as follows: (a) evidence of aphasia or poor English language skills that significantly impact on the understanding of information and reduces engagement in a group setting; (b) living in residential care settings (or anywhere where transport would be provided); (c) driving with no restrictions.

Participants were recruited from urban areas in Adelaide, South Australia. The urban area is sprawling, with public transport predominantly being buses, with limited options for trains/trams. Supported transportation services are available for people with disabilities from local councils and community service providers for activities such as shopping or medical appointments. Driving a motor vehicle is the predominant form of transport and national medical fitness to drive guidelines https://austroads.com.au/publications/assessing-fitness-to-drive inform decision-making related to driving for people with traumatic injuries.

The study was approved by the ethics committee of Southern Adelaide Clinical Health (OFR # 42.16 – HREC/16/SAC/47) and all participants provided written informed consent. All

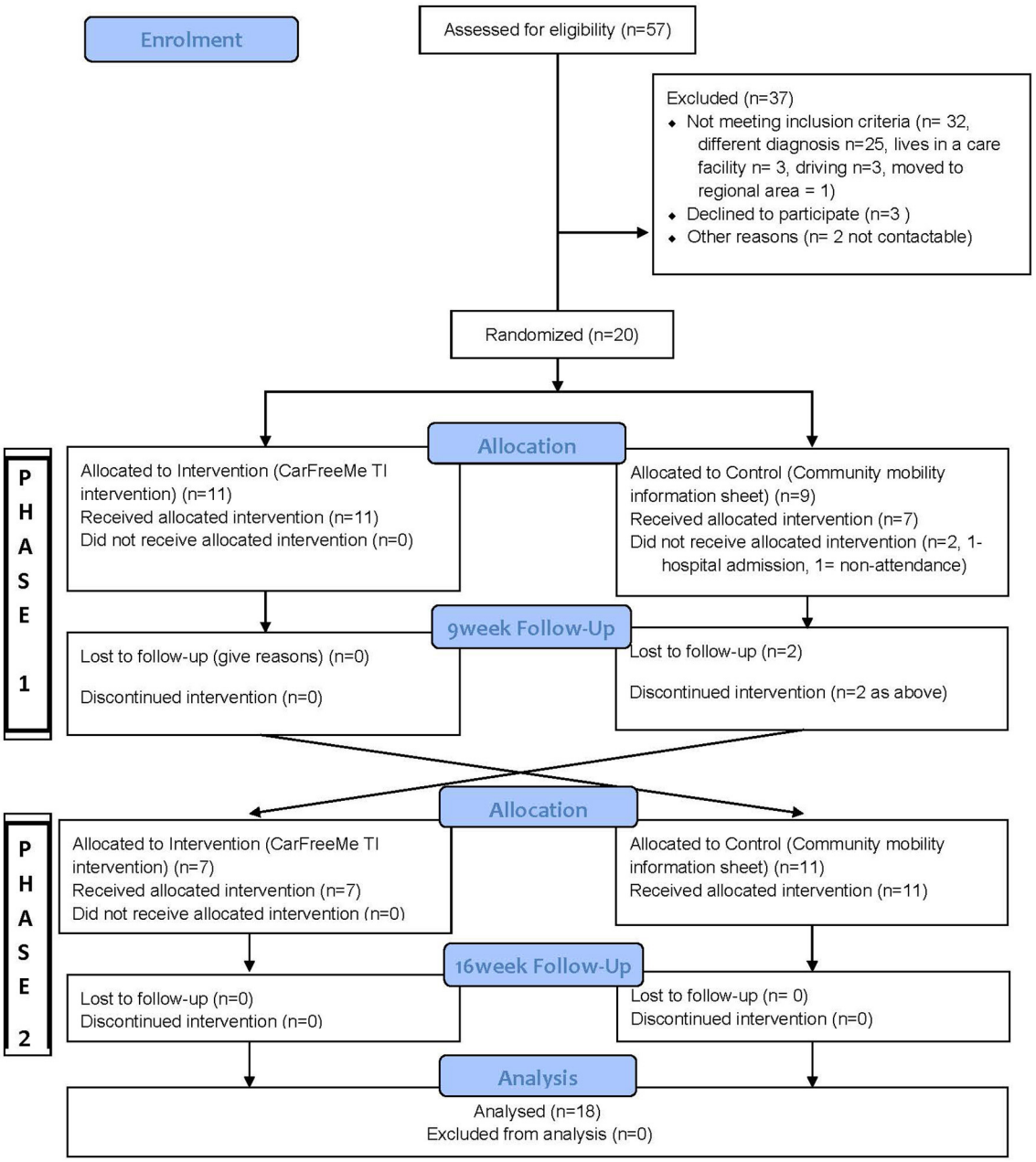

FIGURE 1 | Flow diagram.

procedures were conducted in accordance with the Helsinki Declaration of 1975, as revised in 2008. The study was registered with the Australian and New Zealand Clinical Trials Register (https://www.anzctr.org.au/ACTRN12616001254482).

Procedure

In Phase One of the study, participants underwent a baseline assessment and were randomly allocated to either 6 weeks of the CarFreeMe TI support and education program (intervention) or received information related to transport options (control). In Phase Two of the study those who were in the intervention group crossed over to receive the control and vice versa. A computer-generated randomization schedule with one:one allocation occurred by an investigator not involved in recruitment or assessments.

Primary and secondary outcome assessments were performed at baseline, before any interventions (Week One-Two), Week Nine (following completion of Phase One) and week 16 (following completion of Phase Two). Assessors, blinded to the group allocation, were research Occupational Therapists

who have received training in the standardized use of the outcome tools.

Instruments

Primary Outcome

The primary outcome measure of community participation was a Global Positioning System (GPS) to record the location and number of outings from home. Hordacre et al. (30) and Gough (29) were able to accurately record a range of categorized community participation events using wearable GPS devices integrated with geographic information systems. The GPS units were worn for a 7-day period at the end of the 6-week intervention, at each phase of the study. Participants were provided with a GPS device, as used in our previous studies in amputees (30) and older community dwelling adults (29). The device was worn on a lanyard or belt hook for a period of seven consecutive days and shows location during daily community activities. The particular GPS model used was the QSTARZ BT-Q1000XT, considered the gold standard for research (29). The device measures 72.2 mm (L) × 46.5 mm (W) × 20.0 mm (H), weighs eight and a half grams. Battery life of the device was 42 h, and participants were instructed to charge the device each night. The Occupational Therapist regularly checked in with participants via telephone to remind participants to wear the tracker and instructions/education were provided to participants and carers. Researchers were unable to check the data remotely to check if the GPS was accurately recording. The data collected provided longitude and latitude coordinates time-stamped for every 5 s. Data were linked to Google Maps for a graphic representation of where participants traveled within the community. Participants were made aware of the nature of the data that is obtained from the GPS device prior to giving consent to participate in the study.

From the coordinate data, the following were calculated: Trips per day, furthest distance traveled, average daily distance and percentage of time at home. The types of places participants visited were categorized such as: employment, residential, commercial, health services, recreational and social.

Secondary Outcomes

The secondary outcomes measured offer a broader picture of quality of life, health care resource use, transport use, and confidence with participation without driving, for participants and confidence and strain for carer's and included:

a. **CarFree Me TI Transport Questionnaire:** included data on modes of transport used, as well as a diary record of community mobility in the last 7 days to support GPS data. Basic satisfaction with transport arrangements was measured by a five-point scale with five very satisfied and one very dissatisfied. This questionnaire was developed for the study evaluating the effectiveness of the CarFreeMe for older drivers (19) which found the intervention was significantly associated with a higher number of episodes away from home per week and an increase in modes of transport and higher satisfaction with transport use. Psychometric properties of this bespoke questionnaire are not available. In the original CarFreeMe trial, a difference of one additional trip in the community within a week was defined as clinically meaningful (19).
b. **Community Mobility Self-efficacy Scale:** measured participant confidence with participation in life roles and activities without driving. For example, "How confident do you feel about being able to stay in contact with friends and family without driving?" This questionnaire assessed the level of confidence on a ten-point scale ranging from one, not confident at all, to ten, very confident. This was developed from an adaptation of Lorig et al. (34) scale for a study evaluating the effectiveness of the CarFreeMe intervention with older drivers (19). The results of this study were that some features of the Community Mobility Self-efficacy Scale demonstrated significant improvements following intervention including: "How confident do you feel about being able to stay involved in the community without driving?", Item five: "How confident do you feel about finding alternative transport options to get to necessary community activities and appointments?", and Item six: "How confident do you feel about staying involved in activities that are important to you without driving?" (19). Psychometric properties for this adapted scale are not available. The scale from which it was developed has indicated high internal consistency, sensitivity to change and appropriate correlation with relevant health outcomes in the context of chronic disease self-management programs, over a range of contexts and languages (35). There has not been a formal indication of clinically significant magnitude of change in this scale of which we are aware.
c. **Health-related quality of life of participants** was measured using two instruments: the Assessment of Quality of Life Six Dimension (AQoL-6D) (36) and EuroQoL 5 dimensions five levels (EQ-5D-5L) (37). The AQoL-6D is an instrument which measures health-related quality of life across six dimensions, independent living, mental health, coping, relationships, pain, senses, and visual impairment. There are 20 questions in total for the instrument. Participants were asked to rate their situation over the previous week. The AQoL-6D can be scored a number of ways, including using a simple additive summary score to give an indication of overall quality of life, where scores range from 20 to 97 where a lower score indicates a better quality of life (38). The instrument has the required validity (construct, concurrent, and convergent) (39), has undergone psychometric construct and validation processes and generates health utilities that are comparable with other major health utility instruments (40). The EQ-5D-5L is a generic-preference based instrument for measuring health-related quality of life which has five questions covering five dimensions (mobility, self-care, usual activities, pain and anxiety and depression) plus a visual analog scale (VAS) which asks participants to rate their overall health on a zero (indicating the worst health imaginable) to 100 (the best health imaginable) scale. It is described as having excellent psychometric characteristics across setting and groups, having moderate responsiveness in groups experiencing health improvements (41). Participants are asked to rate how they would describe themselves across the five

questions today using the five possible levels of response. The EQ-5D-5L can be used to generate utility scores which are scores indicating the overall quality of life weighted according to the preferences of the general population for the health state described by the five dimensions. The EQ-5D-5L was scored using the weighted scoring algorithm generated from the preferences of the Australian general population, which gives scores on a scale between zero and one, where zero indicates a health state equivalent to death, and one the best possible health state (42).

d. **Individual goals:** were set only by participants undertaking the intervention condition, just prior to the group starting. Participants were assisted to set transport and lifestyle goals using a modified Canadian Occupational Performance Measure (COPM) (43). The COPM has been described as clinically useful, responsive, valid and reliable (44). Participants identified their goals for participation and rated their current performance, and satisfaction for each goal on a 10- point Likert scale ranked from one-10, where one indicated poor performance and low satisfaction, respectively, whilst 10 indicates very good performance and high satisfaction. Goal performance and satisfaction were rerated at the completion of the intervention. This is consistent with the approach undertaken in the trial with older people (45). Clinically meaningful change in the COPM has been defined as a change of two or more points (46).
e. **Cost and resource use**: A health-system perspective was adopted for the analysis of the costs and resource use within the study. The costs of the intervention were calculated using study based records of the Occupational Therapists time, and resources used. Health and aged care service utilization was accessed from self-reported weekly records of service use. Participants were asked to complete a calendar recording instances of health and social care services input such as care provided at home, visits from allied health professionals or to clinicians. Unit costs for the health system resources used to provide the intervention were derived from health service data. Costs for the other resources used in the intervention were based on market rates.
f. **Participant satisfaction survey and researcher logs:** A satisfaction questionnaire was completed at the end of the group education and included questions rated on a Likert scale of one-10, where one indicated not satisfied and 10 extremely satisfied related to content, presentation and organization of the education program. This represented a bespoke questionnaire where psychometric properties are not known. Then open questions related to what you would keep, take out, relevance, influence on knowledge/confidence and suggestions for improvment.The Occupational Therapist research assistant also maintained logs throughout the study.
g. **Carers outcomes:** For the carers of participants with traumatic injuries who consented to participating in the trial, including the option of also attending the CarFreeMe TI group sessions, outcomes included the Carer's Community Mobility Self-efficacy Scale and the Modified Carer Strain Index. The Carer's Community Mobility Self-efficacy Scale is a 10 point Likert scale measuring perceived confidence of participants ability maintaining community mobility following driving cessation adapted from the Community Mobility Self Efficacy Scale (18); The Modified Carer Strain Index (47) is a questionnaire of 13 items measuring perceived burden of carers rated on a Likert scale ranging from "experiencing on a regular basis, sometimes, to not at all". This tool has been used with a range of caregivers, is brief and convenient and has high internal and test-retest reliability, and has been used across cultures and languages (47).

Adverse effects were monitored including unlicensed driving and any injuries related to community mobility, and referral to support services (physiotherapy, psychologist, social work) made if required, as determined by the research Occupational Therapist. A steering committee consisting of authors and representatives from Paraquad South Australia (SA), Brain Injury South Australia oversaw the monitoring of data and dissemination.

Intervention

Both interventions were provided by an experienced rehabilitation Occupational Therapist (AN) who had received training by the developer of the CarFreeMe TI (JL) program.

Intervention Protocol

The intervention was a group-based support and education program, the CarFreeMe TI delivered in community settings. Prior to commencement of the group a home visit was conducted to identify individual goals and discuss practical challenges with group attendance. The intervention included up to eight participants per group, with six sessions conducted once a week and each session was up to two and a half hours in duration. Content of sessions followed an established protocol and included: adjusting to loss and change; experiences of stopping driving; alternative transport; lifestyle planning; and advocacy and support. Session content was modified to be relevant to the goals identified by group members and were interactive and facilitated for information sharing, using peer leaders and guest speakers including meditation experts, representatives from local council and carer support organizations. Outings were also included which offered the opportunity to trial alternate transport methods such as public transport. Attendance was recorded at each session by the Occupational Therapist, to monitor adherence.

Control Protocol

The control intervention received standard information related to transport options available, which was a one-page written information sheet.

Data Analysis

Sample size was calculated based on data reported in a study assessing community participation in amputees (30). In this study, the mean number of community participation visits over the course of a continuous week for amputees classified as having limited mobility was 7.2, and for those with basic to normal activity was 13.7. Using the group SD of 10.9, and assuming a

TABLE 2 | Baseline comparison of demographics between groups.

	Group 1 ($n = 11$)	Group 2 ($n = 9$)	Statistic	p-value
Age years median (IQR)	56 (35–59)	58 (53–64.5)	$U = 63.5$	*0.30*
Age years range	21–69	46–80		
Male *n* (%)	9 (82)	5 (56)	$X^2 = 1.63$	*0.20*
Time (months) since injury Median (IQR)	97 (25–209)	46 (15–330)	*U = 43*	*0.66*
Time months since injury range	10–548	10–507		
Injury type			$X^2 = 1.81$	*0.61*
Traumatic Brain Injury (TBI)	10 (91%)	6 (67%)		
Spinal Cord Injury (SCI)	0	2 (22%)		
TBI/SCI	0	1 (11%)		
Orthopedic Injury	1 (9%)	0		
Referral source			$X^2 = 4.23$	*0.12*
Self	2 (18%)	4 (44%)		
Lifetime Support Agency (Public Insurer)	1 (9%)	1 (11%)		
Inpatient rehab	1 (9%)	1 (11%)		
Community rehabilitation	9 (%)	3 (%)		

power of 0.8 and alpha of 0.05, a sample size of 45 would be required to detect a similar difference. Assuming a 20% drop-out, we therefore aimed to recruit 54 participants.

Data was entered into an SPSS database with all identifying information removed. Statistical analysis was undertaken using SPSS version 23 Statistical software (IBM, Chicago). Intention-to-treat analysis was conducted and was blinded (i.e., groups identified by number only).

Baseline demographics were compared between the groups using Mann-Whitney *U*-tests, as the data was not normally distributed, for continuous variables and X^2 for categorical variables. For Phase One, at the end of the RCT section of the study, differences in community participation were assessed via GLM Analysis of Variance (ANOVA) with group allocation and time as factors. After Phase One was completed and no carry over effect was confirmed the data from Phase One and Phase Two were pooled to allow analysis as a pre-post study. Paired *t*-tests were conducted to assess the effect of the intervention on the use of transport methods for all participants. Finally, the frequency of episodes away from home for each category of location and total episodes recorded were compared for all participants between baseline, after the intervention period, and after the control period, using a repeated measures ANOVA. For all outcomes alpha was set at 0.05.

A preliminary exploratory study of the health-service resource use and costs associated with the intervention was undertaken. Costs accrued over the 6 week intervention period were estimated for each participant. Descriptive statistics were calculated for the costs of providing the intervention. The nature of the goals set prior to intervention participation were analyzed using an inductive content analysis (48). Goals were worded using the expression of participants. These were deidentified, read and grouped according to key content areas apparent in the data by a member of the investigator team (JL). Preliminary coding was checked and verified by other members of the research team (AN, SG). Feedback about the experience of group participation was analyzed in the same way.

RESULTS

Twenty participants with a mean age of 53.8 years (SD 13.9 years) were recruited to the study. Types of injuries included Traumatic Brain Injury–16, Spinal Cord Injury–3, and Orthopedic–1. Median time since injury was 6.0 years with Inter Quartile Range (IQR) 1.9–18.8. Participants in Group One and Group Two had no significant differences in demographics (see **Table 2**). A Mann-Whitney *U* Test revealed no significant difference in the age in Group One (Md = 56, $n = 11$) and Group Two (Md = 58, $n = 9$), $U = 63.5$, $z = 0.29$, $p = 0.30$, $r = 0.0.06$, and time since injury (months) in Group One (Md = 97, $n = 11$) and Group Two (Md = 46, $n = 9$) $U = 43$, $z = -0.50$, $p = 0.66$, $r = 0.11$. A Chi square test revealed no significant differences between Group One and Group Two in gender [$X^2_{(1)} = 1.63$, $p = 0.20$], type of injury [$X^2_{(3)} = 1.81$, $p = 0.6$] and referral source [$X^2_{(3)} = 1.81$, $p = 0.61$]. Two participants in the control group withdrew, one due to a hospital admission and one due to non-attendance at subsequent outcome assessment timepoints. **Table 2** shows a baseline comparison of demographics.

Primary Outcome

In terms of the primary outcome measure, the Global Positioning System device, average data collection was low (mean 8.3–17.6%) and thus could not be included in the analysis. In the other studies (28, 29) 80–90% has been used as the cut point for "complete" data. In this study the mean of eight-17 across the three timepoints is artificially high because at each point one full data set (over 90%) was there for one person, with the rest of participants averaging 1–2%. No individual had a full set of data—three individuals had a full set of data at one timepoint only. Reasons reported by the Occupational Therapist research assistant describes participants turned the devices off when they

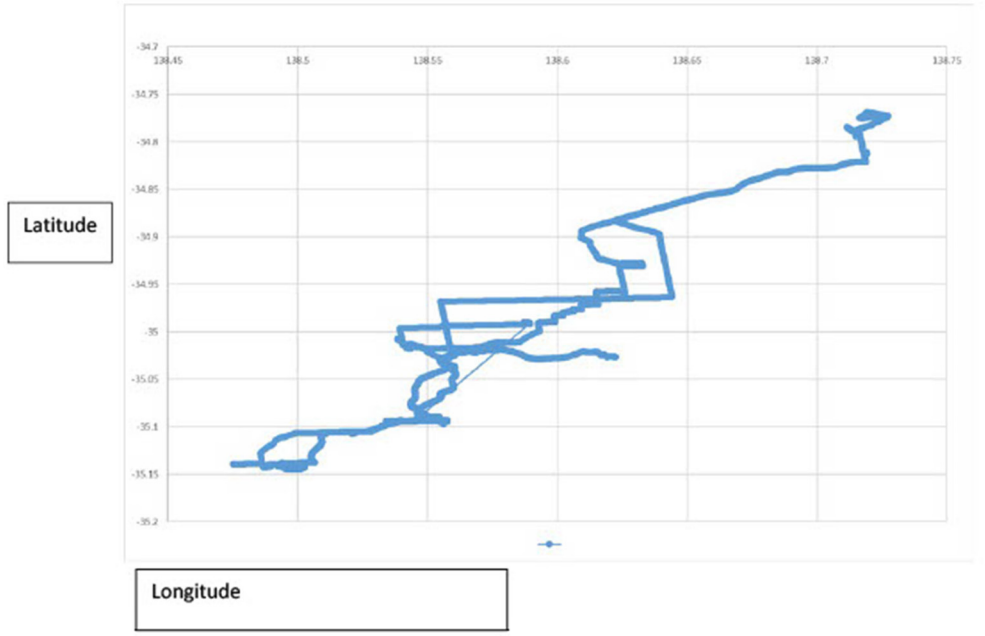

FIGURE 2 | Global positioning system data.

were at home, they did not turn them on properly when turning them back on, they pressed a button that changed the data collection mode, did not charge nor take the devices with them when left the house.

A pictorial presentation of the GPS data from one participant is presented in **Figure 2**—this can be overlaid onto a map to identify location, however was not for publication purposes for deidentification, demonstrates for this participant that using public transport they traveled 60 km in one outing from home to attend study activities.

Secondary Outcomes

CarFree Me TI Transport Questionnaire

The total number of trips out of home and the use of different transport methods used at the end of phase one of the study are presented in **Table 3**. There was a significant effect of group allocation over time for the use of a transport service, indicating an increase in service use in the intervention group ($F = 5.102$, $p = 0.037$). Supported transport services included the equivalent of transport provided by disability services, local government council drivers and courtesy buses, that are required to be organized in advance of a trip. Despite the increase in use of a service for the intervention group over time there was no significant interaction of group allocation over time for any of the other methods or total trips out of home ($F = 1.093$, $p = 0.310$).

As there was no effect of group allocation on any aspect of transport uses, the data was pooled and treated as a delayed intervention study to compare the transport methods and total trips out of home for all ($n = 18$) participants before vs. after completion of the intervention period, presented in **Table 4**. Paired *t*-tests demonstrated that a significant reduction in the use of lifts ($p = 0.014$), coupled with non-significant increases in other modes of transport, resulted in an overall reduction in total number of episodes away from home ($p = 0.031$). There was a significant increase in the number of times public transport was used ($p = 0.035$) between pre and post intervention. If modes of transport are combined, i.e., bus, taxi, service, train, courtesy bus (defined as "self- initiated" transport), there was a significant increase between pre and post intervention [M (SD) Pre: 3.55 (5.6), Post 6.05 (5.9) $p = 0.016$].

There was no significant change in transport satisfaction across all participants from before [median (IQR) 2 (1–3)] to the time after [Median (IQR) 2 (2–2) $p = 0.3$].

In terms of reporting where the participants went, this is described in **Table 5**. There were no significant changes in reason

TABLE 3 | Use of transport methods to leave the home M (SD) over a 7-day period at the end of Phase 1.

	Baseline		9 week	
Type of transport	**Intervention**	**Control**	**Intervention**	**Control**
Walking	2.7 (4.4)	0.4 (1.1)	1.3 (3.6)	0.6 (1.2)
Bus	2.2 (3.0)	1.9 (4.2)	3.5 (4.3)	2.0 (3.7)
Train	0.7 (2.4)	0.9 (2.5)	0.7 (1.6)	0.9 (2.5)
Taxi	0.5 (0.8)	1.3 (1.9)	1.6 (1.9)	1.4 (2.7)
Service*	1.0 (3.3)	0.4 (0.7)	1.4 (3.6)	0 (0)
Lift	4.7 (3.6)	4.1 (3.2)	2.8 (4.0)	4.8 (5.1)
Courtesy bus	0 (0)	0.1 (0.4)	0.1 (0.3)	0 (0)
Other	1.6 (2.5)	1.2 (2.8)	1.7 (2.1)	1.8 (4.9)
Total	7.3 (3.6)	5.9 (2.3)	5.6 (2.2)	6.0 (4.1)

**Significant interaction effect of group allocation by time.*

participants described they left home. There was a reduction in recreational reasons for leaving the house post intervention, however this was not significant.

Community Mobility Self-Efficacy Scale

Scores on the Community Mobility Self-Efficacy Scale are described in **Table 6**. No significant differences were observed between baseline, post intervention, or post control ($p > 0.05$).

Health-Related Quality of Life

The summary scores from the quality of life questionnaires are presented in **Table 7**. There was a large increase in the EQ-5D-5L utility scores between the baseline (0.53) and post control (0.52), and the post intervention period (0.89), however this did not reach statistical significance. There was no evidence of a significant change in the EQ-5D VAS or AQoL-6D additive summary score between the between baseline, after the intervention period, or after the control period.

TABLE 4 | Pairwise comparison of before vs. after the intervention period ($n = 18$) M (SD).

Type of transport	Pre	Post	*p*-value
Walking	1.8 (3.5)	1.2 (2.7)	0.389
Bus	2.1 (3.2)	3.1 (4.2)	0.315
Train	0.8 (2.4)	1.3 (2.4)	0.386
Taxi	0.8 (1.8)	1.5 (2.1)	0.142
Service	0.6 (2.5)	0.8 (2.8)	0.104
Lift	4.7 (4.2)	2.8 (3.7)	0.014
Courtesy bus	0 (0)	0.1 (0.2)	0.331
Other	1.7 (3.6)	1.4 (2.0)	0.537
Total	6.7 (3.7)	5.3 (2.0)	0.031

Individual Goals

Participation Goals: Thirty-four individual goals were set by 16 participants, with significant increases in both performance from 3.9 (SD 3.0) before the intervention to 7.0 (SD 2.1), and satisfaction from 4.9 (SD 2.8) to 7.3 (SD 1.8) (both $p < 0.001$). These changes are regarded as clinically significant as they are higher than the 2 points of change defined (46). Four major types of goals were identified: 1. Transport information and experience: these goals related to gaining information, experience and confidence in relation to relevant transport services related to their lives. This was the most common type of goal with 16 being set. An example goal was "To feel more confident using buses for longer trips" (Participant 19). 2. Participation (activities and roles) was a category of goals based on the participation outcomes they wished to achieve through involvement in the program. These included social, leisure, work and feeling busy enough. There were 11 of these goals set. An example goal was, Find out about supported work opportunities" (Participant 12). 3. Emotions and attitudes: These goals focused on emotional responses and personal feelings about themselves and driving cessation. Four goals in this category were identified. An example goal was: "To feel less angry about not being able to drive" (Participant 11); 4. Making a change/contributing was a category of goals related to advocacy and changing the overall situations for others as well as themselves. Three of these goals were set. An example goal was "Having a voice to feedback issues associated with transport use" (Participant 9).

Cost and Resource Use

Costs of intervention were calculated in Australian Dollars (AUSD), see **Table 8**. Where costs occurred as a group cost (e.g., Occupational Therapists time, room bookings) the value per person is calculated on the basis of six people attending a group and 1/6 of the cost allocated to each individual. Where

TABLE 5 | Self-reported episodes away from home M (SD).

	Education/employment	Residential	Commercial	Health	Recreational	Social	Total
Baseline	0.4 (0.9)	0.5 (0.7)	1.2 (1.2)	1.2 (1.6)	1.4 (1.9)	1.7 (2.0)	6.4 (3.1)
Post intervention	0.7 (1.2)	0.1 (0.2)	1.1 (1.1)	1.3 (1.6)	0.5 (0.6)	2.3 (1.3)	5.9 (2.7)
Post control	0.4 (0.8)	0.4 (1.0)	1.6 (1.7)	1.5 (1.9)	0.7 (1.1)	1.9 (1.9)	6.4 (3.6)

TABLE 6 | Community mobility self-efficacy scale.

How confident do you feel about	Baseline M (SD)	Post interventionM (SD)	Post control M (SD)
Being able to stay involved in the community without driving?	6.2 (2.7)	6.7 (2.8)	6.2 (3.2)
Having your health and medical needs met without driving?	7.5 (2.9)	7.6 (3.2)	7.2 (3.2)
About discussing driving and no longer driving with your family and/or health professional?	8.3 (1.8)	6.9 (3.0)	7.3 (3.0)
Finding alternative transport options to get to necessary community activities and appointments?	6.5 (3.0)	6.9 (3.0)	6.9 (3.0)
Staying involved in activities that are important to you without driving?	6.8 (3.0)	6.9 (2.9)	6.6 (3.0)
Staying safe while getting around in the community without driving?	7.1 (2.5)	7.3 (3.2)	7.3 (2.7)
Being able to leave the house without driving?	7.5 (2.6)	7.3 (3.1)	7.2 (3.2)
Being able to stay in contact with friends and family without driving?	6.8 (3.3)	7.2 (3.0)	7.1 (3.4)
Talking about no longer driving with your friends and peers?	8.0 (2.4)	7.7 (2.5)	7.6 (2.6)
Total	63.8 (21.1)	61.7 (24.9)	63.1 (25.4)

TABLE 7 | Quality of life scores.

	EQ-5D utility scores Mean (SD)	EQ-5D (VAS) Mean (SD)	AQoL-6D Mean (SD)
Baseline	0.53 (0.34)	69.5 (17.1)	66.2 (16.0)
Post intervention	0.89 (1.10)	71.1 (21.5)	63.8 (17.0)
Post control	0.52 (0.49)	70.6 (23.2)	64.2 (15.2)

TABLE 8 | Costs of CarFreeMe T1 intervention.

