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The intersection of cognitive, motor, and sensory processing in aging: Links to functional outcomes, volume II

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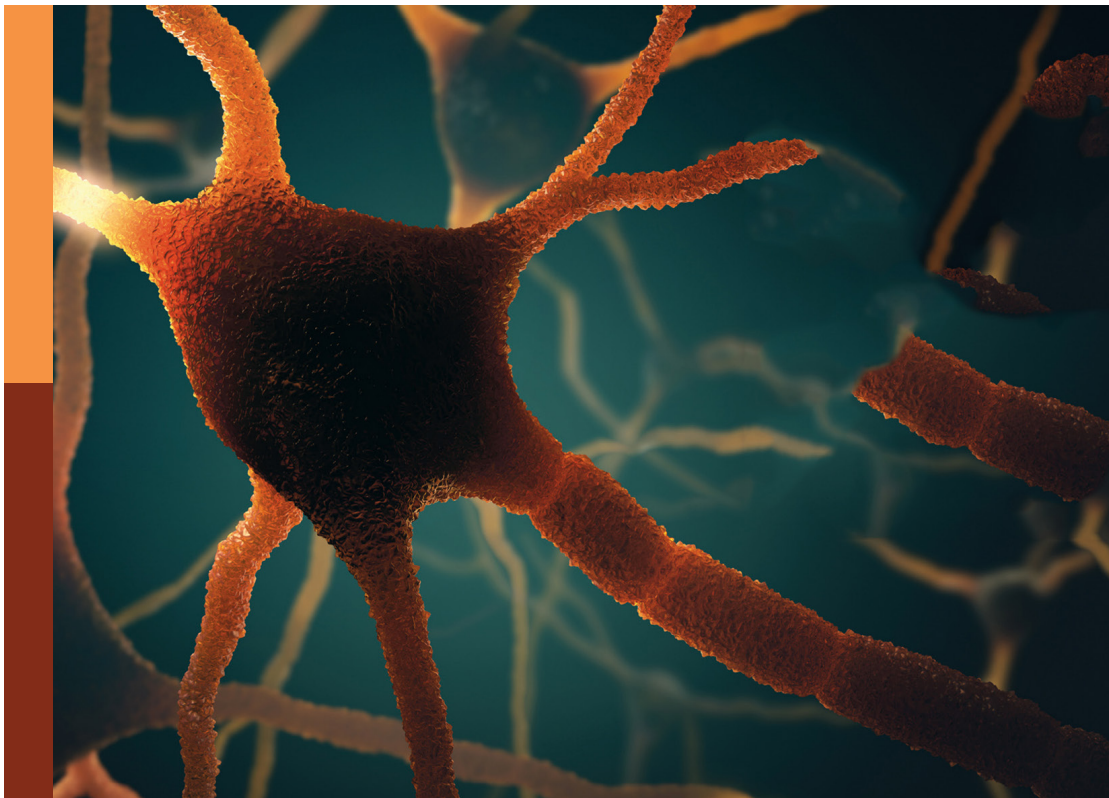

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The intersection of cognitive, motor, and sensory processing in aging: Links to functional outcomes, volume II

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Editorial: The intersection of cognitive, motor, and sensory processing in aging: links to functional outcomes, volume II

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Editorial on the Research Topic
The intersection of cognitive, motor, and sensory processing in aging: links to functional outcomes, volume II

The cognitive processes of encoding, decoding, and interpreting information about biologically significant events represent fundamental neural functions that require extensive integrated neural networks. These processes have played a central role in the course of evolution, giving rise to a variety of specialized sensory organs, each intricately connected to multiple specialized brain regions (Stein and Stanford, 2008). While the sophisticated interactions between neural circuits are of great scientific interest, it is the practical manifestation of these processes that allows us to monitor and understand the physical execution of activities of daily living (ADL). Whether it is the rhythmic act of walking, the successful balancing act needed to avoid falling, the efficient performance of daily activities needed to bathe or eat, or the complex cognitive-motor interplay involved in activities such as dancing, our ability to engage in such structured multisensory endeavors underscores the importance of these neural functions in our daily lives.

Multisensory integration (MSI) is a multimodal process in which the brain combines and coordinates information from multiple sensory modalities such as vision, hearing, touch, and proprioception to produce a unified and coherent perceptual experience. This integration enhances our understanding of the external world, promotes more accurate and reliable perception, and enables effective responses to the environment (Stein et al., 2014). These processes, which are evident at both neural and behavioral levels, can lead to enhancement or attenuation of responses (Wallace et al., 1998; Stein et al., 2009) and significantly influence our sensations, perceptions, and associated behaviors. Response enhancement, which often affects the accuracy and speed of stimulus detection, localization, and identification (Hughes et al., 1994; Ernst and Banks, 2002; Foxe and Schroeder, 2005; Hecht et al., 2008), serves as a reliable index of MSI, which involves a wide range of computations that combine information from multiple sensory modalities.