Item	Utilization per person	Cost per person (AUD)
OT salary plus on costs $63,010 for 5 groups	1/6 of cost of each group	$2,100.33
OT parking costs x 6 sessions per group	1/6 of cost of each group	$14.00
Guest presenters and lifeflow per group	1/6 of each group	$35.00
Stationary (booklets)	Per person	$57.01
Catering costs × 6 sessions	1/6 of cost of each group	$25.05
Taxi costs for participants	12 journeys per person	$385.98
Room bookings	Free *via* organizations	$0.00
Total per person cost		$2,617.37

costs occurred per individual (e.g., taxis, printing), the individual cost of these resources per person are presented. Taxi costs are averaged over each individual taxi journey and 12 taxi trips allocated per person. The cost of the CarFreeMe Intervention TI, based on six people in each group, was $2617 AUSD each.

Carers

Only four participants had people who identified as carers and they did not complete the outcomes, thus this information could not be used in analysis.

Participant Satisfaction Survey and Researcher Logs

On the completion of the program participants provided feedback on their experiences. They rated satisfaction with aspects of the program and provided feedback on what was useful and what should change. Feedback from 18 participants was analyzed. Satisfaction was rated highly across content (8.83/10), Presentation (9.23/10) and organization (9.06/10). Open responses to questions about the experience were grouped according to content. Feedback included identifying the most useful aspects of the program, and aspects that could change. Positive aspects were grouped into most useful aspects [social, tailored (personalized), skills, information and experience] and outcomes (attitude, confidence, acceptance, feeling not alone, having more knowledge). Examples of verbatim feedback were: "meeting with other people in similar situations gives us confidence to deal with problems" (Group 2), "the immediate hands on experiences" (Group 6), Things that could change—three major issues were identified: increase length to help with learning; reduce time spent on content I am already familiar with (content was not consistently identified) and consider timing in the rehabilitation process (mainly identifying that they could have benefited from earlier access). Example feedback included "Needs to be a little longer as to become more long term. That is so I can retain in my long term memory" (Group 6).

Researcher logs and reflections indicated that the optimal timing for recruitment was an important consideration, in particular engaging with potential participants within the first 1–2 years following traumatic injury. During this time, people with traumatic injuries were often engaged in other rehabilitation services so their perceived need for the program was reduced. Potential participants were also reluctant to participate in a program outside their existing clinical service where there was established trust and rapport with clinicians. Finally, some participants expressed being unwilling to participate in a community mobility support and education program due to their expectation of being able to return to driving in future.

DISCUSSION

This study compared the benefits of a 6-week group based support and education program, the CarFreeMe TI, delivered in community settings, to an information sheet of community transport options and was unable to show any difference in community mobility on the primary outcome measure the GPS, however outcome data was incomplete. Despite a standardized process of information provision, regular reminders, the participants had difficulty keeping the devices charged and consistently carrying them when they left the house for their activity over the 7-day data collection period. The QSTARZ BT-Q1000XT is considered the gold standard for research with accuracy within one meter (28), and we have previously utilized to effectively collect full data sets for people following amputations ($n = 47$) (30) and community dwelling older people ($n = 46$) (29) to measure community mobility. **Figure 2** shows how the data is recorded and can be presented to show community participation journeys.

Other research by an investigator (JL) has successful recorded outdoor locations using GPS on a smartphone, a passive data collection method with older people with mild cognitive impairment and dementia (31). This approach resulted in participants recording a mean of 161.5/168 h in a week of recording. An accessible, supportive approach was used to support understanding, consent, and practical considerations. Benefits of the approach included being able to monitor whether data were coming in through a data portal, and lower stigma of a mainstream device. As the majority of the participants had a TBI (80%) in the study reported on in this article, there is likely to have been cognitive changes which would have influenced their ability to remember to charge and take the QSTARZ device with them. The method used by Liddle et al. is recommended in future research as this technology reduces burden on participants, compared to self-reported diaries, and may increase accuracy (31) as a complete data set is more likely as a smartphone is generally routinely taken on outings. An approach which

combines passively collects data in an accessible way, with self-reported satisfaction and meaning of travel is recommended to enable richer insights.

There was little change in the number or type of visits away from home, after the CarfreeMe T1 intervention, in fact there was a slight reduction. Some potential reasons for this reduction include that since the outcome was taken the week after completing the intervention, participants may have been fatigued after attending a program for 6 weeks, and therefore not venture out as much that week. Also, the nature of changes in transport use that the participants identified in their goals are likely to have slower changes to everyday routines. Participant feedback was that they felt they needed a longer time for intervention, so less intensive support over a longer period of time, with consideration of check-ins or a number of follow up sessions over time to reinforce learnings and problem solve issues identified as confidence with community participation develops, should be considered. This need for repetition and ongoing practice are known clinical strategies for rehabilitation following TBI.

What is not known from the objective GPS data is whether when participants in this study went out, they visited multiple locations and went further distances following the intervention. Other research related to older drivers (18) aimed to increase the trips out of home by a frequency of one, given that when people stop driving, they tend to go out for longer and do multiple activities. Thus, objective measurement of the nature of visit, which are potentially multiple as well of locations, need to be considered in future studies.

From the self-reported data of the participants community mobility, the intervention did not essentially change the patterns (when and where they went), however was effective in changing the mode of transport use, which achieved significance (how they traveled there). At baseline the participants main mode of transport was lifts from others, considered a passive form of transport. At the end of Phase two there was an increased use of public transport, with an average of two episodes per week increase, and self-initiated transport overall. There was also a trend in the reduction of lifts and walking post intervention. Therefore, there was an overall trend of more independence in organizing transport with less reliance on favors or just walking, following the intervention. Immediately post-intervention there was an increased use of services for transport which required the participants to pre organize, demonstrating more independence. This may also be a factor in the reduction of the number of times participants went out following the interventions as it was more effortful, and people may require time to adjust to this within their daily routine. This was found in the study examining the adjustment to loss of driving in TBI, where community participation without driving was complicated because of the difficulties and complexities of examining the use of alternative forms of transport (49).

Within this small sample, there was no change in community self-efficacy. These results are not in concordance with other studies, for example in the context of older drivers where after the intervention of the UQDRIVE (an earlier version of the CarFreeMe TI) (18), aspects of the Community Mobility Self-efficacy Scale demonstrated significant improvements following intervention including: "How confident do you feel about being able to stay involved in the community without driving?", Item 5: "How confident do you feel about finding alternative transport options to get to necessary community activities and appointments?", and Item 6: "How confident do you feel about staying involved in activities that are important to you without driving?" (18). In comparison the participants with traumatic injuries in this study were a relatively long time after their injuries (median 6 years) and self-efficacy scores related to community mobility were relatively high at baseline. It could be assumed that due to the length of time since their injury and thus driving cessation they had mostly adapted to the new normal, whereas the older drivers recruited in the Liddle et al. study (18) had stopped driving for any reason and considered driving cessation to be a current issue. Research describing the process of driving cessation for people after TBI identified that the process was very different from the typical experience of older people who stop driving for a variety of reasons. Clinical approaches that consider the timing and processes have been identified as important by health teams working with people after acquired brain injury (17).

Results show an improved self-rated satisfaction and performance in individualized goals related to community mobility and participation in the Phase One intervention group, which was statistically significant. This suggests the CarFreeMe TI intervention, was effective in supporting the personalized goals around community mobility such as confidence in use of public transport, emotions about driving cessation, advocacy related to not driving, and exploring work opportunities. Thus, the CarfreeMe T1 intervention led to an increased perception of goal satisfaction, suggesting that these had not been addressed in other rehabilitation settings, or potentially they had not been willing to accept intervention related to community mobility when hoping to return to driving. The continued meeting of transport and lifestyle goals also suggests that people may need access to therapy in this area for a prolonged period after the traumatic injuries. Additionally, the sharing of experiences, which was embedded throughout the program modules was reported as being highly valued by participants.

This is supported by research with stakeholders in the TBI field (49), which found that supports and clinical processes need to consider multiple factors, including a person's readiness to consider alternatives, formal requirements (legal requirements related to medical fitness to drive, waiting lists for assessments) and participation needs (49). A particularly challenging period during early rehabilitation was noted. It was called the "on hold" period, where a person's main focus is on driving, but they are not able to progress this goal. Not being able to successful navigate this time with the rehabilitation team can lead to distress, disengagement from rehabilitation generally, conflict with family and unsafe driving decisions (unlicensed driving). A need for clinical approaches responsive to the process of driving and driving cessation after traumatic injury is clear, and consideration of both practical and emotional aspects. This was the case for one participant who described as still feeling angry about not driving, when over 2 years after injury—supporting the need for education to focus on the emotion surrounding not driving. It is

important that in terms of understanding community mobility and participation that we move beyond assuming more is better, and to also consider perceptions, meaning and satisfaction (50) for each individual. The improvements in participant goal performance and satisfaction illustrate that people are still meeting clinical goals in this stage of their rehabilitation, a long time after the injury has occurred.

The results showed a large increase in mean EQ-5D utility scores between baseline (0.53) and post intervention (0.89, difference 0.36), and post control (0.52) and post intervention (difference of 0.37). Although this did not reach statistical significance, it is three times the minimal clinically important differences reported in stroke patients undergoing rehabilitation (0.1) and larger than those reported for multiple countries using a simulation approach (0.072–0.101) (51, 52). The post-intervention utility score shows a return to health-related quality of life levels similar to the South Australian general population norms, the context of which the study occurred, which includes a large proportion of healthy and young (aged 15 years and over) individuals (0.91) (53). However, we did not find a significant change in our other measures of quality of life. EQ-5D VAS scores did not significantly change. Minimal responsiveness to change for the EQ-5D VAS in people undergoing stroke rehabilitation has previously been reported (46).

The costs of providing the program were $2,617 per person, with the vast majority of those costs in the Occupational Therapists' salary. This program appears relatively low cost, when compared with other rehabilitation interventions aiming to increase community reintegration including those conducted in an in-patient setting, which can cost over €60,000 (24, 25). When compared against a potential to increase the quality of life of the person, the costs of the current program appear worthwhile.

The main limitation of this study is the lack of a complete data set for the primary outcome. The frequency of phone call reminders was based on the clinical recommendation of the blinded assessor (who issued the device) and the participant self-identified preference. For some participants, this was every 1 or 2 days but for other participants it was less regular. For example, if a participant identified having a carer who would monitor use and charging the device, then only one reminder was given. Signs were also used as visual reminders for charging and carrying the GPS (i.e., sign on front door as a prompt before leaving). A standardized approach, such as a daily text message to all participants and follow-up phone calls where indicated, may have resulted in better usage of trackers. We also did not have the option to access GPS data remotely to verify compliance, so this meant researchers relied on participant self-report of compliance with usage and charging. Future studies examining traumatic injuries and community participation should use other community mobility outcomes measures such as GPS location on smartphones to support data collection.

The other limitation is the small sample size and thus results should be interpreted with caution. With the sample size calculation based on a mean difference of one trip out of home, the total number of trips in both intervention and control group were much lower than that reported in the Hordacre et al. (30) study on which the calculations were based, thus it is unlikely that a difference was possible even if the sample size was reached. Potentially the population of people after traumatic injuries may have different patterns of community mobility and a more in-depth understanding of lifespace in detail, may be required prior to establishing power calculations for future trials. Furthermore, the results may not be generalizable as are specific to the participants locations and context of transport and the environment in terms of community mobility.

The number of eligible individuals was not high with the main reason for those who enquired to not being included was a different diagnosis, with stroke being the most common. This suggests that future work should consider the effectiveness of a community group-based education group to improve community participation with stroke survivors. The population of interest, that is people with traumatic injuries, were more challenging to recruit than other studies evaluating a group-based community mobility intervention, in an earlier version of CarFreeMe, the UQDrive, in which a total sample of older drivers of 131 were recruited (18). Recruitment of people following traumatic injuries, was uniquely affected by those earlier on after a TBI still having a goal of return to driving (49) and thus not open to education related to community participation without driving, which was provided in feedback from referral sources to the study. Furthermore, recruitment would have been enhanced if the intervention was embedded in a rehabilitation service, rather than from community sources. The completion of this research has led to a change in practice which although not as comprehensive as the CarFreeMe TI, is a driving cessation clinic implemented in the rehabilitation service for people to be referred when they are do not successfully resume driving to be offered support by an occupational therapist to adjust to not driving and promote community mobility.

Integration of education and support programs like the CarFreeMe TI earlier in rehabilitation to support confidence in community mobility should be considered, as there may be a delay in medical clearance to undergo driving assessment, or the need to wait for recovery and some people will not be capable to return to driving after traumatic injuries. Flexible delivery approaches of the program where it may be available intermittently over a much longer period, spanning from awareness raising and interim experiences with alternative transport while driving is still a goal, to support the transition to participating in the community, and ongoing support as new issues arise, need exploration. This may also reduce the costs of providing the program as would be scaffolded into existing clinical approaches and processes.

Despite these limitations, the study provides the first evidence that community mobility group-based education offers benefits for people with traumatic injuries, and proposes a comprehensive education program for implementation. This program should include individualized goals, with content to include planning and use of alternative transport, advocacy, adjustment to loss and change related to driving. Future research should consider driving and mobility habits prior to traumatic injuries and evaluation over time to see if changes are made and sustained in community mobility after completion of the program. This was beyond the scope of this study, which would have required more resources.

In conclusion, the findings from this study show that the Community Mobility Group Intervention (CarFreeMe TI) is effective in improving mode of transport use and perception of goal performance/satisfaction and quality of life for people with traumatic injuries. Further investigation is required to explore how community mobility intervention can occur earlier in the injury trajectory, with and without driving cessation, and ways to offer the intervention within a rehabilitation pathway/system more gradually over time.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study was carried out in accordance with Good Clinical Practice (GCP), according to the National Statement on Ethical Conduct in Human Research, and within the laws and regulations of the country in which the research is conducted. All subjects gave written informed consent in accordance with the declaration of Helsinki. The protocol was approved by the Southern Adelaide Clinical Health Research committee (OFR # 42.16 - HREC/16/SAC/47) and published.

AUTHOR CONTRIBUTIONS

SG and JL conceived the study and participated in its design/coordination and drafted the manuscript. CB participated in design of the trial process and data analysis. AB and ZA-W participated in oversight of the trial process. AN was involved in the recruitment and data acquisition of all participants and helped draft the manuscript. All authors contributed to the design and conduct of the clinical trial, read, and approved the final manuscript.

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Conflict of Interest: JL is a founder of the CarFreeMe intervention.

The remaining 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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An innovative therapeutic educational program to support older drivers with cognitive disorders: Description of a randomized controlled trial study protocol

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Older drivers face the prospect of having to adjust their driving habits because of health problems, which can include neurocognitive disorders. Self-awareness of driving difficulties and the interaction between individual with neurocognitive disorders and natural caregiver seem to be important levers for the implementation of adaptation strategies and for the subsequent voluntary cessation of driving when the cognitive disorders become too severe. This study aims to evaluate an educational program for patient/natural caregiver dyads who wish to implement self-regulation strategies in driving activity, and to improve self-awareness of driving ability. The ACCOMPAGNE program is based on seven group workshops, which target the dyad. The workshops deal with the impact of cognitive, sensory and iatrogenic disorders on driving. They tackle questions about responsibility, and about autonomy and social life. They also provide alternative solutions aimed at maintaining outward-looking activities even if driving is reduced or stopped. A randomized controlled trial is planned to evaluate the effectiveness of the program 2 months and 6 months after inclusion, and to compare this to the effectiveness of conventional approaches. The main outcome of this trial (i.e., the implementation of self-regulated driving strategies), will be measured based on scores on the "Current Self-Regulatory Practices" subscale of the Driver Perception and Practices Questionnaire. The Driving Habits Questionnaire will be used to measure secondary outcomes (indicators of driving changes; indicators of changes in mood, quality of life and caregiver burden; and self-awareness of driving abilities). Indicators will be collected for both patients and natural caregivers. This cognitive, social and psychological program should allow older individuals with cognitive disorders to drive more safely, and help to maintain the quality of life and mood of both patient and natural caregiver despite driving limitations.

The patient's care path would be optimized, as he/she would become an actor in the process of giving up driving, which will, most certainly, be needed at some point in the progress of neurocognitive disorders. This process ranges from becoming aware of driving difficulties, to implementing self-regulation strategies, through to complete cessation of driving when necessary.

Clinical trial registration number: NCT04493957.

KEYWORDS

cognitive impairment, driving cessation, education, self-regulation, caregiver

Introduction

Older drivers are faced with the decision to continue or discontinue driving because of health problems, which may also include cognitive disorders. Due to population aging, the number of individuals with major cognitive disorders is increasing and should reach 65.7 million by 2030 (1). Consequently, the number of older drivers with cognitive disorders will increase over the next few years. Individuals with cognitive disorders have an increased risk of traffic accidents (2–4). The risk of individuals with major cognitive disorders being involved in a collision is up to 4.5 times higher than for older people without cognitive disorders (4, 5). Most on-road studies (4, 6–10) and simulator studies (9, 11) have also shown that, on average, the ability to drive is more affected in drivers with cognitive disorders than in drivers without cognitive disorders. Studies which take a naturalistic approach have also shown that drivers with cognitive disorders have poorer self-regulatory behavior than healthy older drivers (12). However, more than 40% of people with cognitive disorders, whose accident risk is 2–5 times higher than older adults without cognitive disorders, continue to drive (13). Almost half of the patients studied were involved in a crash in the 3 years leading up to the diagnosis of cognitive disorder (14). Driving a car may therefore become an important road-safety issue for patients with cognitive disorders.

Giving up driving is a challenging transition for older drivers, and can sometimes be difficult (15). It is a significant life-event, and can lead to major changes in lifestyle, such as a decrease in outward-looking activities, increased loneliness and social isolation. It may also result in depression (16). In France, only a certified physician (i.e., certified by the Prefect of the Department) is qualified to authorize or prohibit driving activity. Medical confidentiality regulations mean that attending physicians, geriatricians and neurologists cannot oblige patients to see their certified physician. They can only advise patients to adapt their driving or give up driving completely. Only patients themselves can impart information about their medical conditions. It is up to the patient or the family caregiver to make an appointment with their certified physician. The patient might then be required to undergo a medical check-up. Then, the certified physician will provide a medical decision about the ability to drive based on the advice of professionals. He/she also specifies the duration of this authorization or prohibition whether any restriction is recommended (e.g., vehicle adaptation, automatic gearboxes). This could lead to suspension of the driving license by the authorities (i.e., the Prefect of the Department). Unfortunately, very few patients take the step as observed in our clinical practice.

A number of intervention programs aimed at managing driving cessation in older adults have been proposed in different countries. A recent review underlined the encouraging results of these intervention programs on processing the decision (17). Only two controlled randomized studies were identified in the course of this review of the literature. One proposed an intervention based on emotional management strategies related to the issue of giving up driving. The results showed a decrease in depressive symptoms in participants who participated in the emotional management intervention, compared to those who did not (control group) (18). The other study proposed an intervention based on an interactive psychoeducational and motivational method for caregivers of patients with cognitive disorders who were still driving. Caregivers in the group which participated in the psychoeducational intervention felt better prepared to discuss giving up driving with the patient, and were less anxious about triggering anger or hurting the patient (19). However, the authors highlighted the lack of methodological consistency in the various studies. A more recent study investigated the effectiveness of a program composed of classroom workshops. These provided peripheral visual field and dynamic vision training, and a driving simulator training session to enable better prediction of driving risk. Results showed a significant increase in safe driving performance in older adults (20). An Australian study is currently being carried out in order to determine the effectiveness of an individualized self-awareness and adjustment program on improving or maintaining mobility after the transition from driving, to driving cessation (21). However, some aspects of driving cessation have never been considered in a cessation management program in older adults with major cognitive disorders. These include: the ability to implement adaptation strategies; the crucial role of

the natural caregiver in the cessation process; and work on individuals' self-awareness of their difficulties, aimed at making them actors in the decision to stop driving.

A recent study suggested that older drivers with minor cognitive disorders were more likely to self-regulate their driving than drivers without cognitive disorders (22). These results are consistent with those of Raedt and Ponjaert-Kristoffersen, which showed that adaptation strategies such as avoidance of certain situations (e.g., night-time trips, peak-hour trips, on unfamiliar roads, or on roads with rough or damaged surfaces) may reduce accident risk in older adults with no major cognitive disorders (23). Charlton et al. also confirms that older adults engaged in self-regulatory driving strategies like reducing driving exposure (driving distance and/or frequency) (24). However, only 1 in 5 elderly drivers whose driving performance is declining over time correctly detect this change (25), which may hinder implementation of regulatory strategies. In addition to these factors, it also seems important to improve the use of regulatory strategies that help older drivers to anticipate and prepare for the consequences of driving cessation before it occurs. The implementation of regulatory strategies is modulated by different variables: self-awareness of health issues, the reasons that push people to continue driving (social representation, maintenance of lifestyle habits, independence), and available resources (social and family environment, infrastructure, and legislation) (26). Intervention programs based on these factors showed effectiveness in driving cessation. Studies have been carried out on older people with ophthalmological conditions-but no cognitive disorders - to find out how an educational program affects their perception of the driving difficulties they experience and of any self-regulatory strategies they may use (27). The Driving Habits Questionnaire (DHQ) was used to measure the perception of driving difficulties, and the Driver Perception and Practices Questionnaire (DDPQ) was used to evaluate drivers' attitude to road safety and self-regulation strategies. Six months after the program, results showed improvements in these measurements compared to those recorded before the intervention (e.g., drivers made fewer trips, traveled shorter distances, and avoided visually difficult situations, such as driving at night, or in foggy conditions).

The studies mentioned focus on programs which target either the patient or the caregiver. However, the interaction between patient and natural caregiver appears to be at the heart of this process (17, 28). A recent study showed that spouses play a significant role in their partners' decision to self-regulate their driving (29). The authors pointed out that intervention programs for driving cessation needed to consider the importance of interdependency in couples and its impact on their driving decisions and outcomes.

Finally, work on drivers' self-awareness and on their ability to anticipate their own difficulties also needs to be done (15). Older adults who stop driving appear to be those who are the most aware of their difficulties (26, 30).

The ACCOMPAGNE educational program presented here (ACCompanying Older drivers in the decision to Maintain or abandon the Pursuit of driving Activity in Geriatric and Neurological units) puts precisely this notion of self-awareness at the heart of the program. The objective of the proposed intervention is to help participants to become aware of their driving difficulties. The intervention was designed following the principles of therapeutic patient education. Therapeutic patient education is "a patient-centered process that addresses patient needs, resources, values, and strategies. It allows patients to improve their knowledge and skills in relation to their illness and its treatment" (31). It has positive impacts on the patient quality of life, treatment adherence and reduction in complications in different diseases such as asthma (32), diabetes (33), osteoarthritis (34) or Alzheimer's disease (35).

Natural caregivers play a major role in this intervention, whose aim is to support both the patient and the caregiver in dealing with the psycho-socio-economic consequences of driving restrictions. Indeed, programs combining caregivers and patients interventions has shown to be effective in increasing the general mental health of both caregivers and patients as well as delay the admittance in long-stay care (36). The role of the natural caregiver in the program is also to help the patient to recall the information learned during the program. The majority of patients with cognitive disorders have episodic memory impairment, which makes it difficult for them to memorize new information. This could be an obstacle to the implementation of self-regulation strategies.

Aims and hypotheses

A randomized, controlled, single-blind trial will be conducted to assess the impact of the ACCOMPAGNE program on the implementation of self-regulatory strategies in the short and long-term in participants with mild to major cognitive disorders. We hypothesize that participants who benefit from the ACCOMPAGNE program will implement more self-regulatory strategies than those who receive conventional recommendations. The implementation of self-regulatory strategies will be assessed 2 and 6 months after the intervention. Because the objective is to investigate the effects of the ACCOMPAGNE program on the implementation of driving strategies, and the link with awareness of driving difficulties, rather than to examine participants' real driving ability, the driving simulator was chosen over on-road testing. This places drivers in a reproducible and controlled driving environment, and will be used to collect objectives as well as subjective measures of driving ability and self-awareness of this ability. For the same reasons, we will use the differences between the points of view of participants and their natural caregivers to measure the changes after the program.

The secondary objectives are to determine the effects of the ACCOMPAGNE program on (a) self-awareness of driving ability, (b) the mood and quality of life of both participant and natural caregiver, and (c) the natural caregiver's burden. We expect that the ACCOMPAGNE program will (a) increase self-awareness of driving ability (b) maintain participants' mood and quality of life despite any changes made, and (c) maintain the mood and quality of life of natural caregivers, and alleviate their burden to a greater degree than conventional care can.

Methods/design

Design

A national randomized, controlled, trial will be conducted. Two-hundred dyads (consisting of participants and natural caregivers) will be randomly assigned either to the ACCOMPAGNE group or to a control group. The trial will take place in four centers in France: memory clinics and geriatric units of the University Hospitals of Lyon, Reims and Tours, and the Geriatric Hospital of Mont d'Or. The effects of the ACCOMPAGNE program will be assessed 2 months and 6 months after the intervention. For 40 participants in the center in Lyon, a test will also be conducted on a driving simulator.

Participants

Inclusion criteria: Participants must be aged between 50 and 95 years-old, must have a current driving license, and have to drive at least twice a week. Participants must have been diagnosed with a major or minor cognitive disorder in accordance with the DSM-V criteria (e.g., Alzheimer's disease, vascular disease). They must score over 18 on the Mini Mental State Examination (MMSE), and be sufficiently able to speak and write French to perform clinical evaluations and participate in workshops. The cut-off value for the MMSE was fixed at 18 because, below 18/30, patients generally present important cognitive disorders which may greatly hinder their involvement, contribution and understanding of the group intervention. Indeed, some authors used the cut-off of 18/30 to discriminate between mild and moderate or severe neurocognitive disorders (37, 38). There is no upper limit since participants are only included if they have a diagnosis of Mild or Major Neurocognitive Disorders. Thus, the presence of cognitive impairment is objectified by other means than the MMSE score.

A family member will have to accompany them and be present for at least 4 h a week. The natural caregivers must be involved in helping the participant with the activities of daily living and be able to speak and write sufficiently well to perform the clinical assessments. All participants will provide free and informed consent.

Exclusion criteria: Participants must not have any history of major psychiatric disorder, alcoholism, they should not be undergoing non-stabilized antidepressant treatment (i.e., it should not have been changed or started <6 months prior to the study), or have any sensory problems which would prevent them from participating in workshops. They must not suffer from any pathology which compromises their health in the short or medium term, and they must be able to express their consent. The natural caregivers must not have any sensory disturbances which would prevent them from participating in workshops.

To recruit the patient-caregiver dyads corresponding to the inclusion/exclusion criteria, physicians will give them information about the study when seeing them in their care pathway about cognitive complaints. Oral and (comprehensive) written information will be given to them as well as a leaflet summarizing the most important pieces of information about the aims of the study, their roles and what they could expect from it. The fact that the study cannot leads to the authorization or the prohibition of driving was emphasized. You can find the English version of the leaflet in Figure 1.

Randomization

Randomization between the two groups will be stratified in the individual recruitment centers, based on participants' level of cognitive disorder (two levels: minor or major). Randomization by block permutation will be carried out in order to balance the two groups (experimental and control groups), and to allow the workshops to start in the experimental group, which requires a minimum of four dyads. The block permutations will differ in size to ensure the unpredictability of the random allocation.

Participant timeline

There will be three assessments: a baseline assessment (Time 1), another 2 months after baseline (Time 2) and a third 6 months after baseline (Time 3), as shown in Figure 2. Participants will be randomized between two sequences (i) Baseline (Time 1)>Intervention>Time 2>Time 3 or (ii) Baseline (Time 1) >Control>Time 2>Time 3 (as shown in Figure 2). The intervention will be based on seven collective workshops, spread over three half-days (once a week for three consecutive weeks). For participants recruited by Lyon Hospital, the evaluation will also include a driving simulator test at Baseline (Time 1), Time 2 and Time 3.

Intervention description

Experimental group

Dyads included in the ACCOMPAGNE educational program group will take part in seven collective workshops,

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FIGURE 1
English version of the recruitment leaflet.

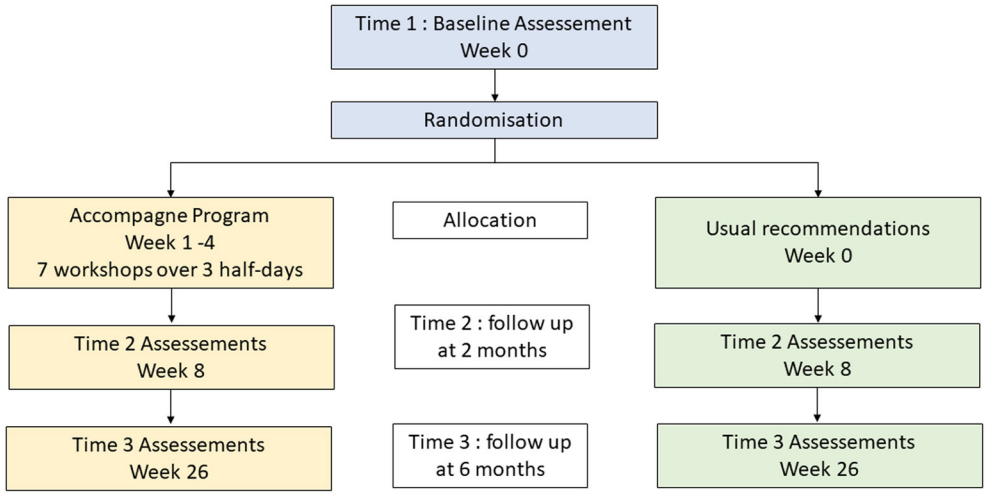

FIGURE 2
Abridged CONSORT diagram.

spread over three half-days (once a week for three consecutive weeks). Each workshop lasts approximately an hour and a half and uses educational content and pedagogical methods. Materials and methods of each workshop are described in Table 1.

A neuropsychologist begins by introducing the program and explains the educational objectives in the *Introductory workshop*.

The neuropsychologist then proposes the *Cognitive skills workshop*. The objective is to help participants and their caregivers to understand the main cognitive functions and behavioral skills (self-control, stress management, compliance with instructions) involved in driving activity. The material provided for this workshop consists of photographs showing several driving situations which are known to be complex for older individuals (heavy traffic, unexpected events, dangerous intersections). The material will help individuals to think about the cognitive functions involved in driving activity, and to better understand the impact of these functions on driving activity. Participants are invited to think about the consequences of cognitive disorders in each of these situations. At the end of the workshop, participants ask any questions they might have, and explain their position regarding the continuation of driving activity.

Next, a physician or a nurse introduces the *Perception and environment workshop*. The objective is to help participants to be aware of the sensorimotor skills needed for safe driving (visual, auditory, motor, gestural skills, proprioception). For each skill (visual acuity for distance and near visual field sensitivity to glare, contrast vision, auditory skills, balance and proprioception functions, motor skills and gestures), participant groups determine the impact of aging and of the main age-related diseases. In this workshop, the effects of medication on driving are discussed, as well as anything else that can impact alertness at the wheel (fatigability, drowsiness). Participants are asked to classify each skill based on their personal situations as either green lights (no risk identified), vigilance points, or red lights (identified danger), and to list the possible actions needed to avoid any risks related to impaired skills (for example, avoiding driving at night).

In the following stage the physician presents the *Responsibilities workshop*. The objective is to help participants to put themselves in the position of a responsible driver, and to fully understand the responsibilities of everyone involved in a given situation. A brainstorming method is used. Stories are presented. These feature characters in driving situations in which their responsibility is involved. Participants are then asked questions. A number of legal aspects are discussed, particularly those related to medical conditions which result in an inability to drive. The procedure for responding to a certified physician, the responsibilities of each person, the legal obligations of health professionals and personal obligations relating to the driver and the vehicle are all described and detailed. The procedures used to assess their fitness to drive are also presented.

A psychologist then goes on to present the *Patient workshop*. The objective is to provide a listening place for participants only. Representations, fears, projections related to driving and cessation are discussed. The photo language method is used. Participants are invited to express the value they place on driving, and their feelings about a possible cessation.

At the same time another psychologist presents the *Caregiver workshop*. The objective is to provide a listening place for caregivers only. Questions related to the procedure involved in the fitness to drive assessment, to anosognosia or defensive

TABLE 1 ACCOMPAGNE program workshops.

Workshop (duration)	Main objective and methods	Materials (example)
Workshop introduction (1 h)	Main objective: To increase participant's involvement by considering him/her as a key member of the workshops and to initiate a group dynamic. Method: Round table: each participant answers the questions on the "question wheel": Name, first name, age, place of residence. Do you like to drive? Do you drive often? For which activities? Do you experience any difficulties when driving? Motor skills? Concentration? Memory problems?	
Cognitive skills workshop (1h30)	Main objective: to facilitate awareness of the cognitive skills involved in driving (visuo-spatial, attentional, memory, executive). Method: After defining the different cognitive mechanisms involved in driving, role plays are distributed. The participants have to imagine the cognitive mechanisms involved in each situation.	
Perception and environment workshop (1h30)	Main objective: To facilitate awareness of sensorimotor skills required to drive safely. Method: For each visual skill (acuity, accommodation, contrast and distance vision) the facilitator creates a discussion around the questions "What role does this skill play in driving? What is the risk if this skill is impaired?" Establishment of a checklist based on sensory status and level of alertness green light = safe driving/orange = adaptation required/red = do not drive	
Driving responsibilities workshop (1 h30)	Main objective: To facilitate awareness of accident risks linked to a driving affected by cognitive disorders or illness. To facilitate awareness of one's own responsibilities as a driver. Method: Reflection on situation vignettes. What are the responsibilities? Does she need to have her driving assessed? In the long term, what steps can she take to assess her driving?	"Mrs. A., 82 years old, attends memory clinic for cognitive disorders and attentional difficulties. She also has a cataract. She uses her car several times a week to do her shopping. On this particular day, it is raining. Mrs A has to turn right, she does not see the bicycle that was riding behind her and hits it. The cyclist is injured and apparently has a broken arm. The cyclist is taken to hospital by the fire brigade and will probably need an operation." What do you think are the administrative steps to be taken for Mrs A.?

(Continued)

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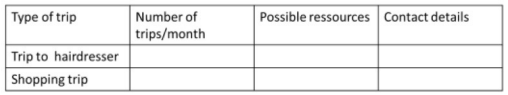
TABLE 1 Continued

Workshop (duration)	Main objective and methods	Materials (example)
Patient workshop (1 h)	Main objective: To share personal experience with driving and with driving adjustments because of cognitive or sensory disorders. Method: Patients are asked to write 8 words or short sentences on 8 post-its (one idea per post-it) around the question "What are the abilities needed to drive safely? A collective meta-plan is made to synthesize all the ideas. Each patient then chooses a photo. The psychologist allows the patients to discuss their representations, and relies on the sharing of experiences to soften the impact of giving up driving.	
Caregiver workshop (1 h) (at the same time than representation workshop)	Main objective: To allow speaking time to the caregivers so they can ask the questions they cannot ask when their relative is present. Method: Envelope method. The natural caregivers ask their questions freely. The facilitators write down each question on a different envelope. Each participant will have to provide solutions to the questions in each envelope in turn (based on their own experience or on information acquired in the previous workshops). A collective discussion then allows the proposed solutions and possible adaptations to be listed.	
Driving strategies and alternatives workshop	Main objective: To establish required strategies or means for safe and autonomous driving. Method: Presentation of risky situations (Night driving, rush hour, city traffic, unfamiliar or long routes, intersections, roundabouts, bends, insertions, difficult weather conditions, motorways, telephones, radio, chatter, physical pain, drunkenness, emotional stress..) and group discussion on possible solutions or alternatives (avoidance, adaptations like turn off the radio in challenging situations, planning the journey ahead of time…). Brainstorming about resources that can be used to avoid some driving situations and making a dyad specific alternative transportation plan.	

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positions, and to their relative's potential opposition to giving up driving are all discussed. This workshop also presents the attitudes that should be adopted and the adaptive measures that can be implemented.

An occupational therapist or a nurse holds a *Driving strategies and alternatives workshop*. Risky driving situations will be presented to the participants and they will discuss, in the group, about possible solutions or alternatives to such situations (avoidance but also other adaptive strategies like turn off the radio in challenging situations, planning journeys ahead of time…). Participants identify which trips are essential in their daily life, and decide which travel mode corresponds best to their needs and capacities. Various strategic or tactical adaptation behaviors for safer driving are discussed with the participants, such as the use of family, friends, associative and municipal resources, alternative transport options and strategies for avoiding risky situations. This workshop will be adapted to each dyad with a list of alternatives depending on the dyad's living place.

The interventions will be standardized, and each center will be provided with a kit containing an educational guide with the specific objectives of each workshop, the key messages, the facilitation techniques to be used, with detailed instructions, the duration of each activity in each workshop and the tools needed during the workshop. An explanatory workshop will take place for all participating health-care professionals before the start of the study. Moreover, to be involved in the workshop, professionals must be trained as a group facilitator and must have at least 3 years' experience in geriatric units.

Control group

participants and caregivers included in the non-experimental group will receive the conventional recommendations for driving a car. These will be provided by their physician during a consultation in the memory clinic, either when they are given their diagnosis or during a follow-up visit. These recommendations consist of a description of the participant's cognitive and sensorimotor risk factors for driving, advice on ways to adapt driving, or a recommendation to stop driving. Information about the procedure involved in responding to a certified physician is also provided.

Outcomes and assessment tools

Main outcome: Implementation of self-regulation strategies

The main outcome is the implementation of self-regulation strategies in driving. Self-regulation strategies will be measured by the participants' scores on the DPPQ "Current Self-Regulatory Practices" subscale (29). The 2-month and 6-month scores of the control group and the experimental group will be compared. The subscale includes eight questions about the frequency of drivers' self-regulation strategies. These strategies consist of: waiting for the rain to stop before driving; asking someone to accompany them rather than driving alone; looking for parking lots to avoid parallel parking; avoiding turning left in traffic; avoiding taking the freeway; avoiding rush-hour traffic; avoiding driving in crowded places; and avoiding driving at night. A four-point scale (0: never, 1: rarely, 2: sometimes, 3: often) reflects the frequency of each item, creating a total score ranging from 0 (never uses any of these strategies) to 24 (uses all strategies often).

Secondary outcomes

- Driving changes:

The secondary objectives focus on driving changes observed by the participants themselves, and changes in the participant observed by the caregiver (see Table 2). Several indicators will be used to obtain these measurements.

Indicators of driving changes in participants will be measured at 2 months and 6 months by a composite score calculated using the first part of the Driving Habits Questionnaire (DHQ) (30) and the other DPPQ sub-scales. Indicators of driving changes perceived by the natural caregiver will be measured at 2 months and 6 months by a composite score which includes scores from the DPPQ and DHQ scales, and scores calculated from observations made by the caregivers about participants' driving. Indicators of self-awareness of driving ability will be measured at 2 months and 6 months by the score obtained in the second part of the DHQ scale filled out by the participant. Those questionnaires (DPPQ and DHQ scale) are self-reported measures but since the patient and the caregiver both answer about the patient driving, we may control for most of the bias induced by such measures. Moreover, authors such as Charlton et al. showed that results with objective methods about self-regulation of driving are coherent with self reported measures (24) which supports our use of those questionnaires.

- Driving performance and self-awareness of driving ability:

Driving performance and indicators of self-awareness of driving ability will be measured for participants who perform tasks on the driving simulator. Driving performance will be evaluated by 6 driving tasks, each of which will represent one scenario: (1) A speed maintenance task to measure the ability to respect a speed limit of 80 km/h and to maintain lane position; (2) A car-following task to measure the ability to keep the vehicle in lane while maintaining a safe distance; (3) an overtaking task to assess the ability to make correct decisions when overtaking a vehicle when driving on a high-speed road; (4) Driving in a rural area to measure the capacity to adapt to different road situations such as stop signs; (5) Driving in an urban area to evaluate the ability to adapt when driving in town, i.e. responding to traffic lights and adapting to unexpected events such as pedestrians crossing,

TABLE 2 Measurements at baseline, 2 months and 6 months after the intervention on the patient and his caregiver.

Outcome	Measure	Filled out by the:		
		Patient	Caregiver about the patient	Caregiver about himself
Implementation of self-regulation strategies in driving	DPPQ's "Current Self-Regulatory Practices" (29)	x		
Indicators of driving changes	DHQ (30)	x		
Indicators of changes perceived by the caregiver	DHQ and DPPQ scales		x	
Indicators of driving ability self-awareness	Second part of the DHQ scale, objective measures from driving simulator and subjective measures from a questionnaire administered just after each simulator task.	x		
Indicators of mood effects of driving modifications	GDS (39)	x		x
Indicators of quality of life effect of driving modifications	QoL-AD scale (40)	x		x
Indicators of caregiver burden of driving modifications	ZBI (41)			x

a vehicle pulling out of a parking space suddenly; (6) A braking task to measure the ability to brake quickly. These tasks were designed to assess driving performance in different situations varying in difficulty. That is why we used a variety of driving situations often encountered while driving: high-speed road, rural area and an urban area. Moreover, the variety of the tasks [following a vehicle (1), respect speed limit and maintain lane position (2), overtaking (3), adapt to different road situations and unexpected events (4, 5) and braking (6)] assess different abilities (e.g., motor, attentional) required for driving and are frequently used in driving simulator studies (42–44). To avoid fatigue effects, the driving tasks are short (no longer than 5 min).

For each task, means and standard deviations of speed, lane position, steering angle, reaction times to traffic lights or unexpected events will be measured. In addition to the objective measures obtained from simulator data, subjective measures will be collected from a questionnaire administered to the participant immediately after each simulator task. While the participant will perform the driving task, the experimenter will fill out the same questionnaire about participant's driving ability (i.e., perception of participant's driving ability). The comparison between the scores obtained from the participant and the experimenter will inform on the participant's driving ability self-awareness. Finally, objective as well as subjective measures will inform on the participant's driving ability and his/her self-awareness of this ability, respectively.

- Mood:

Indicators of mood effects on driving modifications will be measured by the Geriatric Depression Scale 15-item version (GDS 15) (39) in both participants and their natural caregivers at 2 and 6 months.

- Quality of life:

Indicators of quality of life following driving changes will be measured by the Quality of Life in Alzheimer's Disease Scale (QoL-AD) (40) in both participants and their natural caregivers at 2 and 6 months.

- Caregiver burden:

Indicators of caregiver burden following driving changes by the participant will be measured 2 and 6 months by the Zarit Burden Inventory (ZBI) (41) for natural caregivers.

Sample size and data analyses

The self-regulation strategy in driving will be considered beneficial if the score of "Self-Regulatory Practice" increases on average by two points (24) 2 months from inclusion. The number of subjects was computed by considering a Student *t*-test for equal variances between the two groups, with a two-sided alpha risk of 5% and a power of 80%. Based on the sample size calculation, 90 participants per group is considered sufficient to detect differences between the two assessments. Because a 10% loss of dyads is expected during the follow-up period, 100 participants per group will have to be recruited, i.e. a total of 200 participants.

Kolmogorov-Smirnov tests will be used to determine the normality of variables. For demographic, clinical, neuropsychological variables, and scores obtained from scales (e.g., the DPPQ), between-group differences will be examined using Fisher's Exact tests, independent Student *t*-tests or Wilcoxon rank-sum tests, as appropriate. The effect size in the intervention group compared to the control group will be quantified by estimating the difference in mean scores between the 2 groups (experimental vs. control) with a 95% confidence interval. A multiple linear regression model will be performed with DPPQ "Current Self-Regulatory Practices" as the dependent variable, and the level of cognitive impairment at inclusion and other characteristics that may have an effect on the outcome criterion as factors. A mixed-effect linear regression model will also be computed with DHQ, GDS-15, Qol-AD and ZBI as dependents variables, and the group (experimental vs. control) and follow-up time (inclusion, 2 and 6 months) as independent variables. The interaction between the intervention group and the follow-up time will be observed.

The concordance between the performance on the driving simulator and the perception of driving ability measured immediately after simulated driving will be estimated by the Lin concordance correlation coefficient and by the Bland & Altman method for continuous criteria, and by the Cohen Kappa coefficient for ordinal criteria. The number of participants who significantly change their estimation at 2 and 6 months compared to before the intervention will be measured from objective and subjective measures at the different points in time.

Procedure

Participants who are more likely to participate in the study will be identified during attendance at the memory clinics or in the geriatric departments of the four centers. The inclusion criteria will be checked during the pre-inclusion visit. During the visit to determine inclusion, a physician will take the medical history and note any comorbidities (including a diagnosis of cognitive disorder). He/she will also perform a sensory-motor examination using the Short Physical Performance Battery (balance, walking speed, chair raising), the Stop Walking when Talking (motor and verbal double task) and the Handgrip strength to detect physical frailty (Fried's criteria). Socio-demographic data and current medication will also be noted. A nurse will perform a visual examination by assessing the uni and binocular distance visual acuity (Monoyer scale) and near visual acuity (Parinaud scale). He/she will also perform a screening for age-related macular degeneration (Amsler grid), explore the visual field (with a finger) and examine the color perception. A neurocognitive examination will be performed by a neuropsychologist using the Victoria Stroop Test, the Trail Making Test (A and B), verbal fluencies ("P" and "Animals" in 2 min), the Rey Figure copy, and Digit Span and Coding from the WAIS-IV.

On the day of the inclusion visit, the neuropsychologist will administer the DPPQ, DHQ, QoL-AD, GDS-15 scales to the participant. Natural caregivers will respond by themselves to the DPPQ and DHQ scales (based on observations made about the participant's behavior), and to QoL-AD, GDS-15, ZBI. The dyads included in the control group will receive the usual medical recommendations on the same day. The dyads included in the intervention group will be invited to the three half-day workshops. Workshops will start as soon as the experimental group contains four dyads. At 2 and 6 months, the neuropsychologist will administer the DPPQ, DHQ, QoL-AD, GDS-15 scales to the participant. Caregivers will complete the DPPQ and DHQ scales, (based on observations regarding the participant's behavior), and the QoL-AD, GDS-15, ZBI on their own. A questionnaire about life events that took place between each visit will also be administered to the patient and the caregiver at 2 and 6 months. For 40 participants recruited in the Lyon center, observations on a driving simulator will be collected at inclusion, at the 2-month visit and at the 6-month visit.

Potential pitfalls and unintended effects

This study may face different difficulties. As it tackles the delicate question of driving among olders and more specifically among olders with neurocognitive disorders, we could face difficulties in recruiting participants. Indeed, it is possible that participants with neurocognitive disorders may not take part in this study due to a fear of license loss, even if there is no implication for reporting medically at-risk drivers to the jurisdiction's governing authority. Moreover, we need to include patient/caregiver dyads, thus, in order to be involved in the study, the patient will need to have a natural caregiver, available and willing to participate which reduces the number of potential participants. If recruitment difficulties turn out to be too important, it could lead to a small sample size, which may limit the generalisability of the results. In addition, uncontrolled intercurrent variables related to the individual history of the disease could bias our result. That is why, we choose to control for such variables as best as possible by using questionnaires about life events at 2 and 6 months. Furthermore, the intervention duration (i.e., 3 weeks) may not be sufficient to produce the expected outcomes. Lastly, for the subgroup of patients who undergo a driving task, the use of the driving simulator can generate simulator sickness and may frighten or shock the patient if he/she makes a serious mistake in the driving scenarios such as hitting a pedestrian or another car.

Discussion/conclusion

For older people with cognitive disorders, driving cessation can lead to a series of negative changes in terms of autonomy

and mood for both the patient and the natural caregiver. Recent studies agree on the need to implement interventions to provide support for patients and natural caregivers during the process of adaptation, and then on cessation of driving (14, 15). However, the studies carried out so far have focused on targeted interventions for patients only or natural caregivers only (16, 19, 20), even though interactions between patient and caregiver seem to be at the heart of this process. The onset of cognitive impairment requires the adaptation of driving activity, rather than its abrupt cessation. An intervention program which makes both the patient and the natural caregiver actors in the process of giving up driving seems therefore necessary. This should cover all aspects involved, beginning with an awareness of driving ability, and the subsequent implementation of self-regulated driving strategies, all the way through to complete cessation of driving. This cognitive, social and psychological support should also help to maintain the quality of life and mood of patients and their natural caregivers despite driving limitations. It is also important to consider the environment in which the patient lives. Travel needs and dependence on a car are not the same depending on where the patient lives (e.g., in the countryside or in the city). Severity of disease and the associated road risks will also have to be estimated in any analysis of the maintenance or cessation of driving for these patients. The results will provide information on how to optimize the care of people suffering from neurocognitive pathologies. If the results are conclusive, this approach could be extended to all other centers dealing with this problem.

Ethics statement

The Regional Ethics Committee (Comité de protection des personnes SUD-OUEST ET OUTRE-MER II) has approved the study (Decision reference number: 20.01612.220050). Authorization for handling these data was granted by the French Data Protection Authority (CNIL: Commission Nationale de l'Informatique et Liberés). The practitioner will give an information document explaining the objectives and the protocol of the study to the patient and the natural caregiver. They will have enough time to think about their participation in the study. Informed written consent will be obtained from all participants before the start of the study.

Author contributions

FD-C and M-HC initial idea, drafted, revised, and approved the protocol and manuscript. RB, MG, and ML drafted, revised, and approved the protocol and manuscript. LP-F and MR initial idea and revised and approved the protocol focusing driving abilities. CG and PK-S drafted, revised, and approved the protocol and manuscript and obtained funding. All authors have made substantial contributions to conception and design, acquisition of data, and read and 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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Rhythmic auditory stimulation promotes gait recovery in Parkinson's patients: A systematic review and meta-analysis

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Objective: Using rhythmic auditory stimulation (RAS) to improve gait disturbance in Parkinson's disease (PD) is an available treatment option, yet a consensus on its effectiveness remains controversial. We summarized the effects of RAS on gait, functional activity and quality of life in PD patients through a systematic review and meta-analysis.

Methods: PubMed, Embase, Web of Science, Medline, and Cochrane Library databases were initially searched to identify relevant literature up to August 2021. Next, the methodological quality of eligible comparative studies was assessed by the Physiotherapy Evidence Database Scale. The treatment effects to clinical outcome in relation to gait, motor activities, and quality of life were analyzed.

Results: A total of 18 studies consisted of 774 subjects were included in this meta-analysis. Comparing with the control group, RAS had significantly increased stride length ($p < 0.001$), accelerated gait speed ($p < 0.001$), reduced the occurrence of freezing events during walking ($P = 0.009$), achieved an improvement in Unified Parkinson's Disease Rating Scale (UPDRS) II ($P = 0.030$), UPDRS-III ($P < 0.001$) and Parkinson's Disease Quality of Life Questionnaire (PDQL) ($p = 0.009$) scores over an interval of 1–26 months.

Conclusion: In this meta-analysis of 18 randomized controlled trials, we have demonstrated that RAS improves the general motor functions (UPDRS-III), particularly in gait, mobility and quality of life, in patients with Parkinson's disease.

KEYWORDS

Parkinson's patients, rhythmic auditory stimulation, gait, mobility, meta-analysis

Introduction

Parkinson's disease (PD) is a common age-related neurodegenerative disease after Alzheimer's disease, affecting 1% of the world's population over the age of 60 years (1). With an aging population, the number PD patients are expected to reach 13 million by 2024, doubling in the next 10 years by 2034 (2–4). PD patients often present with tremor, rigidity, bradykinesia, gait disturbance, balance and coordination disorders, accompanied by non-motor-related symptoms such as cognitive and psychological impairment, neurobehavioral abnormalities, and sleep disturbances (5–7). Motor symptoms are caused by the loss and degeneration of dopaminergic neurons in the dense part of substantia nigra. As there is no curative treatment for Parkinson's disease, symptomatic relief by medications and the Deep Brain Stimulation are regarded as the main management modalities (8). Pharmacological interventions are primarily to increase dopamine levels *via* the use of dopaminergic drugs. However, long-term use of dopaminergic drugs can have serious side effects on patients, such as loss of efficacy and accumulation of toxicity (9, 10). Besides, the axial symptoms of gait disturbances do not respond to pharmacotherapy and deep brain stimulation (11–14). 25–60% of patients experience freezing of gait usually after several years from disease-onset. As Gait disturbances respond poorly to treatments, physical rehabilitation techniques are gaining interest as an adjunct in the management of these patients when the combined therapies of medication and surgery are failing (5, 15, 16).

Physical activity has a positive impact on gait, cognitive function, and quality of life in patients with Parkinson's disease (17, 18). The joy of an independent functional mobility does generate a positive motivation in these patients (19). Music is an effective emotional relaxant that helps relieve anxiety and pain (20). Rhythmic auditory and visual cues can improve all types of freezing of gait, dopamine-responsive or dopamine-resistant, according to the literature, a Level B evidence (4). At present, there is no systematic review or meta-analysis using high quality randomized double-blinded controlled trials of sufficient size and power to lead to a definitive study in the future (4). Therefore, combining music with physical activity is a feasible, enjoyable, and probably sustainable option. Studies have shown that gait training accompanied by music and rhythmic auditory stimulation (RAS) can significantly increase patients' stride length and speed (21). Compared with treadmill gait training alone, treadmill gait training with rhythmic auditory stimulation can significantly improve gait and quality of life (22, 23). Several systematic reviews and meta-analyses have reported the effectiveness of RAS on gait in patients with Parkinson's disease (24, 25). In addition to the retrospective cohort studies, there have been several recent randomized controlled trials (RCTs) in the field. We have updated the published RCTs with a more comprehensive meta-analysis.

Abbreviations: RAS, Rhythmic Auditory Stimulation; PD, Parkinson's disease; RCT, Randomized Controlled Trial; PRISMA, Preferred Reporting Items for Systematic Reviews; PEDro, Physiotherapy Evidence Database; TUG, Timed Up-and-Go test; UPDRS, Unified Parkinson's Disease Rating Scale; PDQL, Parkinson's Disease Quality of Life Questionnaire; BBS, Berg Balance Scale; FES, Falls Efficacy Scale; FOGQ, Freezing of Gait Questionnaire; MD, Mean Difference; CI, Confidence Interval; WMD, Weighted Mean Difference; FoG, Freezing of Gait.

Methods

Study design

This systematic review and meta-analysis were carried out under the statement of Preferred Reporting Items for Systematic Reviews, PRISMA (26).

Retrieval strategy and literature selection

PubMed, Embase, Web of Science, Medline, and Cochrane Library databases were thoroughly searched, to obtain studies published between January 2000 and August 2021. The searching keywords included ("tread," "gait," "train," "exercise," "rehabilitation" or "treatment") and ("Rhythmic," "auditory stimulation," "musical stimulation," "music" or "acoustic") and ("Parkinson's disease").

All eligible studies in this meta-analysis had to meet the following criteria: (1) patients had idiopathic Parkinson's disease; (2) patients in the intervention group received a course of music or rhythmic auditory stimulation during physical therapy whereas the control group received conventional physical therapy; (3) the effects of the intervention on gait, mobility, and quality of life were reported; (4) patients participating in study $\geq$ 10; (5) the study should be publish in English and peer-reviewed journals; (6) the study should be randomized controlled trials.

Exclusion criteria: (1) patients should not be too frail to receive physical therapy. They should not be cognitively impaired to follow instructions of physical therapy; (2) case reports, reviews, letters, comments and abstracts were not included; (3) studies where assessment outcome was unavailable.

Quality evaluation

The Physiotherapy Evidence Database (PEDro) scale was used to assess the quality of included studies (27). The PEDro scale consists of 11 items, including random assignment,

undercover assignment, baseline comparability, subject blinding, therapist blinding, assessor blinding, adequate follow-up, intention-to-treat analysis, between-group comparisons, point measures, and variance measures. The maximum PEDro score is 10. The quality of the study was classified as "excellent" (9–10 points), "good" (6–8 points), and "fair" ($\leq$ 5 points) based on the PEDro score (25). Studies with a PEDro score $\geq$ 6 will be included in this meta-analysis. The quality assessment was performed independently by two researchers (LL and HR). When any disagreements arose, the two researchers resolved them in discussion with a third researcher (YXF).

Data extraction

Two researchers (LL and HR) independently extracted primary data from eligible studies using a standardized form. The following relevant variables would be extracted: (1) study characteristics: first author, year of publication, region of study, and PEDro score; (2) subject characteristics: sample size, age, disease duration, and Hoehn and Yahr staging; (3) gait kinematic parameters: stride length, stride duration, gait speed, stride frequency, swing, and timed up-and-go test (TUG); and (4) clinical parameters: Unified Parkinson's Disease Rating Scale (UPDRS), Parkinson's Disease Quality of Life Questionnaire (PDQL) score, Berg Balance Scale (BBS), Falls Efficacy Scale (FES), and Freezing of Gait Questionnaire (FOGQ). UPDRS-III is the most popular assessment tool for motor function impairment for patients with Parkinson's disease. We have therefore chosen it as the primary outcome for our study.

Both freezing of gait (FoG) and Speed are regarded as refractory symptoms in advanced Parkinson's disease. We have selected them for secondary outcomes (FOGQ and Speed). If the corresponding data could not be extracted directly from the study, it would need to be reanalyzed. Where there were disagreements between the above two researchers, a third researcher (YXF) was asked to review literatures until a consensus was reached. The data management and statistical analysis were performed by YXF and reviewed by statistician JYZ from the core laboratory.

Data analysis

Analyses were conducted using STATA 16.0 SE. As the outcomes investigated were continuous variables and scale of measurement, we used mean difference (MD) and corresponding 95% confidence interval (95% CI) for assessment. When the same scale and units were used for all study outcomes, the weighted mean difference (WMD) and its corresponding 95% CI were used as the pooled statistic in the meta-analysis. Forest plots were used to display the pooled results of the meta-analysis. Between-study heterogeneity was assessed using I^2 and two-tailed p-values (28). No statistically significant heterogeneity was considered when $I^2 < 50\%$, $p > 0.05$, so a fixed-effects model was adopted. Otherwise, a random-effects model was applied (29). The effect size was significant when the pooled 95% CI excluded 0 and the p-value < 0.05.

Results

Flow chart Figure 1 showed the process and results of literature screening. By searching the online database, a total of 1,187 studies were obtained. After excluding the duplicate studies, 634 remained. Five hundred and twenty six studies were removed as they did not meet the eligibility criteria. Finally, 18 studies were included after the full text of 108 literature were read (22, 23, 30–45).