A well-documented phenomenon in aging is the gradual decline of individual sensory modalities and body functions. These age-related changes affect several areas, including visual acuity (Faubert, 2002; Schieber, 2006), auditory abilities (Van Eyken et al., 2007; Murphy et al., 2018), muscle strength (Hortobágyi et al., 1995; Lindle et al., 1997), and postural balance (Laughton et al., 2003; Marusic et al., 2019), among others. However, the extent to which changes in MSI contribute to age-related deterioration in ADLs remains a less explored area of investigation in the existing literature (de Dieuleveult et al., 2017).

Mahoney et al. have generated evidence for robust, but differential MSI effects in healthy aging and discovered significant links with clinically meaningful outcomes (Mahoney et al., 2014, 2015, 2019; Mahoney and Verghese, 2018, 2020). Specifically, they report that older adults with intact levels of visual-somatosensory integration demonstrate better balance, faster gait velocity and lower incidence of falls, compared to those with integrative deficits. Further they reveal that older adults with MCI and dementia demonstrate significantly reduced magnitude of multisensory integration compared to older adults without cognitive impairments.

The current Research Topic of Frontiers in Aging Neuroscience represents a continuation of Volume I entitled "*The intersection of cognitive, motor, and sensory processing in aging: links to functional outcomes*." This latest Research Topic includes ten manuscripts that collectively address various facets of sensory integration along with cognitive and motor performance in the context of aging. The primary goal of this Research Topic is to foster new scientific discoveries detailing the complex inter-relationships between sensory, motor, and cognitive functions in aging. Contributors to this Research Topic examine age-related changes in one or more of these systems—sensory, motor, and cognitive—and discuss the impact of these interactions on important functional outcomes, including but not limited to clinical and social aspects. A better understanding of the effective (or ineffective) convergence of these systems holds promise for the wellbeing of older people and offers insights for improving and adapting multimodal interventions aimed at preventing decline and minimizing disability.

Handling et al. and Thompson et al. both focus on predictors and interactions related to cognitive and physical decline in older adults. Handling et al. identify risk factors for dual decline, with depressive symptoms and APOE-ε4 status increasing the odds of developing cognitive and physical decline. In contrast, Thompson et al. employed canonical correlation analysis, unveiling two interconnected clusters of cognitive and physical function tasks in a cross-sectional cohort of cognitively intact older adults. These findings underscore a predominant emphasis on speed-related tasks in both gait and cognition, along with a secondary focus on complex motor and cognitive tests.

Basharat et al. and Šlosar et al. investigate the impact of multisensory processing and virtual reality (VR). Basharat et al. reveal that immersive VR can enhance multisensory processing and improve performance in untrained cognitive tasks. While Šlosar et al. explore the potential of enriched VR environments in mitigating the effects of prolonged bed rest, offering a novel approach to improving rehabilitation outcomes.

In a mini review Meulenberg et al. discuss the potential of dance therapy as a non-pharmacological intervention for Parkinson's disease. Dance interventions induce neuroplastic changes, improving both motor and cognitive functions in PD patients. The authors conclude that more research is needed to determine the optimal dance style and duration for therapeutic benefit.

Tabei et al. investigate the impact of an online physical exercise program with music on cognitive function, particularly working memory in older adults. Their results show significant improvements in working memory, suggesting the potential of online exercise programs to enhance cognitive functions.

In a study protocol, Mahoney et al. outline the potential use of visual-somatosensory integration as a marker for Alzheimer's disease. This protocol details the methodologies used to examine the interplay of sensory, cognitive, and motor functions, as well as study their impact on mobility decline in aging. The main objective is to assess the validity of MSI as a novel non-cognitive, non-invasive, behavioral marker of preclinical Alzheimer's disease.

In a cross-sectional study, Hu et al. investigated age-related changes in cortical control of standing balance and their effects on falls in older adults. Despite some limitations in the reliability of the mechanical perturbation, the results suggest increased cortical recruitment for postural control in older adults and emphasize the need for further studies to improve the understanding of these mechanisms.

Fatokun et al. investigated the relationship between dual-task gait cost (DTC) and white matter hyperintensities (WMH) in Lewy body disorders. Higher DTC was associated with greater frontal WMH burden, providing insights into cognitive-motor interactions in Parkinson's disease and dementia with Lewy bodies.

Finally, Torre et al. investigated the effects of bimanual coordination training on inhibitory functions in older adults. The training, which involved maintenance of an antiphasic pattern and inhibition of the in-phase pattern, effectively delayed the frequency of spontaneous transitions and transferred the benefits to untrained tasks involving inhibitory functions.