A total of 774 subjects were included in these 18 studies, there were a total of 396 patients in the intervention group and 378 patients in the control group. The sample sizes of subjects included in these studies ranged from 16 to 112. The mean age of the participants in each study ranged from 62 to 72 years. The regions of eligible studies included Italy (22, 33, 36, 38, 42, 44, 45), Sweden (23, 31), Poland (39), Brazil (34) and Romania (30), Canada, (32, 43), the United States (35, 40, 41), China (37). The average disease duration of PD patients included in the study ranged from 4 to 13 years. Three papers did not specify the duration of disease in the included subjects. The Hoehn-Yahr staging of the included Parkinson's patients covered stages 1 to 4. Similarly, three studies did not specify the Hoehn-Yahr staging of the included subjects. The PEDro scores of the included studies were all six and above. All eligible studies were RCT studies. Table 1 demonstrates the essential characteristics of all eligible studies.

Effect of RAS on gait parameters

A total of six studies reported the effect of RAS on the stride length of Parkinson's patients. As no significant heterogeneity was found ($I^2 = 0.0\%$, $p = 0.935$), we used a fixed-effects model for analysis. The stride length of patients in the intervention group significantly increased by 5 cm compared with the control group (WMD = 4.64, 95% CI: 3.12–7.69, $p < 0.001$) (Figure 2A). Three studies with a total of 112 patients reported on the stride duration of patients. The pooled WMD was −0.03 (95% CI: −0.09–0.04, $p = 0.426$), suggesting no significant effect of RAS on shortening stride duration (Figure 2B). Seven studies of published material on stride speed showed that rhythmic auditory stimulation significantly accelerated speed in patients

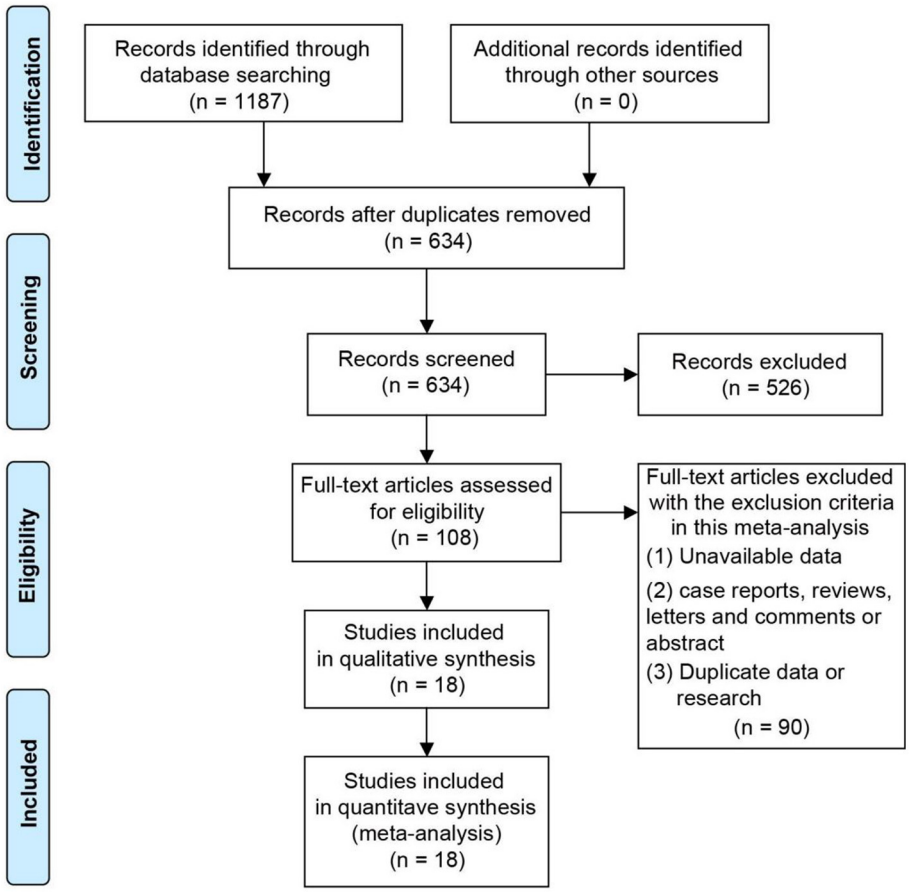

FIGURE 1
Flow chart of the search and screening of the included literature.

compared with the control group (WMD = 0.06, 95% CI: 0.03–0.08, $p < 0.001$) (Figure 2C).

A total of 5 studies with 287 subjects compared patients' step frequency in the intervention and control groups. Due to significant heterogeneity ($I^2 = 79.4\%$, $p < 0.001$), a random-effects model was used to analyze the role of RAS on step frequency. The pooled WMD was 1.57 (95% CI: −4.91–8.05, $P = 0.635$), suggesting that the effect of RAS on step frequency was not significant (Figure 3A). A total of 3 publications reported the percentage of patients swinging. Pooled results showed no statistically significant difference between the rhythmic stimulation and the swing of patients in the control group (WMD = 0.39, 95% CI: −0.44–1.22, $p = 0.468$) (Figure 3B). Seven studies involving 332 Parkinson's patients reported TUG. $I^2 = 87.2\%$, $p < 0.001$, suggesting significant heterogeneity, so a random-effects model was used for the pooled analysis of TUG. There was no significant difference in the effect of RAS in reducing TUG compared to the control group (WMD = −0.68, 95% CI: −3.69–2.33, $P = 0.658$) (Figure 3C).

Effect of RAS on clinical parameters

BBS was used to assess balancing capacity of PD patients. A total of 4 studies, including 242 patients, reported the effect of RAS on BBS. The pooled results showed no statistically significant difference between RAS and the control group in improving the balance of patients (WMD = 1.44, 95% CI: −0.53–3.42, $p = 0.152$) (Figure 4A). Next, we used the FES to assess patients' fear of falling. A total of 3 publications reported FES. The pooled WMD was −1.68 (95% CI: −3.35–0.00, $P = 0.05$), suggesting that no significant difference emerged between the control and intervention groups in improving the effect of FES (Figure 4B). Finally, the FOGQ was used to assess patients reported freezing events during walking. Five studies follow the effect of RAS on FOGQ in patients with PD showed that RAS significantly reduced the occurrence of freezing events during walking compared with the control group (WMD = −2.06, 95% CI: −3.60–0.53, $p = 0.009$) (Figure 4C).

The results obtained in the analysis of the second part of the UPDRS (UPDRS-II) showed that RAS significantly

TABLE 1 Main characteristics of the studies included in the meta-analysis.

References	Region	Total sample size	Age	Disease duration	Hoehn-Yahr stage	PEDro score
Pacchetti et al. (45)	Italy	32	62.85 ± 4.93	5.00 ± 2.52	2–3	8
Frazzitta et al. (44)	Italy	40	71.00 ± 7.42	13.05 ± 4.30	3	7
de Bruin et al. (43)	Canada	22	65.55 ± 6.47	5.45 ± 3.81	2–3	7
Modugno et al. (42)	Italy	20	62.60 ± 4.27	9.70 ± 4.60	2–4	7
Kadivar et al. (41)	USA	16	71.90 ± 6.20	NA	2–4	8
Pohl et al. (23)	Sweden	18	68.20 ± 5.10	8.80 ± 3.80	NA	6
Harro et al. (40)	USA	20	66.10 ± 10.31	4.12 ± 2.26	1–3	6
Song et al. (37)	China	112	65.90 ± 7.97	6.80 ± 2.99	NA	8
De Icco et al. (38)	Italy	35	74.00 ± 7.41	10.34 ± 4.60	2–4	7
Bukowska et al. (39)	Poland	55	63.42 ± 10.10	6.07 ± 4.11	2–3	7
Murgia et al. (36)	Italy	38	68.20 ± 10.51	6.35 ± 5.76	1–3	7
Thaut et al. (35)	USA	60	71.94 ± 7.47	11.04 ± 5.43	3–4	8
Calabro et al. (22)	Italy	50	71.50 ± 8.06	9.65 ± 2.99	2–3	7
De Luca et al. (33)	Italy	40	63.20 ± 8.40	NA	2–3	6
Pohl et al. (31)	Sweden	46	70.00 ± 6.52	6.35 ± 4.05	1–3	8
Mosabbir et al. (32)	Canada	36	69.40 ± 9.50	6.50 ± 4.40	NA	8
Capato et al. (34)	Brazil	102	72.75 ± 8.84	7.44 ± 6.91	1–3	7
Fodor et al. (30)	Romania	32	66.35 ± 5.66	NA	1–3	6

improved impairment in activities of daily living in Parkinson's patients (WMD = −2.76, 95% CI: −5.25 to −0.27, $p = 0.030$) (Figure 5A). The third part of the UPDRS (UPDRS-III) was used to measure motor impairment. A total of 10 studies containing 403 subjects reported the UPDRS-III. The pooled WMD was −4.74 (95% CI: −6.98–2.51, $p < 0.001$), indicating that the RAS significantly reduced the occurrence of dyskinesia with significant heterogeneity ($I^2 = 84.7\%$, $p < 0.001$) (Figure 5B). A total of four papers have examined the effect of RAS on PDQL scores. Compared with the control group, RAS had a positive effect in improving PDQL scores without significant heterogeneity (WMD = −4.52, 95% CI: −8.11– −0.94, $P = 0.009$) (Figure 5C).

Publication bias

The R software was employed to test the publication bias of one primary and two secondary outcomes. These data points represented by individual studies in a funnel plot (Figure 6) were distributed on both sides of the middle solid line, basically in a symmetrical shape. The funnel plots for UPDRS-III, Speed and FOGQ suggest no significant publication bias.

Discussion

Parkinson's disease is a common age-related neurodegenerative disease and has remained a challenging health problem. Most patients will develop disabling symptoms such as gait freezing, despite optimal medical and surgical therapies. Gait training represent a potentially effective aid for managing PD symptoms not responding to dopaminergic drugs, as cues seem to be able to access rhythmic entrainment mechanisms even in the absence of dopaminergic stimulation (7, 38). This current systematic review and meta-analysis summarizing the effects of the 18 selected studies that met the inclusion criteria, generated the pooled results of RAS exhibiting a significant improvement for gait disturbances, motor activities, and quality of life. In addition, concurrent RAS during physiotherapy significantly increased stride length, accelerated stride speed, reduced the occurrence of walking freezes, promoted mobility, and improved PDQL scores in Parkinson's patients.

Moreover, external stimuli such as acoustic, visual, and somatosensory stimuli can modulate motor patterns in Parkinson's patients, helping them start physical activity and maintain the motivation for motor tasks (19, 38, 46). PD can severely affect patient's gait parameters, such as stride length, stride duration, speed, and gait frequency. The temporal and spatial parameters of gait are associated with unhealthy events in the elderly, including falls, functional decline, and even death (47). Studies have shown that providing RAS alongside gait training significantly improved patients' overall gait quality index, balance, strides length and number, consistent with the results of our meta-analysis (22). The pooled results indicated that RAS had no significant effect on cadence in PD patients. The increase or decrease in step frequency had different effects

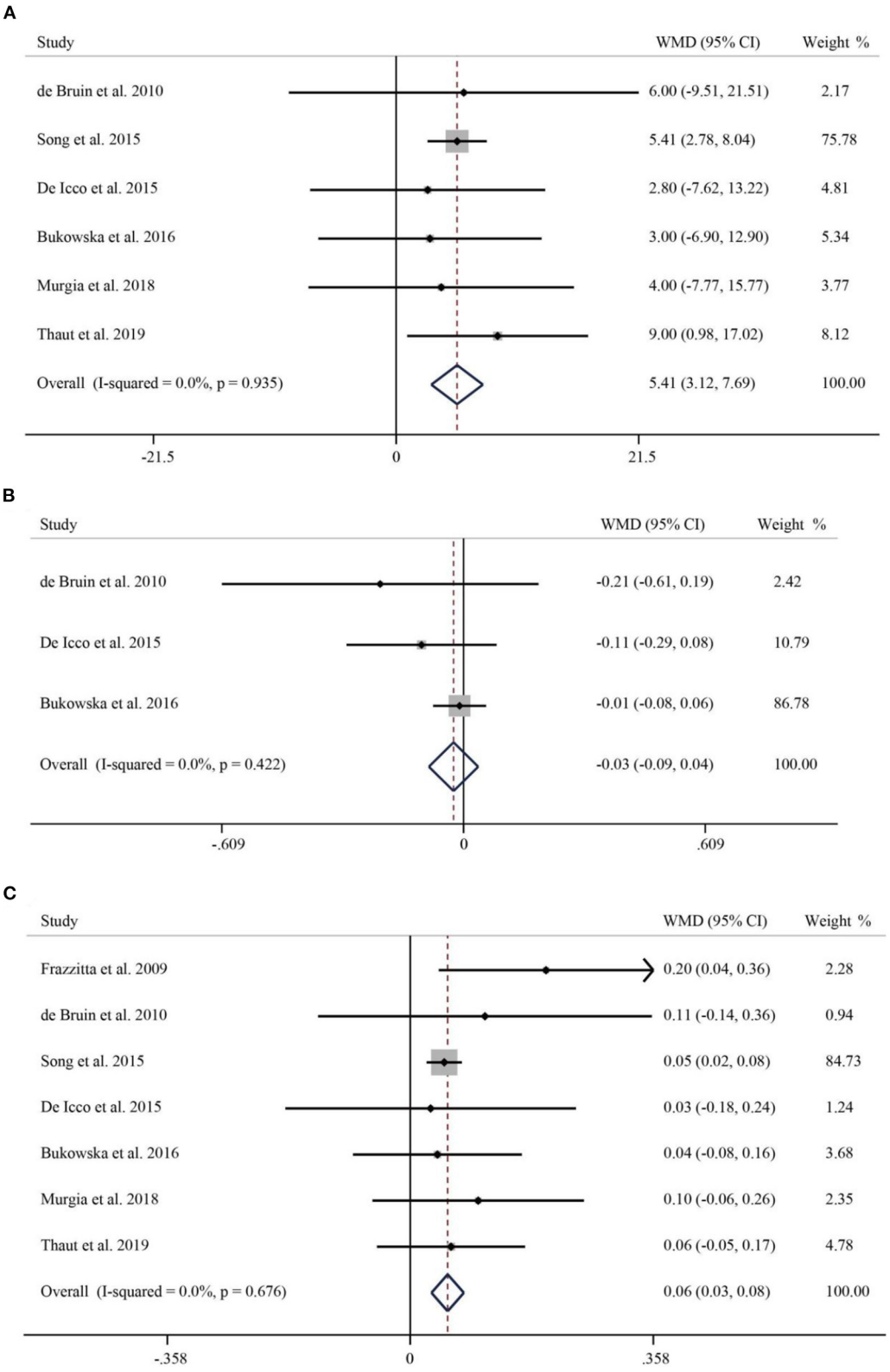

FIGURE 2
Forest plot of RAS vs. the control group for stride length **(A)**, stride duration **(B)**, and speed **(C)**.

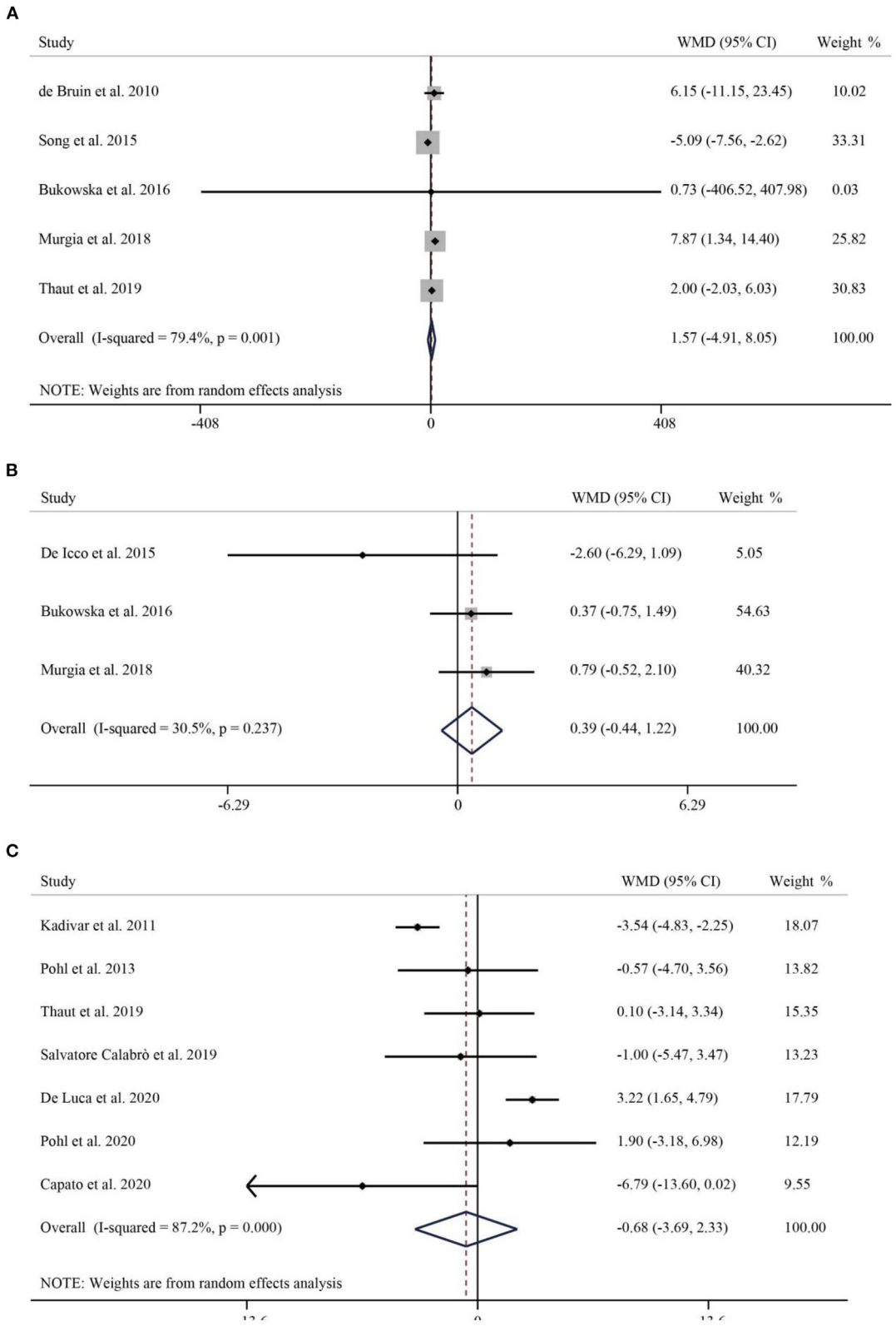

FIGURE 3
Forest plot of RAS vs. the control group for step frequency **(A)**, swing **(B)**, and TUG **(C)**. TUG, Timed Up-and-Go.

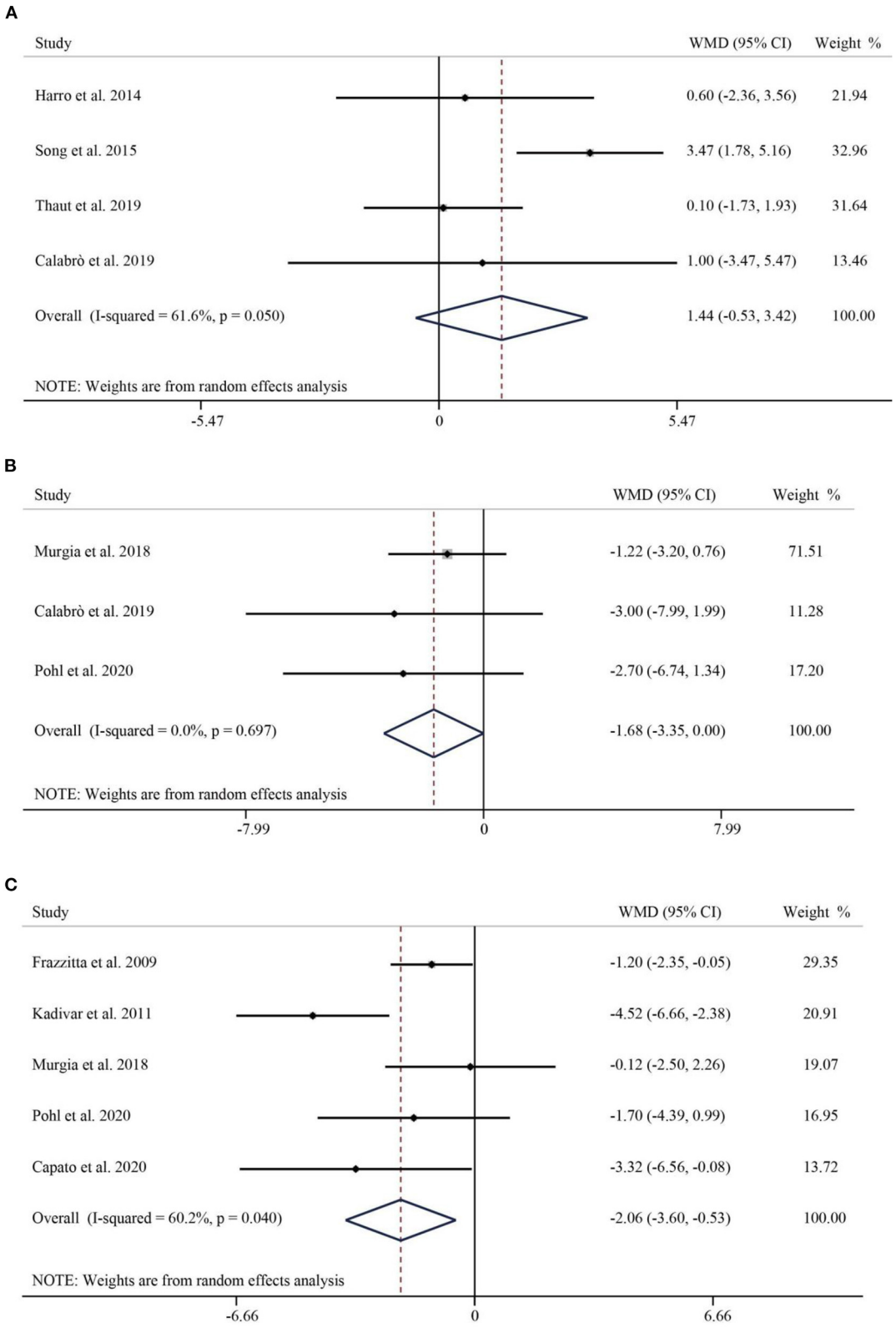

FIGURE 4
Forest plot of RAS vs. the control group for BBS **(A)**, FES **(B)**, and FOGQ **(C)**. BBS, Berg Balance Scale; FES, Falls Efficacy Scale; FOGQ, Freezing of Gait Questionnaire.

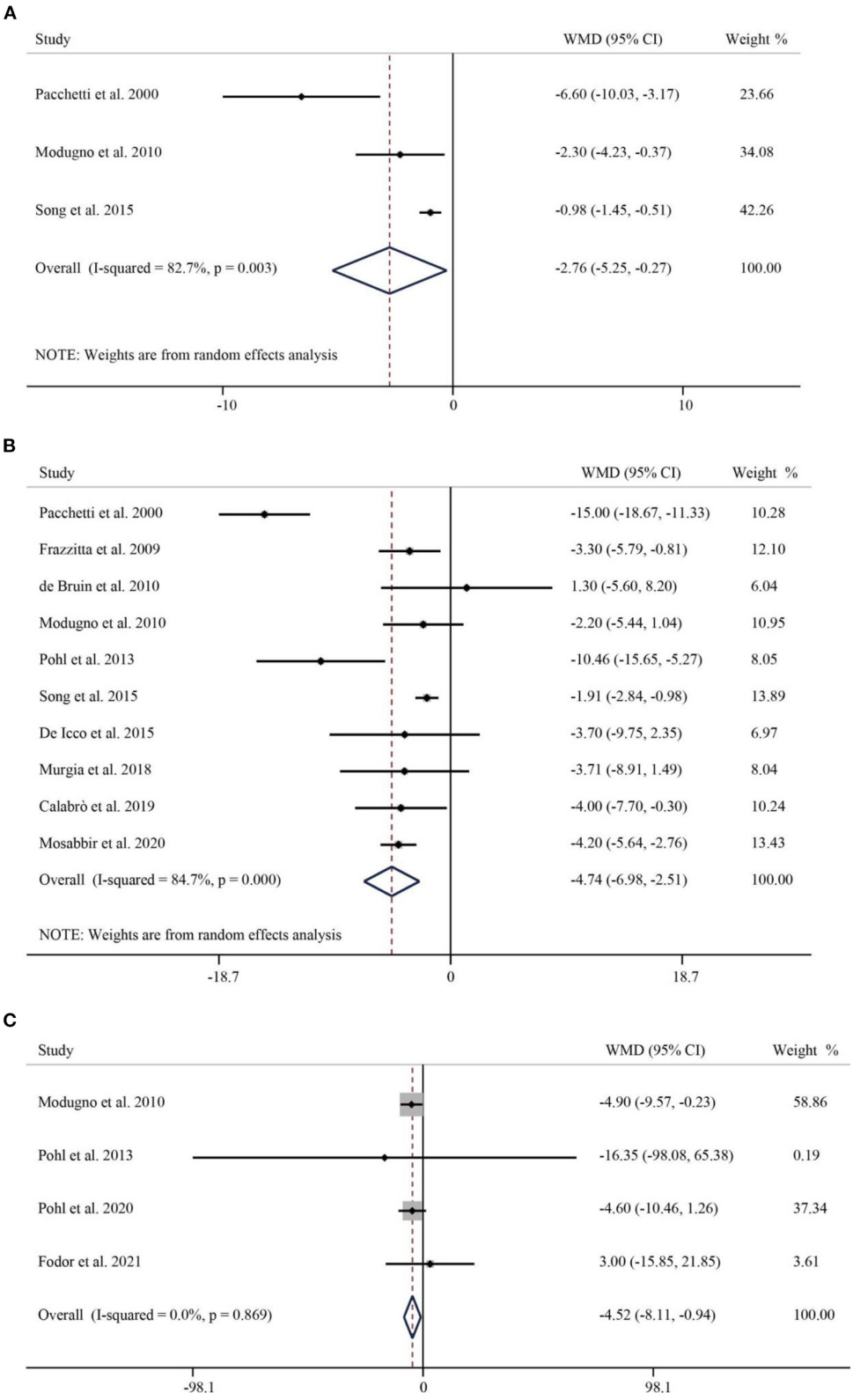

FIGURE 5
Forest plot of RAS vs. the control group for UPDRS-II **(A)**, UPDRS-III **(B)**, and PDQL **(C)**. UPDRS, Unified Parkinson's Disease Rating Scale; UPDRS-II, UPDRS- Activities of Daily Living; UPDRS-III, UPDRS- Motor Symptoms; PDQL, Parkinson's Disease Quality of Life Questionnaire.

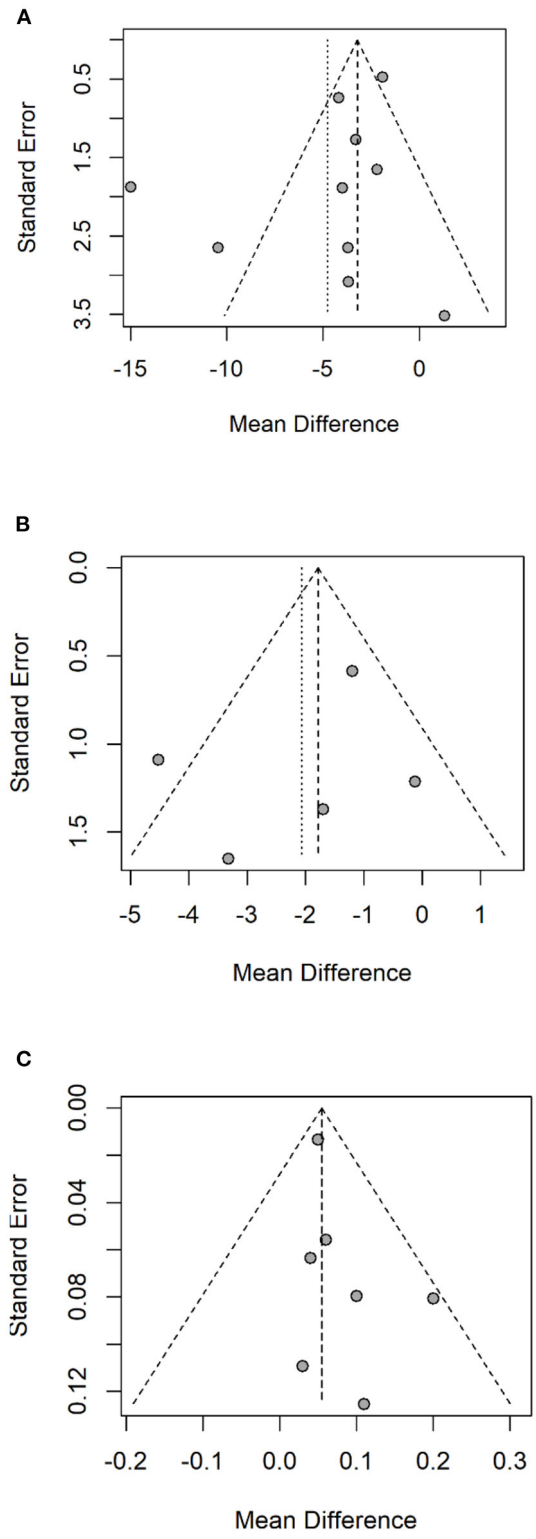

FIGURE 6
Funnel plot of UPDRS-III **(A)**, FOGQ **(B)**, Speed **(C)**. UPDRS-III, Unified Parkinson's Disease Rating Scale - Motor Symptoms; FOGQ, Freezing of Gait Questionnaire.

on patients at different stages of the disease (48). Studies have shown that in order to maintain gait speed, people's gait frequency increases with age. However, the increase in gait frequency can adversely affect the stability of walking (49).

Freezing of gait (FoG), defined as "a brief, intermittent absence or significant reduction in the forward progress of the foot despite intentional walking," is the most distinctive features of patients with advanced Parkinson's disease (50, 51). FoG can lead to reduced mobility, increased incidence of falls, and a significant negative impact on quality of life (52, 53). Wroblewska et al. found that Nordic walking has a lasting improvement effect on PD patients (54). Studies have shown that receiving auditory and visual cues during treadmill training has a better effect on improving gait freezing than traditional treatments (44). Capato et al. proved that compared with conventional training, RAS can have a significant improvement in the overall well-being of PD during the 6-month follow-up (34).

UPDRS is used to measure the severity of Parkinson's disease. Although UPDRS-II does not directly evaluate the walking and mobility of PD patients, it covers the evaluation of the patient's motor and non-motor symptoms, such as walking, mobility, and other activities of daily living. The results of existing studies and this meta-analysis show that RAS intervention significantly improves UPDRS-II (37, 42, 45). On the other hand, UPDRS-III is used to assess motor status, including tremor, rigidity, bradykinesia, gait, and postural instability. Duncan et al. concluded that compared with the control group, tango can significantly improve the UPDRS-III score of PD patients, and it still has a lasting improvement effect after 12 months of follow-up (55). Our pooled results align with previous studies that RAS significantly reduces the disability scores of UPDRS-III (22, 37, 38).

Levodopa, dopamine agonists, and type B monoamine oxidase inhibitors are traditional medications for Parkinson's disease (9). However, pharmacotherapy can only alleviate symptoms, not the underlying pathology (56). In addition, adverse effects such as loss of potency and toxicity may occur with long-term use of dopaminergic drugs, which may be due to a decrease in the integrity of dopamine transport in the striatal nerve endings of the substantia nigra associated with levodopa. Also, the progression of the disease may reduce the effectiveness of the drug (10, 57). Therefore, RAS has increasingly received attention to enhance gait performance in patients with Parkinson's disease. Rhythmic changes are associated with various neurophysiological changes, such as increased activation of neurons in the frontal-occipital network and increased excitability of spinal motor neurons by the reticulospinal pathway (58).

Acceptance of RAS can facilitate motor activation patterns by increasing frontal-occipital network connectivity and

TABLE 2 PICOs (population, intervention, control, outcome and strategy) characteristics of the studies included in the meta-analysis.

References	Population	Intervention	Comparison	Outcome	Study
Pacchetti et al. (45)	Parkinson's disease patients with stable response to levodopa and in Hoehn and Yahr stage 2 or 3	Choral singing, voice exercise, rhythmic and free body movements, and active music involving collective invention	A series of passive stretching exercises, specific motor tasks, and strategies to improve balance and gait	UPDRS-II, UPDRS-III, self-administered HM, and PDQL	RCT
Frazzitta et al. (44)	Patients with a diagnosis of "clinically probable" idiopathic Parkinson's disease	Treadmill training associated with auditory and visual cues	Traditional rehabilitation protocol using only auditory and visual cues	UPDRS III, FOGQ, 6MWT, gait speed, and stride cycle	RCT
de Bruin et al. (43)	Patients with mild to moderate Parkinson's disease	Home training with individual music playlist	Home training with no music	Gait velocity, stride time, stride length, cadence, and UPDRS-III	RCT
Modugno et al. (42)	Patients affected by a moderate form of idiopathic Parkinson's disease	Theater workshop rehabilitation program including vocal music, different emotional moods, performance and physical activities	Physiotherapy Rehabilitation Program	UPDRS, PDQ-39, ESS, SES, and HDRS	RCT
Kadivar et al. (41)	Patients with idiopathic Parkinson's disease	Performed externally paced stepping with rhythmic auditory stimulation	Performed internally paced stepping without rhythmic auditory stimulation	DGI, UPDRS, TUG, and FOGQ	RCT
Pohl et al. (23)	Parkinson's disease patients	Ronnie Gardiner Rhythm and Music Method	Routine drug treatment	UPDRS, SES, PLM, TUG, PDQ-39, CAB, and SDMT	RCT
Harro et al. (40)	Patients with idiopathic Parkinson's disease	Utilized auditory-cued, overground locomotor training on an indoor track while listening to a personalized music playlist set	Utilized moderate intensity treadmill locomotor training with a safety harness	FGS, 6MWT, RST, BBS, LOS, MCT, SOT, fall incidence, ABC-16, and PDQ-39	RCT
Song et al. (37)	Patients with Parkinson's disease	Conventional drug treatment with sound rhythm metronome released as well as the ground fixed ribbon rhythmic visual stimulation walking training	Routine drug treatment with no music	UPDRS-II, UPDRS-III, BBS, and 6MWT	RCT
De Icco et al. (38)	Patients with idiopathic Parkinson's disease	Walking in the presence of rhythmical sounds, or walking on stripes of contrasting color with respect to the floor	Overground training without cues	Gait parameters, gait speed, stride length, UPDRS-III, and FIM	RCT
Bukowska et al. (39)	Patients with idiopathic Parkinson's disease	Daily living, balance, pre-gait and gait training by using sensorimotor NMT techniques (TIMP, PSE, and RAS)	Asked to maintain their daily life activities (changing of position, walking, walking stairs)	Temporal and spatial gait parameters (stance and swing phase, double support, stride time and cadence, step and stride length, velocity and step width)	RCT
Murgia et al. (36)	Patients with Parkinson's disease	Rehabilitation program with ecological RAS 45 min/session, 2/w+3/w home training *5 w; 12 weeks of daily home training	Rehabilitation program with artificial RAS 45 min/session, 2/w+3/w home training *5 w; 12 weeks of daily home training	Spatio-temporal parameters of gait, UPDRS, FIM, SPPB, GDS, PDQ-8, FES, FOGQ, cadence, and gait speed	RCT
Thaut et al. (35)	Patients with idiopathic Parkinson's disease	Completed 24 weeks of RAS training	Discontinued RAS training between weeks 8 and 16	Velocity, stride length, cadence, ankle dorsiflexion, BBS, TUG, FES, and Fall Index	RCT

(Continued)

TABLE 2 Continued

References	Population	Intervention	Comparison	Outcome	Study
Calabro et al. (22)	Patients with idiopathic Parkinson's disease	Treadmill training with rhythmic auditory stimulation	Treadmill gait training without rhythmic auditory stimulation	FES, FGA, TUG, UPDRS, gait parameters, and electrophysiological effects	RCT
De Luca et al. (33)	Patients with Parkinson's disease	Treadmill gait training with music therapy	Traditional over ground gait training	PGWBI, Brief- COPE, FIM, TUG, and 10 mWT	RCT
Pohl et al. (31)	Patients with Parkinson's disease	Soft stretching movements, breathing exercises, and exercises typical for the Ronnie Gardiner Method	Usual care without competing activity	TUG, MCAS, SCWT, SDMT, FES, FOGQ, and PDQ-39	RCT
Mosabbir et al. (32)	Patients with Parkinson's disease	40-Hz Physioacoustic Vibrations	Placebo with current levels of physical activity	UPDRS-III, tremor, rigidity, bradykinesia, and posture and gait measures	RCT
Capato et al. (34)	Patients with Parkinson's disease	RAS-supported multimodal balance training	Received no functional balance or gait training	Mini-BESTest, TUG, and NFOG-Q	RCT
Fodor et al. (30)	Patients with idiopathic Parkinson's disease	Multimodal rehabilitation program with music exposure	Same rehabilitation program without music exposure	PDQ-39	RCT

RAS, rhythmic auditory stimulation; UPDRS, Unified Parkinson's Disease Rating Scale; HM, Happiness Measure; PDQL, Parkinson's Disease Quality of Life Questionnaire; 6MWT, 6-minute walking test; PDQ-39, Parkinson's Disease Quality of Life; ESS, Epworth Sleepiness Scale; SES, The Schwab and England Scale; HDRS, Hamilton Depression Rating Scale; DGI, Dynamic Gait Index; TUG, Timed Up-and-Go; FOGQ, Freezing of Gait Questionnaire; PLM, Posturo-Locomotion-Manual; CAB, Cognitive Assessment Battery; SDMT, the Symbol Digit Modalities Test; BBS, Berg Balance Scale; RST, Rapid Step-Up Test; SOT, NeuroCom Sensory Organization Test; LOS, Limits of Stability; MCT, Motor Control Test; FGS, fast gait speed; ABC-16, Activities-specific Balance Confidence Scale-16; FIM, Functional Independence Measure; SPPB, short physical performance battery; GDS, geriatric depression scale; FES, falls efficacy scale; FGA, Functional Gait Assessment; PGWBI, Psychological General Well-Being Index; Brief- COPE, Brief- Coping Orientation to Problems Experiences; MCAS, Montreal Cognitive Assessment scale; SCWT, Stroop Color-Word Test; SDMT, Symbol Digit Modalities Test; NFOG-Q, New Freezing of Gait Questionnaire; RCT, randomized controlled trial.

beta frequency oscillations in the cortex (59). Both the basal ganglia and cerebellum influence cortical movement and movement-related areas *via* the thalamus (60, 61). Literatures suggest that the cerebellar-thalamocortical motor network can compensate for the deleterious basal ganglia connection-thalamocortical motor network function associated with internal chronotropic processing (62, 63). Stimulating the cerebellum using oscillating transcranial currents delivered at frequencies similar to intrinsic musical rhythms can largely shape the frontal-parietal connections and the sensorimotor rhythms associated with fine adjustment of gait parameters (22, 64). Thus, the cerebellum may participate in internal timing mechanisms when subjected to external rhythmic auditory stimulation.

The literature included in this meta-analysis was all RCTs, which significantly reduced various potential biases and provided high quality evidence. In addition, various parameters and scales assessing gait, mobility, and quality of life in PD patients were included to evaluate the effectiveness of RAS in improving patients' gait and mobility impairment from multiple aspects.

Limitations of this study should be discussed as they may limit the extrapolation of results. First, the majority of the subjects had mild or moderate disease. This lack of information regarding disease severity and their specific deficits have limited their interpretation of outcomes. Second, the number of studies included in the meta-analysis was limited, and the sample size was small. Only two studies had more than 100 subjects, thirteen studies had <50 subjects, making the generalizability of the study survey difficult. Thirdly, by employing the 18 RCTs we had included in this meta-analysis for the PICOs (Population, Intervention, Control and Outcome evaluation), the Table 2 so constructed has demonstrated for each study the specific intervention method: the interventions given to patients in these 18 individual studies were either RAS, (22, 31, 34–39, 41, 44), Rhythm with Musical melody (23, 30, 31, 33, 40, 42, 43, 45) or Physiotherapy on an Acoustic Vibration Chair (32). For control groups, patients would either receive conventional physical therapy, with or without a structured instruction, or an intervention placebo (the vibration chair without rhythm or melody.) These differences in intervention and control could make the comparison's interpretation difficult. Finally, Language bias has always been possible in meta-analysis. Although all 18 RCTs were published in the English language peer-reviewed journals, the minority (5/18) were from native English-speaking countries. Among all these 18 studies: there were 7 studies from Italy, 1 from Poland, 1 from Romania, 2 from Sweden, 3 from the United States, 2 from Canada, 1 from

China and 1 from Brazil. Our Funnel Plots using the UPDRS-III, FoG and Speed as the three major outcomes assessments did not exhibit significant publication biases (Figures 6A–C). However, we are reassured by a recent epidemiology paper by Nussbaumer-Streit 2019 (65) using 59 Cochrane Reviews with or without excluding non-English studies to answer this specific question: excluding non-English publication from evidence syntheses does not change conclusions. In summary, the results of this meta-analysis provide more convincing evidence for the effectiveness of RAS in the rehabilitation of PD patients.

Our study shows the significant efficacy of RAS in improving gait, motor activities and quality of life in Parkinson's patients and suggests its application in clinical practice. However, as the data came from different studies where the sample size, disease severity, stimulation frequency, intervention intensity and functional assessment tools were different. One of the most intriguing examples is the Falls Efficacy Scale (FES). Three out of our 18 studies have independently concluded that rhythmic auditory stimulation can improve gait disturbance (22, 31, 36), however, in combining the original data (a total of 106 patients), the results were of borderline significance ($p = 0.05$). It is desirable to have a multicenter randomized controlled trial that can simultaneously include the key indicators to further determine the RAS efficacy in gait improvement and quality of life in Parkinson's disease.

Conclusion

In this meta-analysis of 18 randomized controlled trials, we have demonstrated that Rhythmic Auditory Stimulation (RAS) could improve gait, mobility and quality of life in patients with Parkinson's disease. A definitive multi-centre study with a well-defined disease severity, treatment intensity and functional assessment tools should be planned in the future.

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.

Author contributions

The paper completed at the suggestion and supervised by WP. Two researchers (LL and RH) independently extracted primary data from eligible studies using a standardized form. If the corresponding data could not be extracted directly from the study, it would need to be reanalyzed. Where there were disagreements between above two researchers, a third researcher (XY) was asked to review literatures until a consensus was reached. The data management and statistical analysis were performed by XY and reviewed by statistician YJ from core laboratory. All authors contributed to the article and approved the submitted version.

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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Rhythmic cueing, dance, resistance training, and Parkinson's disease: A systematic review and meta-analysis

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Objectives: The aim of the present systematic review and meta-analysis was to synthesize evidence associated with the functional and clinical effectiveness of rhythmic cueing, dance, or resistance training (RT) on motor and non-motor parameters in Parkinson's Disease patients, and to provide a comparative perspective not offered by existing systematic reviews.

Methodology: Eligibility criteria for selecting studies retained no restrictions in methodological design and included interventions of rhythmic cueing, dance, RT, and measurements of motor and non-motor parameters. Animal studies, reviews, editorials, conferences, magazines, and gray literature articles were excluded. Two independent investigators searched Cochrane Library, Medline, PubMed, and SPORTDiscus from the date of their inception until 1 June 2021. The ROBINS-I tool was employed for the non-randomized controlled trials, and the updated for Risk of Bias 2 tool of Cochrane Library used for randomized controlled trials. For meta-analyses, the RevMan 5.4.13 software was used. For incompatible meta-analysis studies, a narrative data synthesis was conducted.

Results: A total of 49 studies included in the systematic review involving 3767 PD participants. Meta-analyses revealed that rhythmic cueing training assists gait velocity ($p = 0.01$), stride length ($p = 0.01$), and motor symptoms ($p = 0.03$). Similarly, dance training benefits stride length ($p = 0.05$), lower extremity function-TUG ($p = 0.01$), and motor symptoms ($p = 0.01$), whilst RT improves lower extremity function-TUG ($p = 0.01$), quality of life ($p = 0.01$), knee flexion ($p = 0.02$), and leg press ($p = 0.01$). Subgroup analyses have shown non-significant differences in gait velocity ($p = 0.26$), stride length ($p = 0.80$), functional mobility-TUG ($p = 0.74$), motor symptoms-UPDRS-III ($p = 0.46$), and quality of life-PDQ39 ($p = 0.44$).

Conclusion: Rhythmic cueing, dance, or RT positively affect the examined outcomes, with rhythmic cueing to be associated with three outcomes (Gait, Stride, and UPDRS-III), dance with three outcomes (TUG, Stride, and UPDRS-III), and RT with two outcomes (TUG and PDQ-39). Subgroup analyses confirmed the beneficial effects of these forms of exercise. Clinicians should entertain the idea of more holistic exercise protocols aiming at improving PD manifestations.
International Prospective Register of systematic reviews (PROSPERO) (registration number: CRD42020212380).

KEYWORDS

Parkinson's disease, rhythm, dance, strength, systematic review, meta-analysis

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder, which is mainly characterized by the loss of dopaminergic neurons in the substantia Nigra pars compacta (SNpc) of the midbrain and the accumulation of Lewy bodies and Lewy neuritis (1). Being the second most common neurodegenerative disorder (2), PD affects approximately 10 million people worldwide (3). It is estimated that by 2040 this number will increase over 12 million (4), with aging, as well as genetic and environmental factors contributing to its development (5). Physical exercise accompanied by healthy lifestyle has been shown to exert beneficial effects on the progression of the disease [(6–8)].

Some of the most common non-motor manifestations of PD include sleeping disorders, cognitive impairment (e.g., difficulties in concentrating, learning, remembering, and thinking), anxiety, depression, and lack of motivation (9). Motor manifestations include resting tremor, bradykinesia, freezing of gait, rigidity, and postural impairment. In PD, nigrostriatal degeneration resulting in basal ganglia dysfunction is critically associated with impaired synchronization of regular and periodical movement patterns (10, 11).

Auditory cues are beats that indicate a rhythmic schema, which usually consists of a monotonous tapping. Auditory cues can be any kind of rhythmic stimulation (12), while all beats are by default strong (13). For instance, the use of voice for counting, or syllabi (ya, ta, ta), or use of a tambourine or a metronome, or to move according to the meter of a music piece i.e., 2/4 or 4/4 time. When rhythmic schema is established, it can continue to exist in the listener's mind even when the source of rhythm is paused (13, 14). People usually synchronize their actions through an innate rhythmic entrainment (13), and in a healthy brain, this procedure is related to subcortico-thalamo-cortical network including the pre-supplementary and supplementary motor areas, basal ganglia, and cerebellum (12). Basal ganglia, and especially the putamen, is critically implicated in the sequencing of rhythmic stimuli, and potentially the 'feeling of the beat' (13). Acoustic cues may enhance the connectivity between auditory perception and movement, since rhythm enables the activation of neural circuits associated with motor processing (13). Given that PD patients display difficulties in performing automatized movements, the use of external cues appears to be beneficial (15). Rhythm, as a form of external cue, therefore, seems to reduce the dependence on deficient automatized processes (16) that characterize PD pathophysiology, since movement could be synchronized to the regular expectation of a beat (13).

Indeed, a systematic review, containing 50 studies with 1,892 PD participants, revealed the beneficial effects of external rhythmical cues on gait (17). However, another systematic review underlined the lack of consistency in studies with rhythmic auditory stimulation in most components such as participants, exercise intervention, duration, or design (12).

According to Malloch and Trevarthen (18), rhythm usually stands between music and dance, interacts between music and movement/dance, and forms the first step toward musicality. Dance itself is an activity as old as human civilization (19, 20), and in ancient Greece, it was used to improve or maintain health, especially in older people (21). Studies in dance displayed different methodological characteristics, such as type of dance, duration of intervention, and group comparisons (22). However, recent literature indicates that dance can improve selected motor and non-motor elements, such as gait, cognition, quality of life (QoL), and mood (22, 23), as it increases - brain-derived neurotrophic factor (BDNF) levels that, *inter alia*, trigger dopamine's production, an important aspect of PD pathophysiology (22, 24, 25). In addition, neurophysiological evidence via functional magnetic resonance imaging (fMRI) has shown that dance is associated with enhanced functional connectivity between premotor cortex and basal ganglia, while electroencephalogram (EEG) studies have demonstrated that Tango might alter muscle synergy during balance and walking testing (26). It has been found that dance provides

environmental enrichment that positively affects social and emotional states by stimulating diverse sensory functions during dancing, such as audition, vision, proprioception and tactile perception, balance, and vestibular control that might affect several aspects of motor function, mood, and cognitive impairment of PD patients (25). Although the neuroprotective effects of dance in PD have not been adequately examined, it has been proposed that BDNF upregulation and other molecular pathways may underlie the dance-mediated enhancement of neuronal activation in disrupted sensory-motor areas in PD, thereby resulting in the improvement of motor symptoms (25).

Resistance training (RT) is a renowned part of disease-prevention and disease-therapy protocols (27). It averts muscle loss, as muscle can increase its size through hypertrophy at any age, and improves muscular strength and gait components (2, 28, 29). Muscular weakness is a resultant of PD, as inhibition activation of motor neurons leads to muscle mass losses (7). Gait disturbances, poor balance, falls, and bradykinesia also seem to be associated with lack of strength, muscular imbalances, and differences between left and right sides (2, 30).

Indeed, a review with 401 participants examining the effects of progressive RT on physical function and balance in people with PD demonstrated that after 10 weeks of such training (2–3 times per week at moderate intensity) significantly improved strength, balance, and motor symptoms (28). Other studies found that RT should be combined with different forms of training in order to improve parameters such as balance or gait (2, 29), while there was also evidence that RT improves lower limb strength but not gait and balance (31). It should be stressed that research on RT in relation to PD is rather limited with different characteristics and methodological heterogeneity such as study design, randomization, and/or measurements (2).

Previous systematic reviews have individually examined rhythmic cueing, dance, or RT in relation to PD symptomatology. However, it is not yet entirely clear with which of these three methods would provide the most benefits for different clinical aspects of PD. Therefore, the aim of the present systematic review and meta-analysis was to synthesize evidence associated with the functional and clinical effectiveness of rhythmic cueing, dance, or RT on motor and non-motor parameters in patients with PD. It is anticipated that the findings would form the basis for a new protocol synthesis aiming at improving PD symptoms, through the development of more holistic exercise interventions.

Methodology

The present work was conducted according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines. It was registered with the International Prospective Register of systematic reviews (PROSPERO) (registration number: CRD42020212380).

Eligibility criteria

We considered the studies of any methodological design, which included experimental groups attended any form of rhythmic cueing intervention, any type of dance, or any form of RT, in PD patients. There were no restrictions regarding the duration of interventions. Key outcome domains were gait velocity/speed, stride length, stride time, strength of lower limbs, motor symptoms, functional parameters, QoL, cognition, state of mood, and sleep disorders. Eligible control situation considered either an appropriate control group (non-active or usual care for PD) or baseline measurements that were comparable with post-intervention measurements. Animal studies, case reports, reviews, editorials, conferences, and magazine papers were excluded.

Eligibility criteria for participants were Hoehn & Yahr (H&Y) PD rating scale I–IV (32). We applied no restrictions on disease duration, age, gender, and type of drug therapy, except for stable antiparkinsonian medication. Patients with other neurological problems or deep brain stimulation, cancer, cardiovascular disease, poor visual or auditory capability, and musculoskeletal problems were excluded.

Search and selection strategy

PubMed, Medline, Cochrane Library (trials), and SPORTDiscus were searched from the date of their inception until 1 June 2021. The key words (algorithm) used can be found in the supplement (33). The article selection was undertaken by two researchers (CK and MB). Any discrepancies have been resolved through discussion by a third researcher acting as referee (PCD). In the first step of the selection process, retrieved articles that were obviously irrelevant to our research question were excluded based on screening of titles and abstracts. Considering the aim of the current systematic review, we then checked the full texts of the remaining publications in order to select the eligible ones. Both steps were based on our inclusion and exclusion criteria.

Data extraction

CK and MB extracted the data from the eligible studies. One referee (PCD) ensured that all the necessary data are listed in tables. These included: (1) First author name and date of publication for identification, (2) Methodological design of each study, (3) Population characteristics sample size, groups, age, gender (if available), and H&Y PD rating scale (32), (4) Intervention (type, duration, and frequency), and (5) Eligible outcomes. Outcomes were continuously presented in mean and standard deviation (SD) of unified PD rating scale part III (UPDRS-III), Timed up and go test (TUG), ten meters walk test

(TMWT), gait (velocity/speed), stride length, stride duration, PD questionnaire (PDQ39) score, strength of lower limbs, Montreal cognitive assessment (MoCa), sleep disorders (PSQI), and Brunel mood state (BRUMS). Fill the above outcomes were considered as "critical and meaningful," according to 2022 Cochrane handbook for systematic reviews (34). Included outcomes encompassed the most frequent motor and non-motor parameters that affect every-day life of people with PD (35, 36). It is noteworthy that PDQ-39 is a valid questionnaire to assess quality of life in PD (37), UPDRS-III is an effective scale to assess motor symptoms in PD (38), whereas TUG is a common test to measure functional mobility in PD (39, 40). Similarly, MoCa is a widely used test to detect even mild cognitive impairments in patients with PD (41, 42). The BRUMS (43) evaluates 6 mood states (tension, depression, anger, vigor, fatigue, and mental confusion) in different populations, including PD patients and elderly people (44–47). The extracted data used for the meta-analyses can be found in the supplement in an open depository (33).

Risk of bias

The evaluation of the methodological quality of the eligible studies was independently completed by two researchers (CK and MB). Any conflicts arose between the two researchers, assessment and evaluation, were resolved by the referee researcher (PCD) via discussion. The ROBINS-I tool was used for non-randomized controlled trials (48), and the updated Risk of Bias 2 (ROB2) tool of Cochrane Library used for randomized controlled trials (RCT) (49).

Data synthesis and prospective meta-analysis

For seven eligible studies (50–56), a narrative data synthesis was conducted due to unsuitable data for a meta-analysis, as means and standard deviations (SD) were not included, and we were not able to retrieve the data from the corresponding authors. In addition, two studies (52, 53) were included in the narrative data synthesis due to non-parametric data reported. It has been advised that non-parametric and parametric data should not be mixed in a meta-analysis (34). Finally, a further study (57) provided data for sleep disorders, but this entry appeared only once in the outcomes, and, as such, no meta-analysis could be conducted (34).

For the eligible publications with data suitable for a meta-analysis, a continuous random effect model was employed, with means and SD, to assess motor and non-motor symptoms between experimental and control groups or baseline and post measurements. For the motor and non-motor events, a dichotomous inverse variance random effect model meta-analysis (i.e., odds ratio) was used to assess the effects (acute or chronic) of rhythmic cueing, dance, and/or RT interventions, in patients with PD, against the incidence of an adverse effect or positive effect in a group of patients not exposed to the aforementioned interventions. For all meta-analyses, the RevMan 5.4.13 software was used (58). Outcomes in four eligible studies (53, 59–61) were reported in figures, and therefore, the WebPlotDigitizer (62) software was used to extract data for the meta-analysis. For the eligible studies (59, 63–65) with reported outcomes as means and standard errors, conversions into standard deviations were achieved using the following equation: Standard deviation = standard error* $\sqrt{n}$ (34). The 95% confidence interval and heterogeneity between the eligible studies were evaluated using the I^2 statistic. A statistically significant result for heterogeneity was considered when $p < 0.10$, while interpretation of I^2 index was based on the Cochrane Library Handbook (34). Finally, the standardized mean difference (SMD) was used in cases where meta-analysis included studies that assessed the same outcome but used different measurement scales. Publication bias was assessed using funnel plots, but only for those meta-analyses that include >10 studies/entries (34).

In the comparisons of group of different dance styles (64) or rhythmic cueing (66, 67), pre measurements data were considered as a control situation, and post measurements data were considered as an experimental situation. For the eligible studies (59, 60, 63, 68–72) that compared interventions of dance or RT with other activities, only dance or resistance group was considered. Control groups receiving usual care treatment were considered as appropriate, unless physical activity was part of their usual care treatment. In the absence of appropriate control group (active or healthy) (73–83) or control group (84–86), comparisons focused on pre and post measurements of experimental groups. In one study (78) that comparisons focused on less affected and most affected leg, the latter was considered. In the context of gait measurements, self-selected speed or preferred rhythm (79, 87) was chosen since these two parameters are closer to normality.

Finally, we conducted subgroup analyses to compare each one of the outcomes among rhythmic cueing, dance, and RT. In particular, gait velocity, stride length, functional mobility-TUG, Qol-PDQ-39, and motor symptoms UPDRS-III have been analyzed.

Confidence in cumulative evidence

Meta-analyses quality of evidence was judged via the Grading of Recommendations Assessment, Development and Evaluation (GRADE) analysis (34, 88). Following previous guidelines (34, 88), we considered as an optimal information size more than 110 participants for each meta-analysis. This was based on a power analysis of a conventional sample size using three single trials (59, 66, 89).

Results

Prisma flow diagram shows information regarding article selection and characteristics of included studies (Figure 1).

We included publications from 1996 to 2021 which involved 3,767 participants (933 for rhythmic cueing, 1,470 for dance, and 1,364 for RT). Eight RCTs, two CTs, and one cohort study examined the effect of rhythmic cueing (rhythmical sounds, metronome, rhythmic styles) on PD. 10 RCTs and 12 CTs examined the effect of western theatrical (ballet, contemporary, jazz) social (Waltz, Foxtrot, Tango, Salsa, Samba, Forro), and Folklore (Irish, Sardinian, and Turo) dance protocols on PD. Twelve RCTs and four CTs studies examined the effect of RT protocols on PD. Interventions ranged from one session for a period of 24 months. The characteristics of the eligible studies are available in the supplement (Supplementary Table S1, pages 5–34) in an open depository (33).

Search and selection outcomes

Of the 4,813 retrieved publications, 691 were duplicates and 4,039 were excluded. Of the remaining 134 publications, 53 were reviews and conference papers and 35 did not fulfill the inclusion criteria. Finally, 46 studies were classified eligible, while three additional eligible studies were found in their reference lists. The total number of eligible studies included in the systematic review was 49.

Risk of bias assessments

Regarding the eligible RCTs, one study displayed high risk of bias (90), 12 were found with some concerns (57, 63, 65, 67–69, 73, 74, 91–94), and 18 studies displayed low risk of bias (53, 55, 60, 61, 64, 66, 70, 72, 75, 79, 81, 82, 89, 95–98), in randomization process. With respect to intervention assignment, two studies showed high risk of bias (64, 90), five studies exhibited some concerns (72, 75, 92, 95, 97), while the remaining studies disclosed low risk of bias (53, 55, 57, 60, 61, 63, 66–70, 73, 74, 79, 81, 82, 89, 91, 93, 94, 96, 98). In relation to intervention adherence, six studies displayed high risk of bias [55, 64, 72, 74, 90, 91[, eight exhibited some concerns (63, 65, 70, 81, 92, 95, 97), and 17 low risk of bias (53, 57, 60, 61, 66–69, 73, 75, 79, 82, 89, 93, 94, 96, 98). Considering missing data, three studies displayed some concerns (53, 57, 72), while the remaining studies showed low risk of bias (55, 60, 61, 63–70, 73–75, 79, 81, 82, 89–98). In relation to bias outcome, five studies exhibited some concerns (72–74, 81, 96), and the remaining studies presented low risk of bias (55, 60, 61, 63–70, 72, 75, 79, 82, 89–95, 97, 98). In bias reported outcomes, two studies presented high risk of bias (60, 90) one study displayed some concerns (81) and 27 studies revealed low risk of bias (53, 55, 57, 61, 63–70, 72–75, 79, 82, 89, 91–98).

Regarding the eligible CTs, two studies displayed moderate risk of bias (51, 80) and the remaining studies low risk (31, 50, 52, 54, 56, 59, 76–78, 83–87, 99–101). For bias selection, one study displayed serious risk of bias (99), nine studies showed moderate risk of bias (50, 51, 54, 59, 76, 77, 83, 87, 101), and nine studies showed low risk of bias (31, 52, 56, 78, 80, 83, 84, 86, 100). Regarding bias classification, seven studies showed moderate risk (23, 50, 76, 78, 83, 85, 99) and 12 studies low risk in bias (31, 51, 52, 54, 56, 59, 77, 80, 84, 86, 87, 100). For association to bias deviation of intervention, all studies (23, 31, 50–52, 54, 56, 59, 76–78, 80, 83–87, 99, 100) displayed low risk. Three studies displayed moderate risk (80, 85, 100), and 16 studies low risk in bias missing data (23, 31, 50–52, 54, 56, 59, 76–78, 83, 84, 86, 87, 99). For bias outcome, one study displayed some concerns (76), 14 studies moderate (23, 31, 50, 51, 54, 56, 76–78, 80, 83, 85, 87, 99), and five studies (51, 52, 84, 86, 100) displayed low risk. In bias reported results, three studies showed moderate risk (50, 56, 85) and 16 (23, 31, 51, 52, 54, 59, 76–78, 80, 83, 84, 86, 87, 99, 100) displayed low risk of bias. Risk of bias outcomes can be found in Supplementary Tables S2, S3 and Supplementary Figures S1, S2 (33).

Narrative data synthesis

In relation to the effects of rhythmic cueing on PD, one study examined the acute effects of rhythmic auditory stimulation (RAS) on gait velocity, indicating that RAS can facilitate locomotion (50). Similarly, another study (54) reported that rhythmic auditory cues significantly increased gait parameters, such as walking velocity and stride length, after 8 weeks of training. However, the use of metronomes did not improve mobility or physical functioning or other aspects of QoL (55).

In relation to the effects of dance, one study revealed that Irish dance may improve QoL (52), but another set of data (53) revealed that Irish dance does not improve QoL. A 12-month classical ballet did not affect gait variability (51), but an 8-month dance for PD did improve functional mobility and QoL in patients with PD (56). With respect to RT, a 12-week progressive RT improved sleep quality in this population (57).

However, the narrative review included a small number of studies, and therefore, it is difficult to evaluate the relevance of the findings.

Meta-analysis outcomes

In the supplement (S) of the following can be found: (a) forest plots of rhythmic cueing (Supplementary Figures S3A–C, S6A,B), (b) forest plots of dance (Supplementary Figures S4A–C, S7A–C), (c) funnel plots of dance 4Ba and 4Ca, and d) RT (Supplementary Figures S5A–D, S8A–D). The data used for the meta-analyses can be found in an open depository (33).

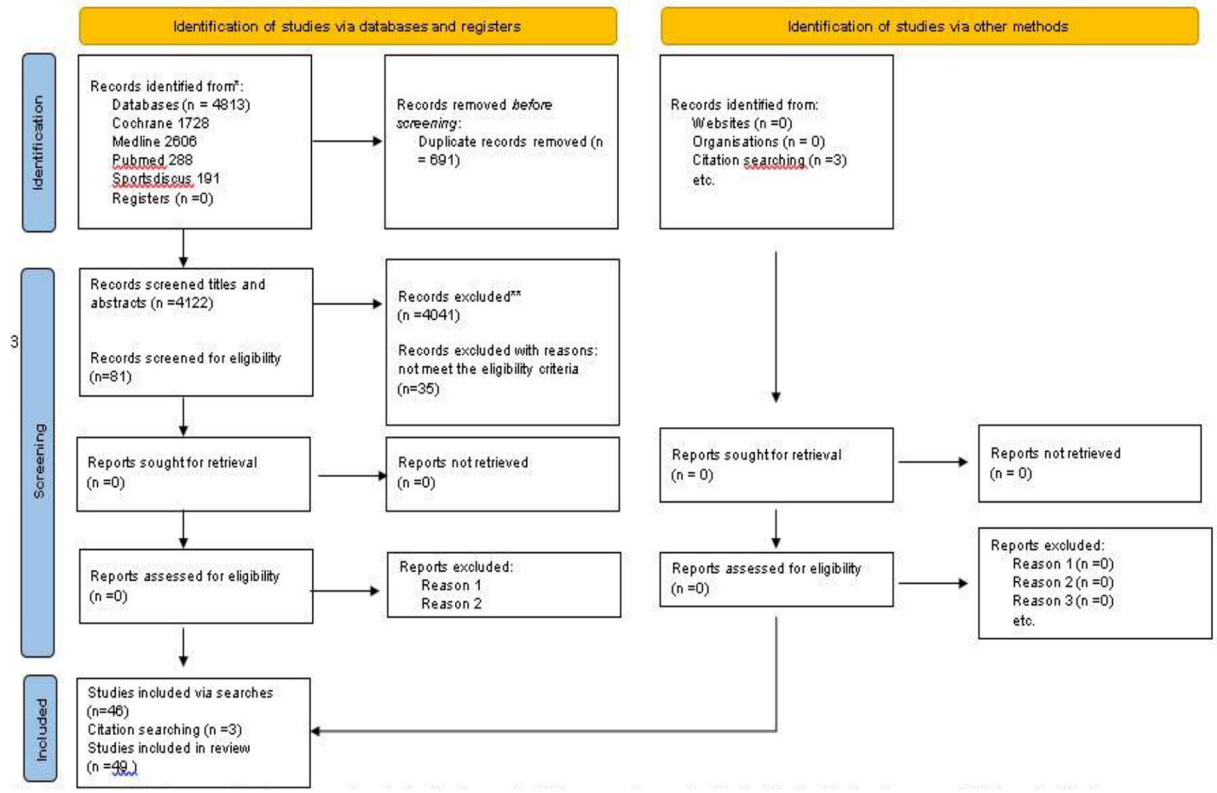

FIGURE 1
PRISMA 2020 flow diagram.

Rhythmic cueing

Meta-analysis results revealed significant effects of rhythmic cueing on gait velocity [(SMD = 0.54, CI = 0.21–0.88, Z = 3.20, I^2 = 46%, p = 0.01, (Supplementary Figure S3A)] and stride length [MD = 0.09, CI = 0.03–0.15, Z = 3.08, I^2 = 37%, p = 0.01, (Supplementary Figure S3B)], whereas no significant effects have been observed on stride time [SMD = 0.21, CI = −0.57 to 0.14, Z = 1.17, I^2 = 0%, p = 0.20, (Supplementary Figure S6A)] in PD patients. Furthermore, rhythmic cues significantly improved motor symptoms-UPDRS-III [MD = −3.94, CI = (−7.47) – (−0.41), Z = 2.19, I^2 = 7%, p = 0.03, (Supplementary Figure S3C)]. No effects of rhythmic cueing have been observed on functional mobility-TUG [MD = 2.31, CI = −7.83, 3.21, Z = 0.82, I^2 = 75%, p = 0.41, (Supplementary Figure S6B)].

Dance

Dance interventions for PD significantly improved stride length [MD = 0.07, CI = 0–0.15, Z = 1.97, I^2 = 0%, p = 0.05, (Supplementary Figure S4A], functional mobility-TUG [MD = −1.26, CI = (−1.77) -(−0.75), Z = 4.82, I^2 = 0% p = 0.01, (Supplementary Figure S4B)], and motor symptoms-UPDRS-III [MD = −5.38, CI = (−8.44) – (−2.32), Z = 3.44, I^2 = 79%, p = .01, (Supplementary Figure S4C)]. On the contrary, no significant effects have been observed on gait velocity [SMD = 0.19, CI = −0.06, 0.44, Z = 1.52, I^2 = 0%, p = .13 (Supplementary Figure S7A)], quality of life-PDQ39 [MD = −2.19, CI = −6.21, 1.84, Z = 1.07, I^2 = 34%, p = 0.29 (Supplementary Figure S7B)], and cognition-MoCa [MD = 0.60, CI = −0.78, 1.97, Z = 0.85, I^2 = 0%, p = 0.13 (Supplementary Figure S7C)].

Resistance training

Significant positive effects of RT in PD have been observed on functional mobility-TUG [MD = −1.75, CI = (−3.07)-(−0.44), Z = 2.61, I^2 = 81%, p = 0.01, (Supplementary Figure S5A)], quality of life-PDQ-39 [SMD = 0.38, CI = (−0.67)–(−0.09), Z = 2.58, I^2 = 31%, p = 0.01, (Supplementary Figure S5B)], leg press [SMD = 3.51, CI = 1.50–5.52, Z = 3.42, I^2 = 91%, p = 0.01, (Supplementary Figure S5C)], and knee flexion [SMD = 1.00, CI = 0.18–1.82, Z = 2.40, I^2 = 65%, p = 0.02,

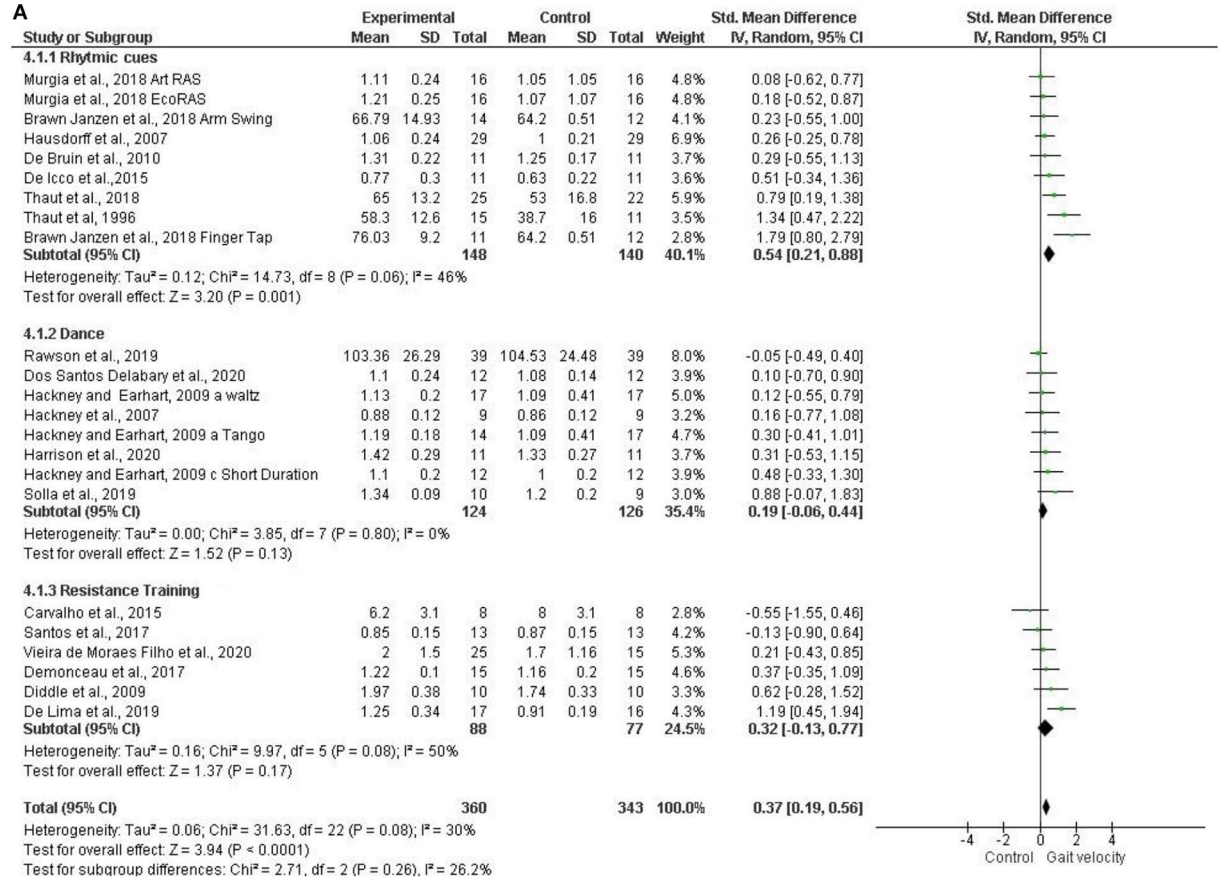

FIGURE 2
Continued

(Supplementary Figure S5D)]. No significant effects have been found on gait velocity/speed [SMD = 0.32, CI = −0.13, 0.77, Z = 1.37, I² = 50%, $p = 0.17$, (Supplementary Figure S8A)], stride length [MD = 0.05, CI = −0.05, 0.16, Z = 1.96, $I^2 = 0\%$, $p = 0.34$, (Supplementary Figure S8B)], in motor symptoms-UPDRS-III [MD = −2.74 CI = −5.55, 0.07, Z = 1.91, $I^2 = 1\%$, $p = 0.06$, (Supplementary Figure S3B)], and knee extension [SMD = 0.88, CI = −0.54, 2.30, Z = 1.22, $I^2 = 91\%$, $p = 0.22$, (Supplementary Figure S8D)].

Subgroup analyses of the outcomes between rhythmic cueing, dance, and resistance training

Subgroup analyses have shown non-significant differences between groups (Rhythmic cueing, Dance, RT) in gait velocity [SMD = 0.37, CI = 0.19, 0.56, $I^2 = 26.2\%$, $p = 0.26$, Figure 2A], while we found a significant overall effect [Z = 3.94, $p < 0.0001$]. Non-significant differences between groups have been observed (Rhythmic cueing, Dance, RT) in stride length [SMD = 0.09, CI = 0.05, 0.13, $I^2 = 0$ %, $p = 0.80$, Figure 2B], while we observed a significant overall effect [Z = 4.45, $p < 0.00001$]. Similarly, non-significant differences have been found between groups (Rhythmic cueing, Dance, RT) in functional mobility-TUG [MD = −1.36, CI = (−2.02, −0.69), $I^2 = 0\%$, $p = 0.74$, Figure 2C], but a significant overall effect [Z = 3.97, $p < 0.0001$]. Non-significant differences between groups have been revealed in motor symptoms-UPDRS-III [MD = −4.62, CI = (−6.96, −2.28), $I^2 = 0\%$, $p = 0.46$], while we detected a significant overall effect [Z = 3.87, $p < 0.0001$, Figure 2D]. Non-significant subgroup (Dance, RT) differences have further been observed for quality of life-PDQ-39 [MD = −36, CI = (−6.02, −0,89), $I^2 = 0\%$, Figure 2E], coupled with a significant overall effect [Z = 2.64, $p < 0.008$].

Confidence in cumulative evidence outcomes

GRADE analysis outcomes can be found in the supplement (Supplementary Table S4) in an open depository (33). The meta-analyses of the effects of rhythmic cueing on gait velocity (#1) and stride length (#2) displayed moderate quality, while on stride time (#3), the quality was very low. The meta analysis of the effects of rhythmic cueing on functional mobility TUG (#4)

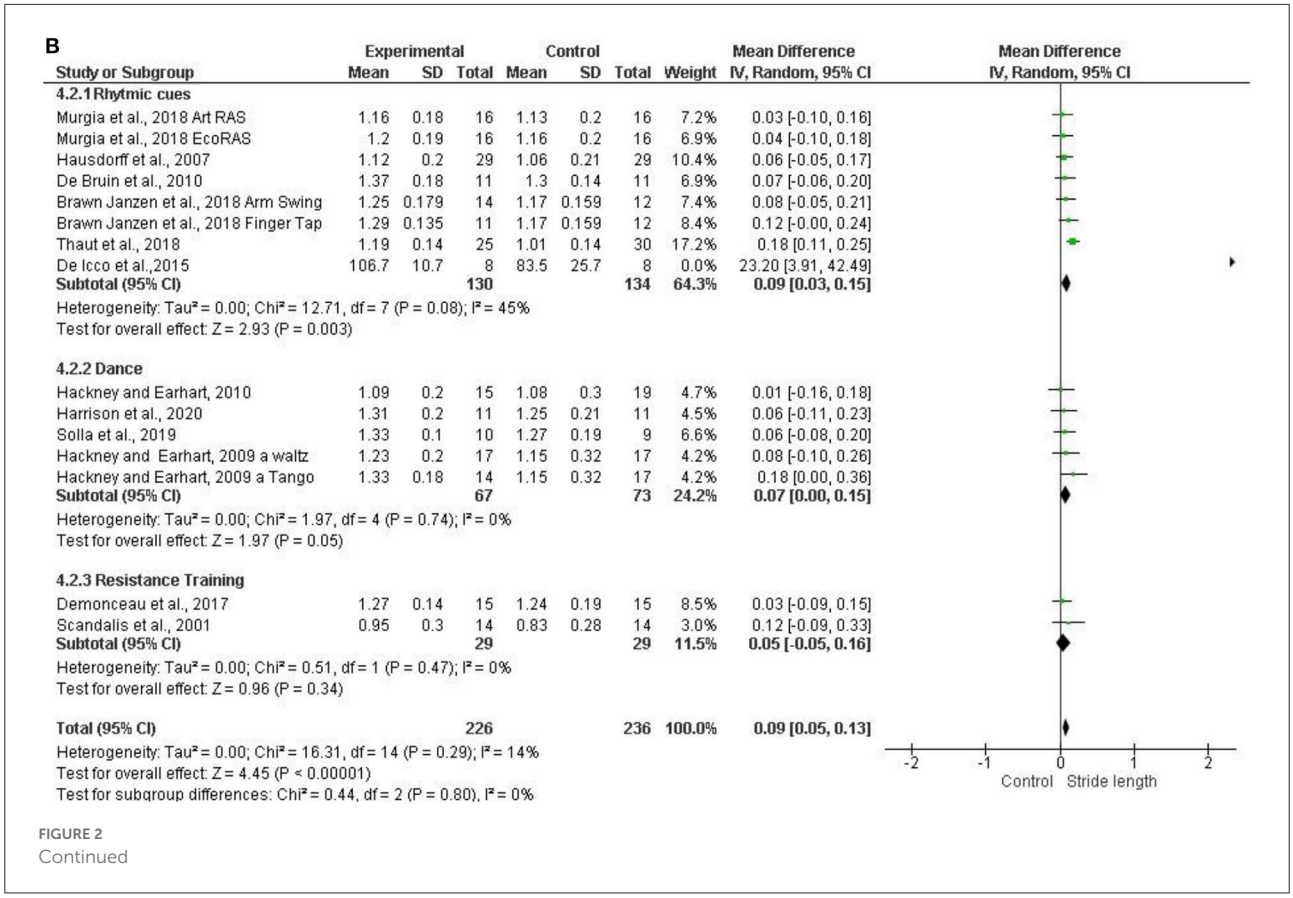

FIGURE 2
Continued

and motor symptoms-UPDRS-III (#5) displayed low quality. The meta-analyses of the effect of dance on gait velocity (#6), stride length (#7), and functional mobility-TUG (#8) exhibited moderate quality. The meta-analyses for motor symptoms-UPDRS-III (#10) exhibited very low quality, whereas QoL-PDQ39 (#10) and cognition-MoCa (#11) exhibited moderate quality. The meta-analyses focused on the effects of RT displayed moderate quality for gait velocity (#12) and very low for stride length (#13); yet, low quality for functional mobility-TUG (#14) and moderate for motor symptoms-UPDRS-III (#15). The meta-analyses of the effects of RT displayed moderate quality for QoL-PDQ39 (#16), low for leg press (#17), very low for knee flexion (#18), and low quality for knee extension (#19).

Discussion

The aim of the present systematic review and meta-analysis was to synthesize evidence associated with the functional and clinical effectiveness of rhythmic cueing, dance, or RT on motor and non-motor parameters in patients with PD. We found that the aforementioned forms of exercise positively affect the examined outcomes, with rhythmic cueing to be associated with three outcomes (Gait, Stride, and UPDRS-III), dance with three (TUG, Stride, and UPDRS-III), and RT with two outcomes (TUG and PDQ-39). However, there is no sufficient evidence to recommend which of these interventions has the greatest effects.

Completeness of evidence

Rhythmic cueing

There was sufficient evidence to assess the effects of rhythmic cueing on gait velocity (nine included in meta-analysis/nine eligible) and stride length (nine included in meta-analysis/nine eligible). The sample was of optimal information size (>110), and GRADE analysis displayed moderate quality of evidence, indicating that rhythmic cueing could be treated as an effective intervention for improving gait characteristics (12, 17). Similarly, there was sufficient evidence to assess the effects of rhythmic cueing on motor symptoms-UPDRS-III (four included in meta-analysis/nine eligible), but the sample size was relatively small (<110), and GRADE analysis displayed low quality of evidence.

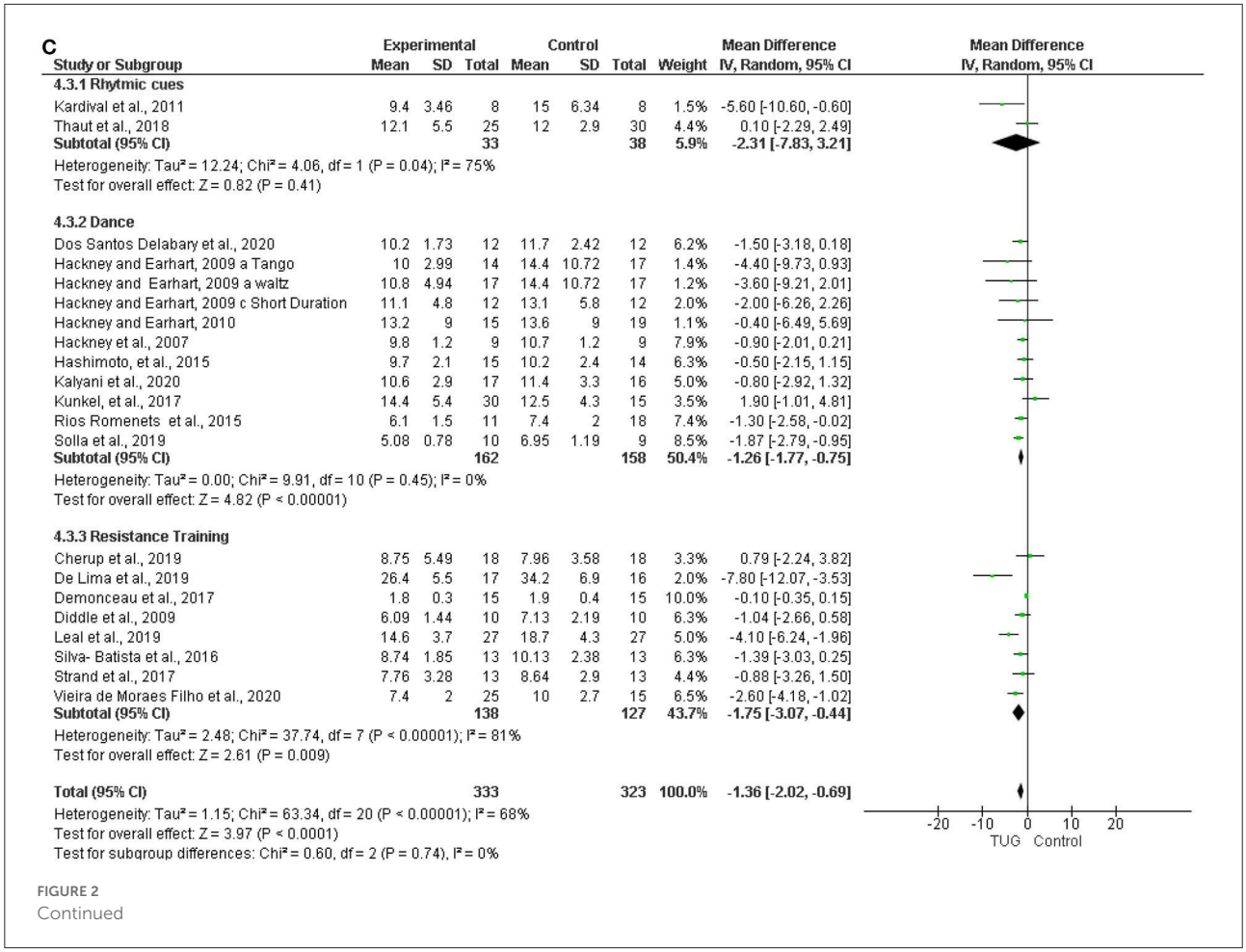

FIGURE 2
Continued

Dance

There was sufficient evidence (>110 participants) assessing the effects of dance protocols on functional mobility-TUG (11 included in meta-analysis/19 eligible), motor symptoms-UPDRS-III (13 included in meta-analysis/19 eligible), and stride length (five included in meta-analysis/19 eligible) in patients with PD. Although GRADE analysis revealed moderate quality for functional mobility-TUG, very low for motor symptoms-UPDRS-III, and moderate quality for stride length, findings indicate the efficacy of dance for improving mobility in this population (22, 102).

Resistance training (RT)

There was sufficient evidence assessing the effects of RT on QoL-PDQ39 (eight included in meta-analysis/16 included studies) with a sample size of >110 and functional mobility-TUG (eight included in meta-analysis/16 eligible) with a sample size of >110. Although GRADE analysis displayed moderate for QoL-PDQ39 and low quality for functional mobility-TUG, it could be argued that RT seems to regulate the majority of parameters associated with daily life. Also, there was sufficient evidence for leg press (four included in meta-analysis/16 eligible) with a sample size of >110, and to a lesser extent for knee flexion (three included in meta-analysis/16 eligible) with a sample size of <110. The aforementioned findings suggest that RT may activate cellular adaptive mechanisms thus, improving muscle strength (2, 103).

Subgroup analysis of the outcomes for rhythmic cueing, dance, and resistance training

Gait velocity, stride length, functional mobility-TUG, motor symptoms UPDRS-III, and Qol-PDQ-3 outcomes were analyzed. Stride time outcome has been detected in rhythm group only, and therefore, was excluded from the subgroup analysis. Also, cognition-MoCa was excluded from the subgroup analysis as it was only detected in the dance group. Similarly, knee flexion, knee extension, and leg press outcomes were detected in RT group only, and they were not included in the subgroup analyses.

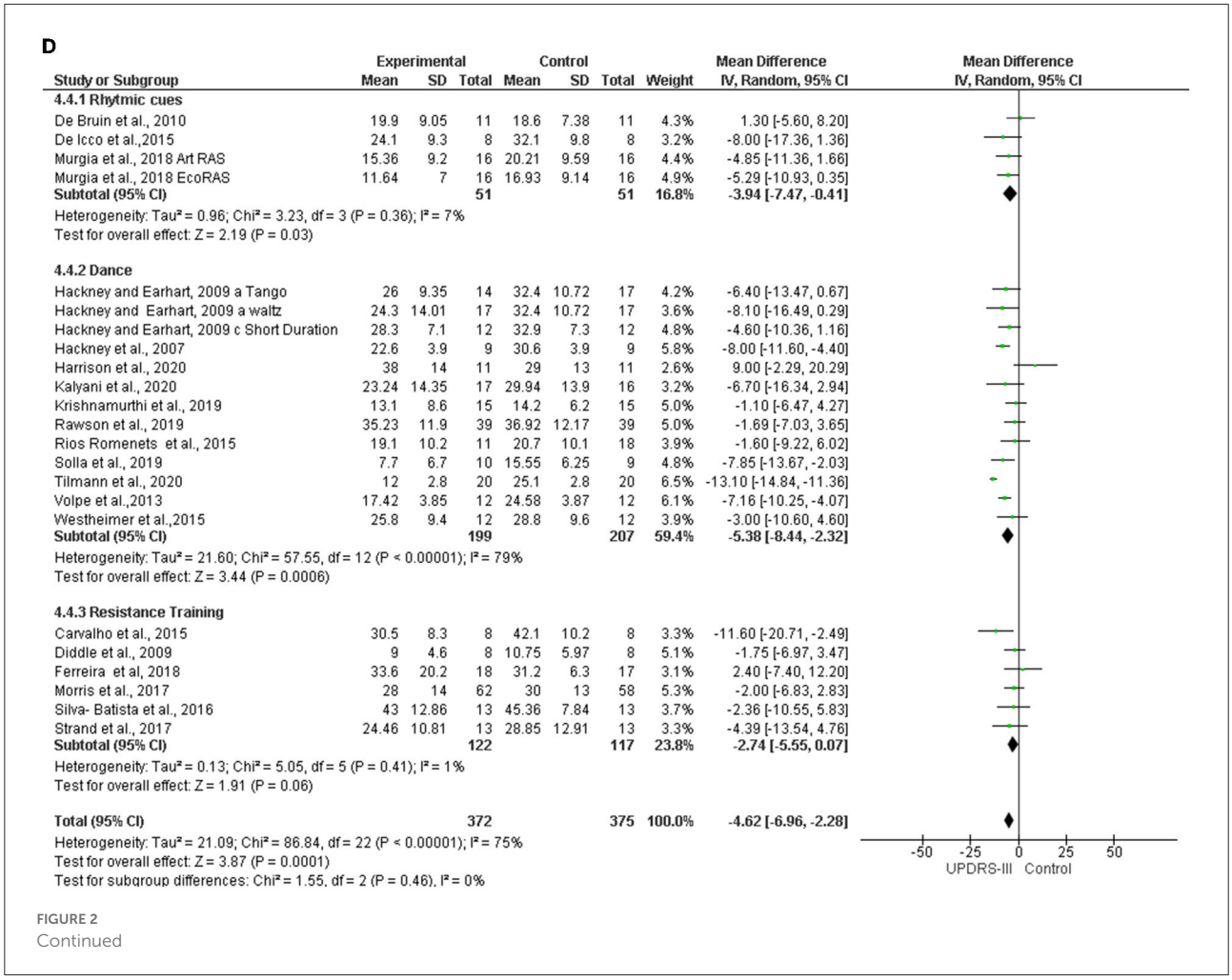

FIGURE 2
Continued

Comparative perspective and applicability of evidence

Subgroup analyses have shown that all three forms of exercise are effective in patients with PD, supporting our hypothesis referring to a holistic approach. This stems from the fact that only outcome common to all three forms of exercise were incorporated in these analyses (Figures 2A–E).

Furthermore, meta-analyses have shown that rhythm cueing improves gait parameters, such as gait velocity, stride length, and motor symptoms, whereas dance seems to improve stride length, motor symptoms, and functional mobility. RT helps to improve QoL, functional mobility and, at the same time, enhances muscular strength in lower limbs. These findings support the notion that a protocol combining rhythmic cues, dance, and RT would probably provide a more holistic approach for improving PD manifestation.

We may theorize that the non-significant effects of dance on QoL could be attributed to the fact that dance is a complicated activity (104), especially for people who experience cognitive impairment in attention, visuospatial skills, and memory. For instance, Western theatrical dance or social dances are complicated activities containing movement combinations, whereas each class may include sections such as rhythm part, improvization, mime, and choreographies. Given that PD symptoms vary from person to person with some patients experiencing cognitive decline, the perception and understanding of movements in a dance class may be stressful for some patients. Relatively, on the one hand, recent systematic reviews examining the impact of dance on QoL revealed contradictory results suggesting that further research is needed (22, 104). On the other hand, a 2021 systematic review provided positive evidence on the effect of dance on quality of life, but the sample size was rather small and prevented generalization (105). An explanation for the aforementioned results may be the complexity of dance activity itself, which renders existing questionnaires not sensitive enough to fully capture elements of QoL (104).

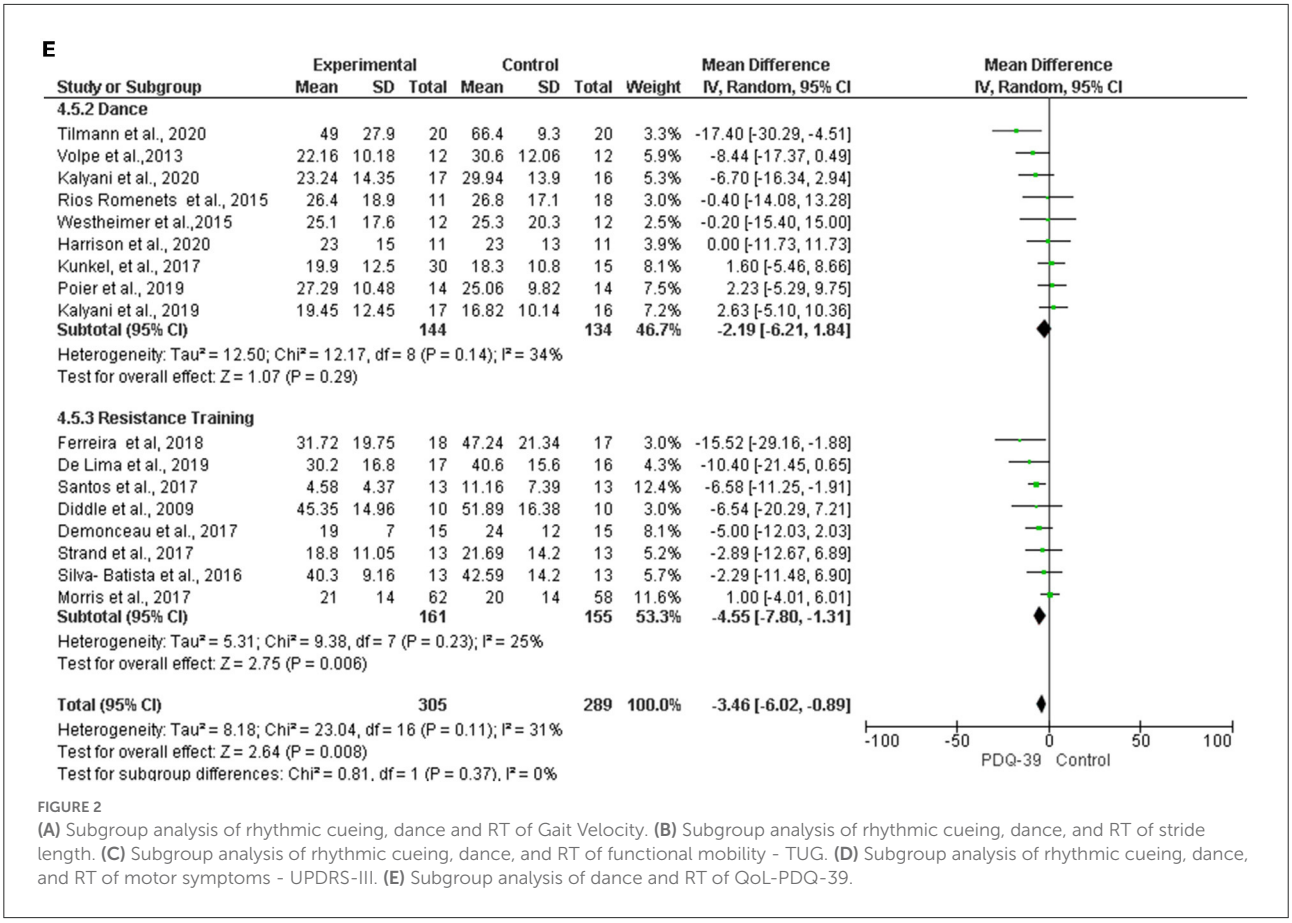

FIGURE 2
(A) Subgroup analysis of rhythmic cueing, dance and RT of Gait Velocity. **(B)** Subgroup analysis of rhythmic cueing, dance, and RT of stride length. **(C)** Subgroup analysis of rhythmic cueing, dance, and RT of functional mobility - TUG. **(D)** Subgroup analysis of rhythmic cueing, dance, and RT of motor symptoms - UPDRS-III. **(E)** Subgroup analysis of dance and RT of QoL-PDQ-39.

Strengths and limitations

To the best of our knowledge, this is the first systematic review and meta-analysis on the effects of rhythmic cues, dance, or RT on PD patients. We searched appropriate databases to develop the key word algorithms, using standardized indexing terms, MeSH terms, and truncations, in order to retrieve publications relevant to our research question (34), while two independent investigators performed the searching, selection, data extraction, and risk of bias assessments.

The current narrative data synthesis included a relatively small number of studies (nine out of 50), which may impose a difficulty to merge their findings with those from the meta-analyses. We did not detect eligible articles for evaluating the state of mood - BRUMS. If more commonly used measures of mood were included in the search, then some effects of the interventions may have been found.

Other limitations include variations in methodological designs, while there was no material indicating whether protocols were designed according to participants' symptomatology. Also, eligible studies did not differentiate disease stages. None of the eligible studies examined fatigue factors, and we detected no information regarding the intensities of dance interventions in most studies. Duration, frequency, and intensity of physical activities are crucial, as fatigue may be an inhibitory factor in parkinsonian populations, similar to that in athletic populations (106, 107). Finally, the eligible dance studies included different dance genres with little information on the structure and/or content.

Conclusions

The present systematic review and meta-analysis indicates that rhythmic cues, dance, or RT positively affect the examined outcomes, with rhythmic cueing to be associated with three outcomes (Gait, Stride, and UPDRS-III), dance with three (TUG, Stride, and UPDRS-III), and RT with two outcomes (TUG and PDQ-39). Subgroup analyses confirmed the beneficial effects of these forms of exercise. Clinicians should entertain the idea of more holistic exercise protocols aiming at improving PD manifestations. Future studies should consider (a) implementation of exercise protocols based on PD patients' symptomatology and disease duration, and (b) standardization of test protocols.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories

and accession number(s) can be found in the article/Supplementary material.

Author contributions

CK and YK did the conceptualization. CK and PD designed the algorithm. CK and MB did article selection and Risk of Bias and the evaluation of the methodological quality of the eligible studies was independently completed. PD acted as referee. CK did the statistical analysis, edited tables and pictures, and wrote the primary manuscript. AH contributed to the methodology and the article. MW, SP, and EA contributed to the article. CK, PD, and YK reviewed the final manuscript. All authors approved the submitted version.

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.2022.875178/full#supplementary-material

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Predicting progression to dementia with "comprehensive visual rating scale" and machine learning algorithms

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Background and Objective: Identifying biomarkers for predicting progression to dementia in patients with mild cognitive impairment (MCI) is crucial. To this end, the comprehensive visual rating scale (CVRS), which is based on magnetic resonance imaging (MRI), was developed for the assessment of structural changes in the brains of patients with MCI. This study aimed to investigate the use of the CVRS score for predicting dementia in patients with MCI over a 2-year follow-up period using various machine learning (ML) algorithms.

Methods: We included 197 patients with MCI who were followed up more than once. The data used for this study were obtained from the Japanese-Alzheimer's Disease Neuroimaging Initiative study. We assessed all the patients using their CVRS scores, cortical thickness data, and clinical data to determine their progression to dementia during a follow-up period of over 2 years. ML algorithms, such as logistic regression, random forest (RF), XGBoost, and LightGBM, were applied to the combination of the dataset. Further, feature importance that contributed to the progression from MCI to dementia was analyzed to confirm the risk predictors among the various variables evaluated.

Results: Of the 197 patients, 108 (54.8%) showed progression from MCI to dementia. Tree-based classifiers, such as XGBoost, LightGBM, and RF, achieved relatively high performance. In addition, the prediction models showed better

performance when clinical data and CVRS score (accuracy 0.701–0.711) were used than when clinical data and cortical thickness (accuracy 0.650–0.685) were used. The features related to CVRS helped predict progression to dementia using the tree-based models compared to logistic regression.

Conclusions: Tree-based ML algorithms can predict progression from MCI to dementia using baseline CVRS scores combined with clinical data.

KEYWORDS

mild cognition impairment, Alzheimer's Disease, brain MRI, machine learning, visual rating scale

Introduction

Mild cognitive impairment (MCI) indicates the transitional stage between a normal cognitive state and Alzheimer's dementia (AD) (1). The annual rate of progression from MCI to dementia reported in community-based studies is ∼6% (2, 3), whereas it was as high as 15% in a clinical study (4). MCI is recognized as a very important public health problem with regard to the risk of dementia. However, MCI comprises a heterogeneous group of conditions and not all of them progress to dementia (4). Therefore, it is necessary to assess the risk of progression from MCI to dementia using biomarkers to identify patients with a high risk of progression to dementia (5).

Brain magnetic resonance imaging (MRI) is commonly used to identify structural changes related to dementia. The National Institute on Aging-Alzheimer's Association has included structural atrophy on MRI scans as a neurodegenerative marker of AD (6–8). An AD-like atrophy pattern primarily observed in the hippocampus is the well-established biomarker of AD (9). However, there is growing evidence that atrophy of other parts of the brain, such as the parietal lobe, provides additional prognostic information (10, 11). Additionally, non-AD conditions, such as cerebrovascular lesions, are also common pathologic findings (12). Considering the multiple pathologies frequently observed in cases of MCI, it is necessary to identify neuroimaging markers that simultaneously reflect neurodegeneration and vascular injury (13).

A quantified comprehensive visual rating scale (CVRS) based on brain MRI has been developed to enable a complete understanding of structural cerebral changes, such as atrophy and cerebrovascular lesions (14). The CVRS integrates the preexisting visual rating scales (hippocampal atrophy, cortical atrophy, ventricular enlargement, and small vessel disease) without losing the value of the subscales (14). Compared to quantitative volumetric measures, visual rating scales are advantageous in that they can be directly applied to clinically-acquired images in less time (15). CVRS has been validated for predicting the progression from MCI to dementia in a longitudinal follow-up study using a dataset from the Alzheimer's Disease Neuroimaging Initiative (ADNI) (16). These suggested that the CVRS scores for MCI could help identify subjects who are likely to be referred for confirmatory studies that are more invasive or expensive, such as CSF analysis or positron emission tomography (PET) scanning. The CVRS scores could also be used in clinical settings without additional advanced biomarkers except for brain MRI. However, whether this scale is also effective for predicting disease progression using other datasets and/or methodologies, such as machine learning (ML), is still unclear. Thus, this study aimed to investigate the use of the CVRS for predicting the progression from MCI to dementia over a 2-year follow-up period using ML algorithms.

Several researchers have investigated the use of ML methods for predicting the progression of AD (17). To be specific, various ML algorithms, including deep learning models, have been studied extensively using different types of data. In this study, we compared the prediction performance of four representative ML algorithms, logistic regression, random forest (RF) (18), XGBoost (19), and LightGBM (20), using a structural table dataset obtained from the Japanese-Alzheimer's Disease Neuroimaging Initiative (J-ADNI) project (21, 22). We also analyzed the most important features and the usefulness of the CVRS score for predicting the progression from MCI to dementia.

Methods

Subjects

The data used in this study were obtained from the J-ADNI project (21, 22). This project was approved by the ethics committee of each site where the J-ADNI data were acquired from. All subjects were native Japanese speakers aged from 60 to 84 years. Data used in this study were downloaded from the J-ADNI database on 1 May 2017. We included patients with MCI who underwent a baseline MRI scan and were followed up at least once after the initial assessment. The primary objective of this study was to predict the progression from MCI to dementia during the follow-up period of up to 2 years. A total of 197 patients from the J-ADNI cohort were finally included in this study.

The diagnosis of MCI was made based on the presence of objective memory impairment that did not meet the criteria for dementia. All the subjects had a Mini Mental State Examination (MMSE) score of 24 or higher, a global Clinical Dementia Rating (CDR) score of 0.5, a CDR memory score of 0.5 or higher, and a score indicating impairment in the delayed recall of Story IIA of the Wechsler Memory Scale-Revised (≥16 years of education: ≤8; 10–15 years of education: ≤4; 0–9 years of education: ≤2) (23). The diagnosis of dementia during the follow-up year was made based on the presence of memory complaints, a CDR score ≥0.5, and significant impairments in objective cognitive measures and activities of daily living. The individuals with AD met the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for probable AD (24). At baseline, the following cognitive and functional measures based on the National Alzheimer's Coordinating Center Uniform Data Set, as used in ADNI, were examined: Digit Span, Category Fluency, Trail Making A and B, Digit Symbol Substitution Test of the Wechsler Adult Intelligence Scale III, Boston Naming Test, Clock Drawing Test, Neuropsychiatric Inventory-Q, AD Assessment Scale-Cognitive Subscale (ADAS-Cog), and Functional Assessment Questionnaire (FAQ). The participants with MCI were evaluated every 6 or 12 months. Then, clinical progression from MCI to dementia was diagnosed by a clinical site investigator at each follow-up visit and verified by an adjudication committee (25).

Acquisition of magnetic resonance images

All subjects underwent MRI, which was performed using a 1.5-T MRI scanner. Data were collected at multiple ADNI sites as per a standardized MRI protocol, which was developed by comparing and evaluating 3D T1-weighted sequences for morphometric analyses (26). MRI acquisition and processing were performed per the standard protocol. Preprocessed T1-weighted MPRAGE MR images, a fluid-attenuated inversion recovery image, and a T2 star weighted image were downloaded from the J-ADNI database.

Comprehensive visual rating scale

The CVRS includes scales of hippocampal atrophy, cortical atrophy, ventricular enlargement (subcortical atrophy), and small vessel disease, which summarize degenerative or vascular injury in the aged brain (Table 1). The details of each scale are described elsewhere (14) and in Supplementary file 1. These existing scales were combined in the CVRS to quantify the effects of multiple brain deficits, thus yielding a scale with scores ranging from 0 to 30 (a higher score represents more deficits).

TABLE 1 Construction of a comprehensive visual rating scale (CVRS).

	Adopted or modified scales	Scale range
Hippocampal atrophy	• Scheltens' scale for coronal image [20] • Kim and Jung's scale for Axial scale [23]	0–8 (bilaterally)
Cortical atrophy	• Victoroff's scale for frontal and temporal lobe [24] • Koedam's scale for parietal lobe [25]	0–9
Subcortical atrophy	• Donovan's scale for anterior and posterior horn of lateral ventricle [26]	0–6
Small vessel disease	• Modified Fazekas and Scheltens' scale for white matter hyperintensity [27]	0–3
	• Lacunes and microbleeds: The total number was graded	0–4

The visual rating was performed by three raters (Jae-Won Jang, Seongheon Kim, and Yeshin Kim), who were blind to the demographic and clinical information of the subjects. Each rater used a template-based scoring method (Supplementary file 2). The inter-rater and intra-rater reliability with 20 randomly selected MRI scans were 0.943 and 0.931, respectively (Supplementary file 3). Cross-sectional validation of a clinical group, including individuals with normal cognition, MCI, and dementia, was performed in a previous study (14).

Neuropsychological data

Longitudinal neuropsychological markers, such as the MMSE score, Alzheimer's Disease Scale-Cognitive Subscale (ADAS-Cog) (27) score, and Clinical Dementia Rating-Sum of Boxes (CDR-SOB) score, were evaluated at baseline and 1-year intervals for up to 2 years.

Statistical analysis

The independent *t*-test and chi-square test were used to examine the between-group differences in continuous variables and categorical variables, respectively. The Mann-Whitney U test was used to analyze continuous variables that were not normally distributed. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using R (Version 4.1.0, The R Foundation for Statistical Computing, 64-bit platform).

Data preprocessing

The dataset consisted of the initial diagnoses of 200 patients and those made at 6, 12, and 24 months after baseline. Our

TABLE 2 Baseline characteristics of the patients with MCI.

	Stable group ($n = 89$)	Progressive group ($n = 108$)	Total ($n = 197$)	p-value
Age, years (mean ± SD)	72.9 ± 5.8	73.3 ± 5.7	73.1 ± 5.8	0.586
Female, *n*	39 (43.8%)	62 (57.4%)	101 (51.3%)	0.079
Education, years	13.5 ± 2.7	12.7 ± 2.9	13.1 ± 2.9	0.056
APOE ε4 carriers, *n*	31 (35.2%)	73 (67.6%)	104 (55.6%)	<0.001
CDR-SOB	1.3 ± 0.9	1.7 ± 1.0	1.5 ± 0.9	0.003
ADAS-cog 11	9.0 ± 3.7	12.3 ± 4.2	10.8 ± 4.3	<0.001
MMSE	26.8 ± 1.9	26.1 ± 1.5	26.4 ± 1.7	0.004
FAQ	2.3 ± 2.7	4.5 ± 4.7	3.5 ± 4.1	<0.001
CVRS (total)	8.7 ± 3.2	9.3 ± 3.9	9.0 ± 3.7	0.223
Hippocampal atrophy	3.4 ± 1.6	3.9 ± 1.6	3.7 ± 1.6	0.069
Cortical atrophy	2.1 ± 1.5	2.5 ± 1.8	2.3 ± 1.7	0.158
Subcortical atrophy	1.6 ± 1.2	1.6 ± 1.2	1.6 ± 1.2	0.858
Small vessel disease	1.5 ± 1.0	1.3 ± 1.2	1.4 ± 1.1	0.343
AD signature	2.8 ± 0.2	2.6 ± 0.2	2.7 ± 0.2	<0.001

Values are presented as mean ± standard deviation or number (%) unless otherwise stated. SD, Standard deviation; CDR-SOB, Clinical dementia rating-sum of boxes; ADAS-Cog, Alzheimer's Disease assessment scale-cognitive subscale; MMSE, Mini mental state examination; FAQ, function in daily living; CVRS, Comprehensive visual rating scale.

goal in this study was to predict the progression from MCI to dementia within a 24 month follow-up period. To this end, we used several clinically important features, such as demographic data, neuropsychological test results, genetic data, CVRS score, and cortical thickness, obtained during the baseline examination (Table 2) and the diagnosis made at 24 months as the target value (y label). Of the 200 patients assessed, only 197 were finally included for the analysis. A total of three patients were excluded because they did not have a diagnosis at 24 months. To examine the usefulness of the CVRS score compared to cortical thickness, the features selected from the screening data were widely used conventional variables, such as age, sex, duration of education, APOE4 genotype, and the results of cognitive function tests (CDR-SOB, ADAS-Cog11, MMSE). MRI visual rating scales, such as the total CVRS score and the hippocampal atrophy, cortical atrophy, subcortical atrophy, and small vessel disease scale scores (14) were used for the analysis. Cortical thickness was adopted as the AD signature (28), that is, the average of eight cortical thickness values computed using the MRI FreeSurfer (https://surfer.nmr.mgh.harvard.edu/). We used three datasets that consisted of clinical data, clinical data with CVRS score, and clinical data with cortical thickness to compare the prediction performance of each feature category.

Machine learning methods

To build a prediction model, we used four representative ML algorithms, namely logistic regression, RF (18), XGBoost (19), and LightGBM (20). Since the size of the dataset was relatively small, we used the leave-one-out cross-validation (LOOCV) method (29) for the analysis of the 197 patients. In addition, we used the KNN imputation method (30) to handle the missing values of one patient who did not have the APOE4 genetic test results and eight patients without the AD signature.

Leave-one-out cross-validation

Leave-one-out cross-validation is a method of learning in which one data is used as a validation set and the remaining n-1 data as a training set. The test is performed once for all sample data (Figure 1). After a model is trained and tested a total of n times, the average of all mean squared errors is calculated. The LOOCV is time-consuming; however, it shows stable performance even when the size of the dataset is small. Thus, we adopted this method for our analysis.

Logistic regression

Logistic regression is a supervised learning algorithm that predicts and classifies a sample to a group with a probability value value between 0 and 1. It learns the relationship between the independent variables $x_1, x_2, \ldots, x_n$ and the dependent variable y as a specific function, namely $y = \sigma(w_1x_1 + \ldots + w_nx_n)$, where $w_1, \ldots, w_n$ are trainable parameters and σ is the sigmoid function, such that $\sigma(t) = 1/(1 + e^{-t})$. In linear regression, the predicted value of the dependent variable falls within the range $[-\infty, \infty]$. In logistic regression, binary classification becomes possible by applying the sigmoid function, which always returns a probability in the range of [0, 1].

Random forest

An RF (18) is a machine learning method widely used to analyze structural tabular data. It is an ensemble model based on a bagging (bootstrap aggregating) method that builds multiple decision trees by using a subset of the training set. Although a single decision tree can often be overfitted, RF can prevent overfitting by using the average prediction of all the decision trees.

Gradient boosting methods

Gradient boosting is a kind of ensemble method that creates a strong classifier by combining weak classifiers. In this study, we used XGBoost (19) and LightGBM (20), which are widely used for analyzing structural tabular data. XGBoost is an ensemble algorithm that combines multiple decision trees and uses classification and regression trees to create them. It expands decision trees horizontally (i.e., level-wise) to reduce their depth. In contrast, LightGBM is a boosting-based ensemble algorithm that expands a decision tree vertically (i.e.,

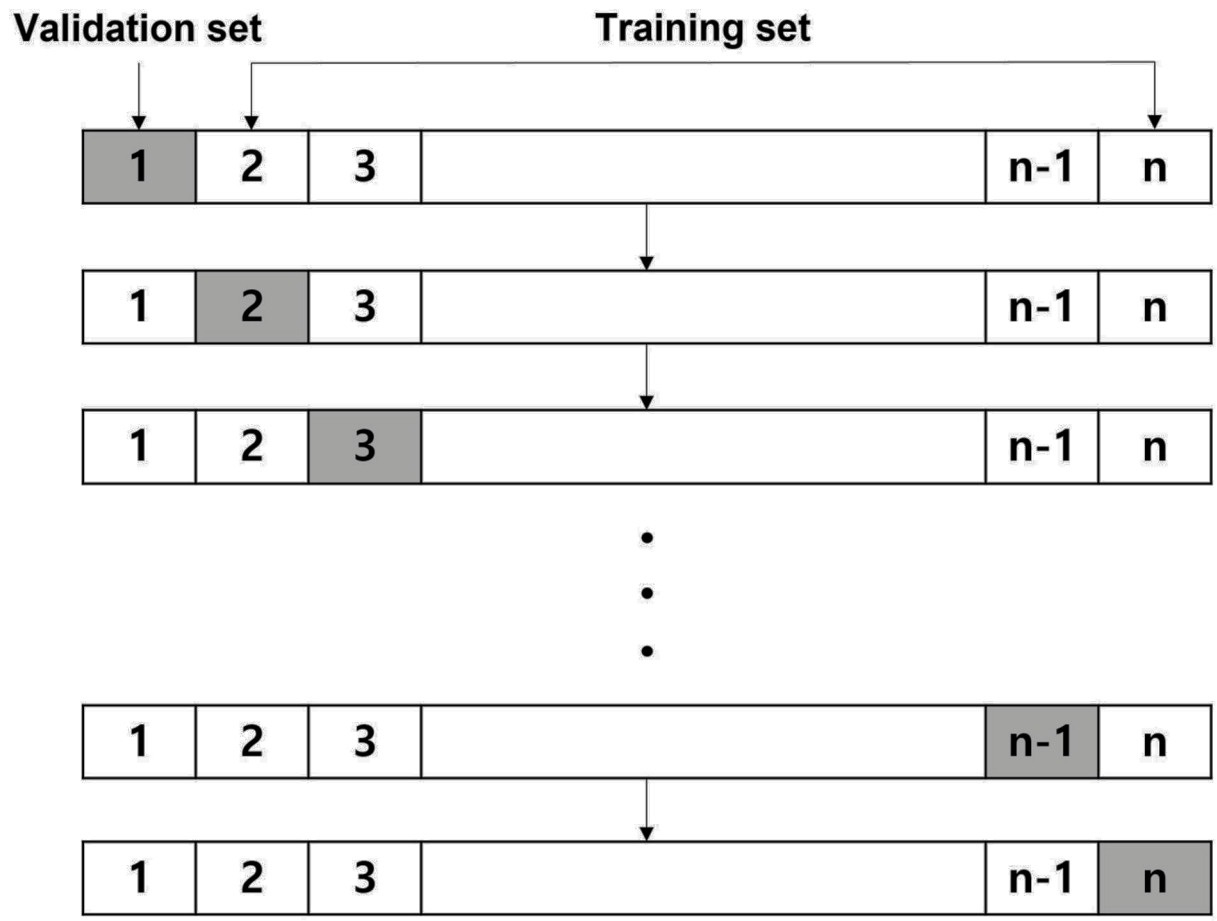

FIGURE 1
Leave-one-out cross-validation.

leaf-wise) while continuously dividing the leaf node with the maximum loss value without balancing the tree. Since both methods have relative strengths and weaknesses, we compared their performances in predicting the progression from MCI to dementia.

Feature importance

For each ML model, we report their feature importance. Standard Python implementations of random forest, XGBoost, and LightGBM automatically compute feature importance while a prediction model is built. These tree-based models usually calculate the importance of each feature using the Gini impurity of each tree node (Other impurities such as entropy may also be used instead). For example, a decision tree is created so that the impurity is lowered while feature importance is maximized. The Gini impurity $G(T)$ of a tree node T is calculated as follows:

$$G(T) = \sum_{i=1}^{n} p_i(i - p_i) = 1 - \sum_{i=1}^{n} p_i^2$$

where n is the number of classes and p_i is the probability of each sample in T to belong to the corresponding class. Then, the importance $I(T_j)$ for a node T_j in a binary tree is calculated as follows:

$$I(T_j) = w_j \cdot G(T_j) - w_{j\_left} \cdot G\left(T_{j\_left}\right) - w_{j\_right} \cdot G\left(T_{j\_right}\right)$$

where w_j is the weight of node T_j concerning the total number of samples while T_{j_left} and T_{j_right}, respectively, denote the left and right child nodes of T_j. Finally, the importance of each feature f_i for a decision tree is calculated as follows:

$$I(f_i) = \frac{\sum_{T_j \in \text{all nodes split by } f_i} I(T_j)}{\sum_{T_k \in \text{all nodes}} I(T_k)}$$

which can then be normalized as follows:

$$I(f_i)^{norm} = \frac{I(f_i)}{\sum_{f_j \in \text{all features}} I(f_j)}$$

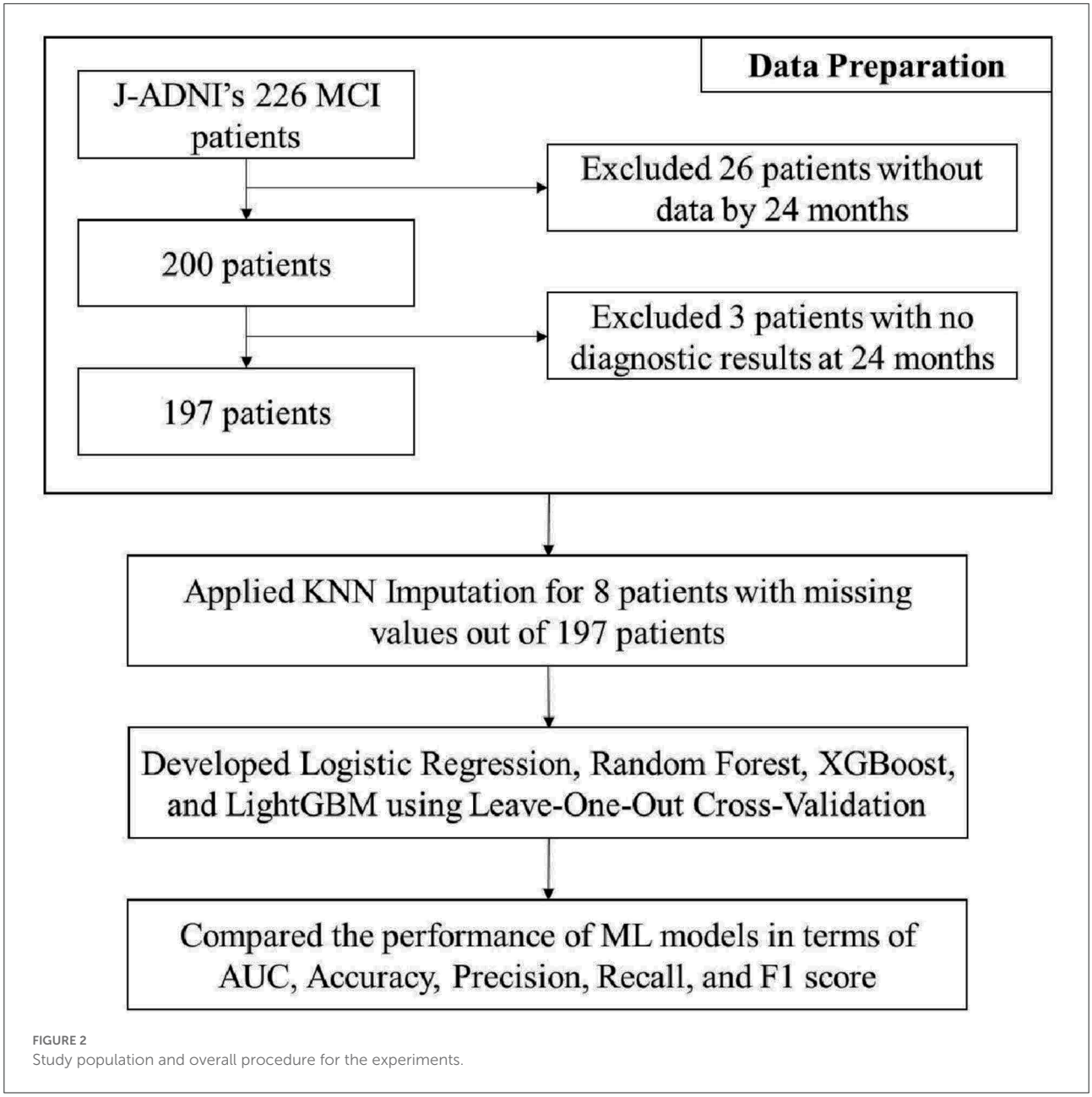

FIGURE 2
Study population and overall procedure for the experiments.

The importance of a feature f_i on a random forest, which consists of many decision trees, is then computed as the average of $I(f_i)$'s over all the trees. The feature importance on XGBoost and LightGBM is also calculated similarly.

Experiments

Figure 2 shows the study population and overall procedure for our experiments, i.e., from data preparation, data preprocessing, and development of machine learning algorithms to performance comparison in terms of various metrics. All the experiments were conducted on a workstation with an Intel(R) Core(TM) i7-8700 3.20 GHz CPU, 32 GB of main memory, and an NVIDIA GeForce RTX 2080 SUPER GPU. The host operating system was Windows 10 (64-bit) and all prediction models were implemented using Python 3 and the Scikit-learn machine learning library.

Results

A total of 197 patients were included in this study. The median age of the patients was 73.11 years and 101 (51.3%) of them were females (Table 2). A total of 104

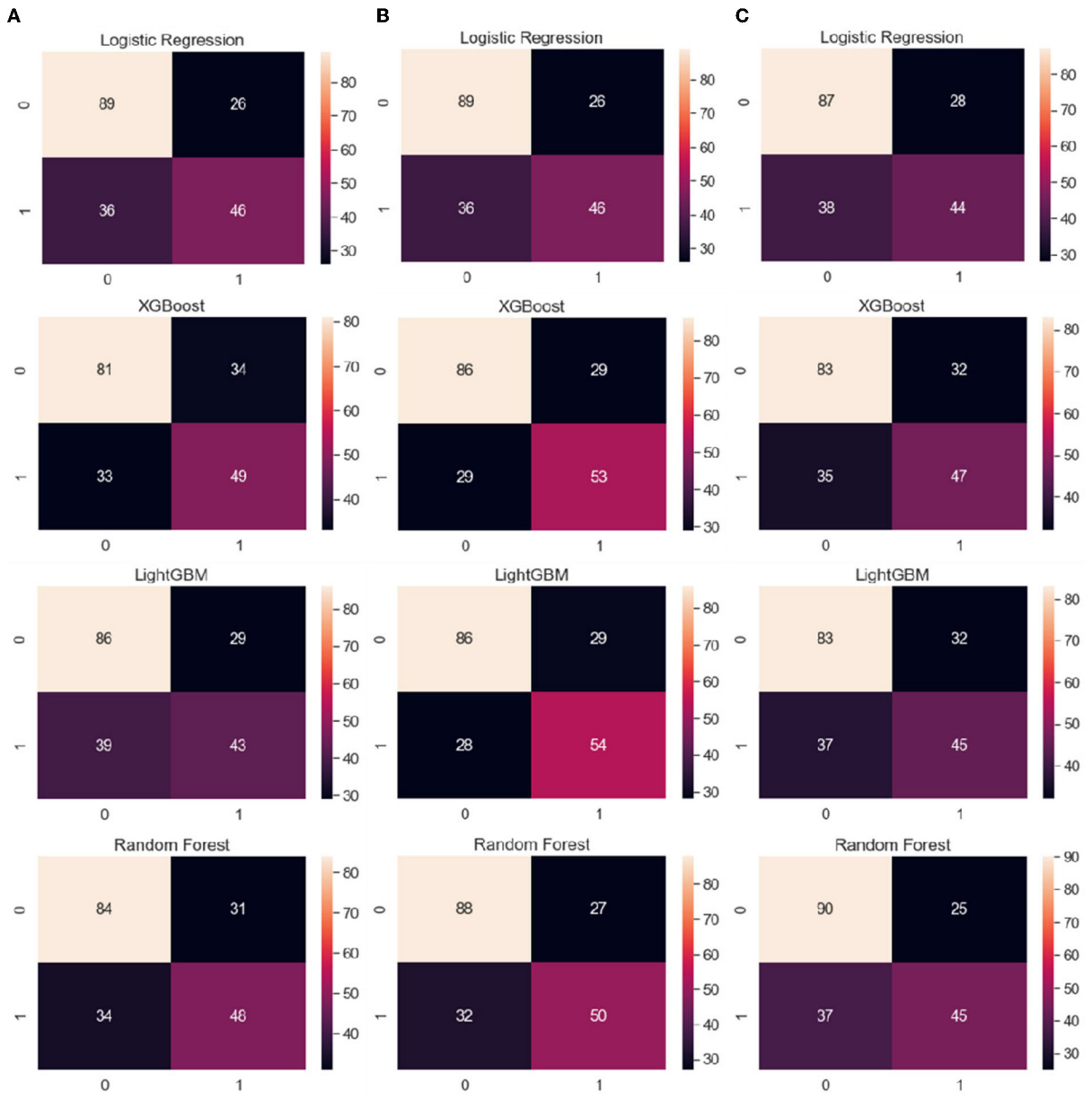

FIGURE 3
From the left, the average confusion matrix for each ML model when using the features of **(A)** clinical data, **(B)** clinical data with CVRS, and **(C)** clinical data with cortical thickness, respectively. The x-axis and y-axis represent the predicted values and the actual ground truth values, respectively.

(55.6%) patients had at least one APOE ε4 allele. During the follow-up period, 108 (54.8%) patients showed progression to dementia, whereas 89 patients did not. The demographic, cognitive, and biomarker characteristics of the patients and their classification in stable MCI and progressive MCI groups based on their progression from MCI to dementia are shown in Table 2. Patients with MCI that progressed to dementia showed poorer cognitive performances at baseline, lower cortical thickness in AD signature, and were more likely to be APOE4 carriers than those that did not show progression to dementia.

Confusion matrix

Figure 3 shows the average confusion matrixes computed for each ML model trained using LOOCV to visualize its

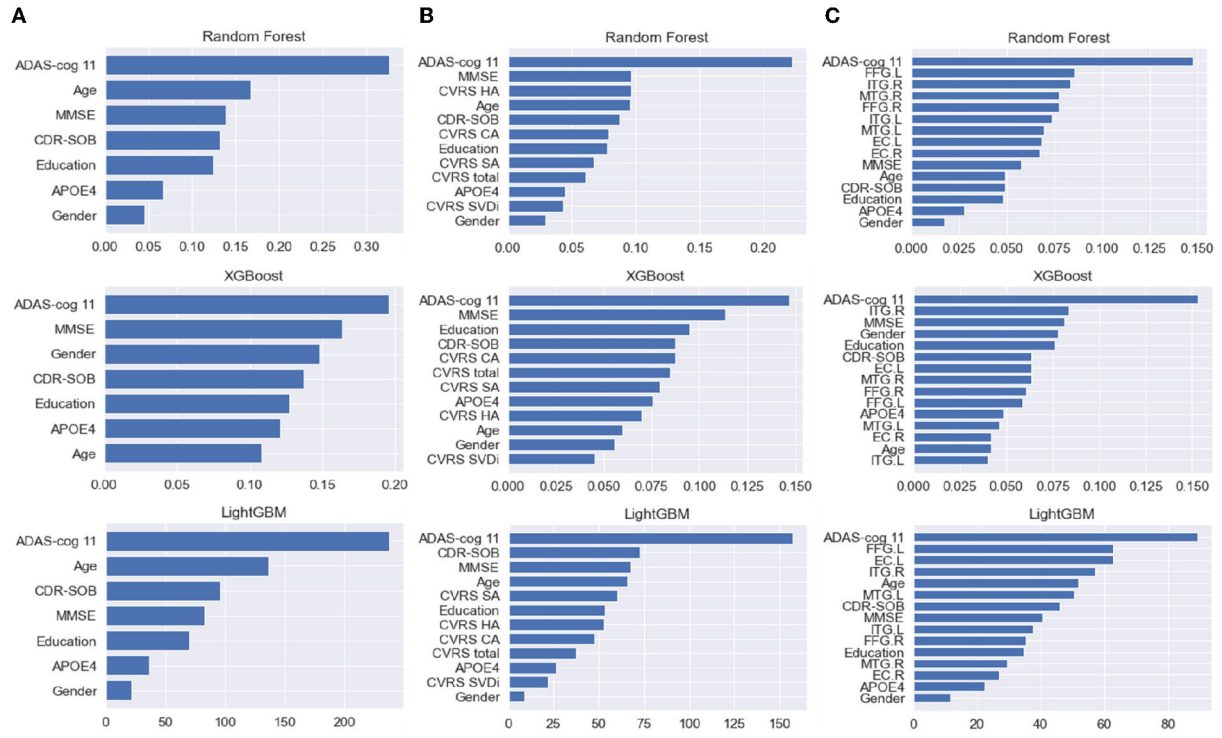

FIGURE 4
(A–C) From the left, the feature importance of each ML model with clinical data, clinical data with CVRS, and clinical data with cortical thickness, respectively. CVRS HA, CVRS hippocampal atrophy; CVRS CA, CVRS cortical atrophy; CVRS SA, CVRS subcortical atrophy; CVRS SVD, CVRS small vessel disease; EC.L/R, entorhinal cortex average thickness left/right; ITG.L/R, inferior temporal gyrus average thickness left/right; MTG.L/R, middle temporal gyrus average thickness left/right; FFG.L/R, fusiform gyrus average thickness left/right.

performance with different sets of features, namely clinical data, clinical data with CVRS score, and clinical data with cortical thickness. A confusion matrix is used to compare the actual ground truth values with the values predicted by the model, where the x-axis represents the predicted values and the y-axis represents the actual values. In the case of logistic regression, clinical data and clinical data with CVRS showed the same numbers, with the number of accurate predictions being 135 (89 + 46), which was 68% of the total data. For RF, XGBoost, and LightGBM, clinical data with CVRS showed more than 70% accuracy, which was higher than those for clinical data and clinical data with cortical thickness. For the gradient boosting models, such as XGBoost and LightGBM, more actual values were correctly predicted using clinical data with CVRS score, owing to their ability to combine different weak classifiers to create a strong classifier.

Feature importance

Figure 4 shows the average feature importance of each ML model, which was computed using the built-in feature importance provided by the implementation of each ML algorithm. We excluded the logistic regression model because we used it as a baseline model solely for comparing its prediction performance with those of the tree-based prediction models and thus did not eliminate multicollinearity between the input features. Regarding clinical data, ADAS-Cog 11 (cognitive function test) showed the highest importance in all models, whereas sex showed relatively little importance (Figure 4). For clinical data with CVRS score, ADAS-Cog 11 and the features related to CVRS score seemed to be helpful in predicting the progression from MCI to dementia to some extent. Regarding clinical data with cortical thickness, the indicators measured using the MRI FreeSurfer were also helpful in predicting the progression to dementia.

Prediction results of the machine learning models

Figure 5 shows the receiver operating characteristic (ROC) curve for each ML model with each feature set (clinical data, clinical data with CVRS score, and clinical data with cortical thickness). Table 3 shows the comprehensive performance of each model, including details such as the area under the ROC

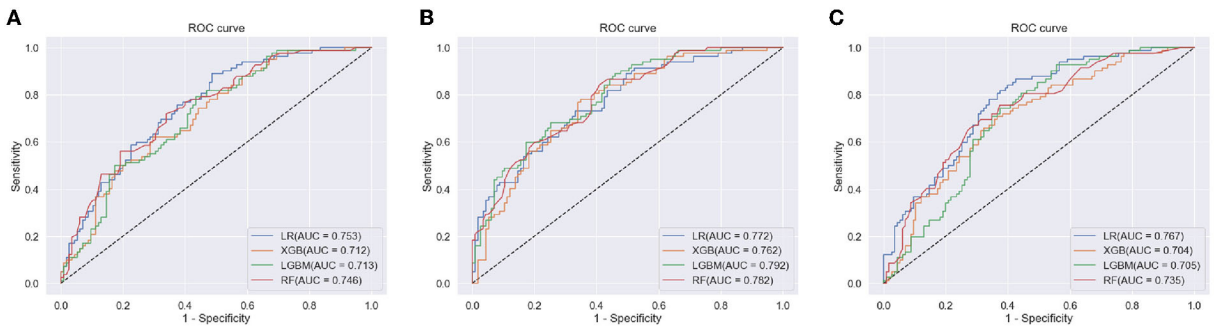

FIGURE 5
The ROC curve of each ML model for the prediction of progression to dementia within 2 years. **(A)** clinical Data, **(B)** clinical data with CVRS, and **(C)** clinical data with cortical thickness.

curve (AUC), accuracy, precision, recall, and F1 score of the model. The AUC of each prediction model was the highest when clinical data with CVRS score were used, whereas the use of clinical data with cortical thickness were not quite effective as the use of clinical data only (Figure 5). For clinical data with CVRS score, which include the CVRS features, LightGBM had the highest AUC, which was 0.792, whereas, for clinical data and clinical data with cortical thickness, logistic regression had the highest AUC, which was 0.753 and 0.767, respectively (Table 3). Each prediction model achieved the highest performance in all evaluation metrics when clinical data with CVRS score were used. All tree-based models achieved a better AUC value when clinical data with cortical thickness were used than when clinical data were used, whereas logistic regression showed the opposite result. Overall, for clinical data with CVRS score, LightGBM showed the best performance in all metrics with an accuracy of 0.711, precision of 0.651, recall of 0.659, and F1 score of 0.655. In contrast, for clinical data, logistic regression showed the best performance in all metrics except for recall.

Discussion

In this study, we have investigated the effects of baseline structural cerebral changes estimated using the CVRS on the progression of MCI to dementia during a 2-year follow-up period using multiple representative ML algorithms. The key finding of this study is that the ML dementia prediction models showed higher accuracy when clinical data with CVRS score were used than when clinical data alone or with cortical thickness were used. This result is in line with that of a previous study (16) on the use of visual rating scales for predicting the progression of MCI to dementia.

The CVRS scores of patients with MCI could help identify individuals who are most likely to progress to dementia without the need for additional high-cost biomarkers. The CVRS score reflects mixed pathological conditions, such as cerebral atrophy and vascular injury. Although automated image analysis of brain MRI scans has been widely used in previous research, visual rating involving scales such as the CVRS is simpler and faster, and more appropriate for individual assessment in a primary clinical setting (14, 31–33). Additionally, the CVRS is a cost-effective diagnostic tool ideally suited for implementation in clinical practice (15). In contrast, automated image analysis tools are more appropriate for detailed research that includes group analyses and a longitudinal follow-up (34). We attempted to utilize a good combination of multi-modal and highly accessible data for the predictive models by considering conventional demographic and cognitive information such as clinical data, MRI features such as CVRS score, and cortical thickness. In this study, a comparison of the predictive accuracy of the models when CVRS score was used and when the cortical thickness was used showed that CVRS had higher predictive accuracy than the cortical thickness (Table 3).

Various performance measures shown in Table 3 confirmed that for each prediction model utilized in this study, CVRS features showed more usefulness than cortical thickness features in all metrics (AUC, accuracy, precision, recall, and F1 score). Every performance measure of each prediction model was always better when clinical data and CVRS score were used together than when clinical data were used alone. In contrast, using clinical data together with cortical thickness was often worse than using clinical data alone. Regarding AUC values, the general guidelines in the book by Hosmer et al. (35) indicate that the prediction performance of all tree-based ensemble algorithms is sufficiently good when CVRS score is used, whereas it is only acceptable when cortical thickness is used. However, regarding other measures, such as accuracy, precision, recall, and F1 score, predictive performance can be improved further by considering more data or conducting hyperparameter tuning.

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TABLE 3 The prediction performance of each ML model with leave-one-out cross-validation.

Dataset	Model	AUC	Accuracy	Precision	Recall	F1 Score
Clinical data	Logistic regression	**0.753** (0.686–0.820)	**0.685**	**0.639**	0.561	**0.597**
	Random forest	0.746 (0.678–0.814)	0.670	0.608	0.585	0.596
	XGBoost	0.712 (0.641–0.783)	0.660	0.590	**0.598**	0.594
	LightGBM	0.713 (0.642–0.784)	0.655	0.597	0.524	0.558
Clinical data with CVRS	Logistic regression	0.772 (0.707–0.837)	0.685	0.639	0.561	0.597
	Random forest	0.782 (0.719–0.845)	0.701	0.649	0.610	0.629
	XGBoost	0.762 (0.696–0.828)	0.706	0.646	0.646	0.646
	LightGBM	**0.792** (0.730–0.853)	**0.711**	**0.651**	**0.659**	**0.655**
Clinical data with cortical thickness	Logistic regression	**0.767** (0.702–0.832)	0.665	0.611	0.537	0.571
	Random forest	0.735 (0.665–0.805)	**0.685**	**0.643**	0.549	**0.592**
	XGBoost	0.704 (0.631–0.777)	0.660	0.595	**0.573**	0.584
	LightGBM	0.705 (0.633–0.777)	0.650	0.584	0.549	0.566

For each dataset and performance metric, we denote the highest value in bold face. For each feature set and each ML model, we show the average AUC and its confidence interval, the average accuracy, precision, recall, and F1 score. ML, machine learning; AUC, area under curve.

It is interesting to note that each ML algorithm employed different feature importance for predicting the progression from MCI to dementia (Figure 4). The results of the multivariate analysis in our previous study with US-ADNI suggested that positive amyloid PET, CDR-SOB, and CVRS are important predictors of progression from MCI to dementia (16). In this study, cognitive measures such as ADAS-Cog, MMSE, and CDR-SOB were used in all three tree-based ensemble models, with high importance for clinical data with multi-modal CVRS data. In particular, RF exploited hippocampal atrophy as the third important feature, followed by other components of CVRS. This result is mostly in line with that of a previous study in terms of the importance of the visual rating scale (15). Meanwhile, regarding clinical data with multi-modal cortical thickness data, components of cortical thickness were ranked as important features following ADAS-Cog, and most features of cortical thickness played important roles, especially for RF.

What is novel in this study compared to previous studies is that it is focused on new Asian longitudinal datasets and analytic methodologies using CVRS (Table 4). The first study used cross-sectional data from a single center that validation was performed just for test-retest reliability and clinical group differentiation (14). The following study used multisite longitudinal US-ADNI data from 63 sites in the US that showed an association between the baseline CVRS score and conversion to dementia using survival analysis (16). Finally, this study applied various ML algorithms to validate the prediction of progression to dementia using multisite longitudinal J-ADNI data from 38 sites in Japan. On top of that, we also showed higher performance of CVRS compared to cortical thickness that implicated this relatively simple tool could be used in clinical practice combined with clinical data to identify MCI subjects with a higher risk of progression. This is valuable for the clinician for the achievement of a more accurate prognosis and following a treatment plan to prevent cognitive decline.

A recent systemic review of 116 studies on the use of ML methods for predicting progression from MCI to AD showed that all the studies of MRI were conducted using automated image analysis such as cortical thickness, 3D-volumetry, tensor-based morphometry, or functional connectivity (17). Nevertheless, a balance is necessary between the advanced

TABLE 4 Comparison of studies using comprehensive visual rating scale (CVRS).

	Data set	Study design	Subjects	Validation
Jang et al. (14)	Data from single Korean center	Cross-Sectional analysis	NC ($n = 65$), MCI ($n = 101$), AD ($n = 94$)	• Test-retest reliability • Clinical group differentiation according to baseline CVRS
Jang et al. (16)	ADNI data from 63 sites in U.S.	Longitudinal analysis over 3 years	MCI ($n = 340$)	• Association between conversion to dementia and baseline CVRS
Current study	J-ADNI data from 38 sites in Japan	Longitudinal analysis over 2 years	MCI ($n = 197$)	• Association between conversion to dementia and baseline CVRS using various ML algorithms • Feature importance • Comparison between cortical thickness and CVRS

NC, Normal cognition; MCI, Mild cognitive impairment; ML, Machine learning.

imaging data and ML algorithms for higher performance and the data and methods that could be available in clinical practice. Therefore, the strength of our study is further validation of the visual rating scale by adopting various ML algorithms focusing on achieving high performance using essential and easily obtainable data such as visually assessed structural MRI, demographic, and cognitive measures.

This study has some limitations. First, accuracy was relatively low compared to previously published studies. A recent systematic review showed that most studies were conducted using MRI and PET and the ADNI dataset (17). In addition, conventional algorithms, such as the support vector machine, were the most commonly used algorithms, and they had a mean accuracy of 75.4%. The highest accuracy in this study was 71.1%, which was achieved by LightGBM using demographic data and CVRS score (Table 3). The relatively low accuracy in this study may be due to the small size of the J-ADNI dataset compared to the much larger ADNI dataset. However, although the ADNI is a very useful public database that includes the data of about 1,700 subjects and has been used as a dataset in more than 3,500 publications since 2004, about 80% of the participants were Whites whereas only 2.7% of them were Asians (36). Therefore, to achieve partial generalizability of our findings for the Asian subjects, we chose the J-ADNI dataset, even though it is much smaller than the ADNI dataset. In addition, the main objective of our study was not just to achieve high accuracy using brain MRI but to compare the effectiveness of the CVRS score and that of cortical thickness for predicting progression to dementia when combined with demographic data. Second, the conversion rate (54.8% in 2 years) in this study was much higher than those reported in other studies (from 10 to 15% per year) (37, 38). A previous study speculated that this higher conversion rate of MCI in J-ADNI might happen because J-ADNI clinicians defined the clinical cutoff for AD more sensitively (25). Third, we included subjects with MCI who performed MRI at baseline without pathologic confirmation by either molecular imaging or CSF. Although J-ADNI included these data, they were not used for the analysis because these methods are either expensive or invasive. Considering the importance of cost-effective biomarker identification that is readily obtainable in a less invasive manner, CVRS of brain MRI was used for clinical implementation. Lastly, there was a decreased score of small vessel disease in the progressive group compared to the stable group although it was not statistically significant (Table 2). This was already a suggested issue that ADNI excluded subjects with a high burden of small vessel disease (16); hence, the effect of small vessel disease needs to be further validated using other datasets.

In conclusion, this study showed that for patients with MCI, a baseline CVRS score combined with clinical data are effective for predicting progression to dementia over a 2-year follow-up period. Moreover, tree-based ensemble ML models demonstrated better performances than the logistic regression model, which implies that the utility of the CVRS score can be enhanced by using appropriate ML algorithms.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: Japan Science and Technology Agency (JST) National Bioscience Database Center (NBDC), http://biosciencedbc.jp/en/, JGAD000051.

Ethics statement

The study procedures were approved by the Institutional Review Board of the Kangwon National University Hospital (No. KNUH-2017-04-012) and written informed consent was obtained from all participants or their authorized representatives.

Japanese-Alzheimer's Disease neuroimaging initiative

Data used in this research were originally obtained by the Japanese Alzheimer's Disease Neuroimaging Initiative http://humandbs.biosciencedbc.jp/en/hum0043-v1 (led by Prof. Takeshi Iwatsubo) and are available at the website of the National Bioscience Database Center (NBDC; http://biosciencedbc.jp/en/) of the Japan Science and Technology Agency (JST).

Author contributions

ChaP, J-WJ, HI, and SaK: designed the study. ChaP, J-WJ, GJ, HI, SP, and PK: analyzed data, composed figures, and drafted the manuscript. ChaP and J-WJ: collection of data. YK, SeK, J-MP, YP, J-SL, H-SC, SY, and ChiP: data processing. YY and HI: interpreted data for the study. HI and SaK: study supervision and critical review of the manuscript for intellectual content. All authors gave their final approval of the version to be published and agree to be accountable for all aspects of the work.

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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.2022.906257/full#supplementary-material

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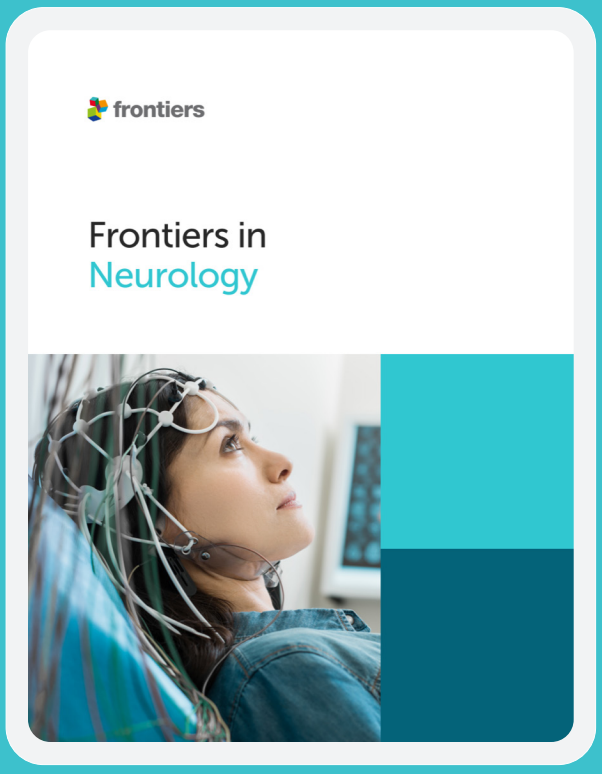

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