Overall, this compilation collectively contributes to our understanding of the complex relationships among sensory, motor, and cognitive functions in the context of aging while shedding light on predictors, interventions, and novel markers that have the potential to improve the wellbeing of older adults. This Research Topic serves as a continuation of ongoing research on the intersection of these functions and highlights the importance of a much-needed multifaceted approach to addressing age-related decline across multiple domains. The research presented here underscores the ongoing commitment to improving the quality of life of older adults and emphasizes the importance of multidisciplinary research in the field of aging neuroscience.

Author contributions

UM: Writing—original draft, Writing—review & editing. JM: Writing—original draft, Writing—review & editing.

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Conflict of interest

JM has a financial interest in JET Worldwide Enterprises Inc., a digital health startup spun out of research conducted at Albert Einstein College of Medicine.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Examining the intersection of cognitive and physical function measures: Results from the brain networks and mobility (B-NET) study

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Background and objectives: Although evidence exists that measures of mobility and cognition are correlated, it is not known to what extent they overlap, especially across various domains. This study aimed to investigate the intersection of 18 different objective cognitive and physical function measures from a sample of unimpaired adults aged 70years and older.

Research design and methods: Canonical correlation analysis was utilized to explore the joint cross-sectional relationship between 13 cognitive and 6 physical function measures in the baseline visit of the Brain Networks and Mobility Function (B-NET) Study (n=192).

Results: Mean age of participants was 76.4 years. Two synthetic functions were identified. Function 1 explained 26.3% of the shared variability between the cognition and physical function variables, whereas Function 2 explained 19.5%. Function 1 termed "cognitive and physical speed" related the expanded Short Physical Performance Battery (eSPPB), 400-m walk speed, and Dual Task gait speed measures of physical function to semantic fluency animals scores, Digit Symbol Coding (DSC), and Trail Making Test B. Function 2 termed "complex motor tasks and cognitive tasks" related the Force Plate Postural Sway Foam Task and Dual Task to the following cognitive variables: MoCA Adjusted Score, Verbal Fluency L words, Craft story immediate and delayed recall, and Trail Making Test B.

Discussion and implications: We identified groups of cognitive and physical functional abilities that were linked in cross-sectional analyses, which may suggest shared underlying neural network pathway(s) related to speed (Function 1) or complexity (Function 2).

Translational significance: Whether such neural processes decline before measurable functional losses or may be important targets for future interventions that aim to prevent disability also remains to be determined.

KEYWORDS

cognitive function, mobility, aging, canonical correlation analysis, physical function

Introduction

Walking is a complex task integrating neuromuscular and cognitive components (Wilson et al., 2019). Several studies have shown that gait speed is associated with cognitive function as measured by a variety of global and domain specific assessments, but the strength and direction of associations have varied depending on the test and cohort, with some studies suggesting slow gait predicts cognitive changes and others that cognitive performance predicts decline in gait speed (Fitzpatrick et al., 2007; Watson et al., 2010; Mielke et al., 2013; Verghese et al., 2013; Morris et al., 2016; Peel et al., 2019; Handing et al., 2021; Jayakody et al., 2021). Many studies include persons with mild cognitive impairment or clinical neurological disease and so some associations may reflect concomitant impairments in both areas. Thus, examining these relationships in a cognitively intact cohort could help to determine whether the observed associations are intrinsic.

Moreover, the majority of the literature examining cognition and physical function to date have focused on gait speed but not particular aspects of physical function that contribute to gait, such as balance, muscle strength, and power. Given the limited range of physical assessments in prior work, it is not clear whether the association of gait and cognition stems from particular components of gait or if these components may differentially relate to different aspects of cognitive function especially on different tests (Clouston et al., 2013; Mignardot et al., 2014; Szturm et al., 2015; Rosano et al., 2016; Bahureksa et al., 2017; Bohannon, 2019; Chou et al., 2019; Wiśniowska-Szurlej et al., 2019; Meunier et al., 2021). A better understanding of the basis of the relationship of cognitive and physical function is needed.

In this analysis, we used canonical correlation analysis (CCA) to describe the patterns of association between 18 different objective measures of physical and cognitive function collected at the baseline visit of the Brain Networks and Mobility Function (B-NET) study. B-NET is a longitudinal study of 192 older adults free of mild cognitive impairment (MCI), dementia, or a clinical history of neurologic disease in order to understand the relationship between functional brain networks involving the sensorimotor cortex and lower extremity mobility function. CCA estimated linear combinations of the cognitive and physical measures in order to maximize the amount of explained shared variance (Sherry and Henson, 2005; Zhuang et al., 2020). Such linear functions describe the intersection of specific cognitive and physical measures, which may reflect shared underlying neural networks that could be considered novel therapeutic targets in future work. While this analysis was exploratory in nature, we expected to replicate prior observations of the association between executive function and gait speed (Fitzpatrick et al., 2007; Watson et al., 2010) as well as better elucidate which particular cognitive functions may be related to specific aspects of physical function.

Materials and methods

Study design

This study includes participants in the baseline visit of the B-NET study, an ongoing longitudinal, observational study of community-dwelling older adults aged 70 and older recruited from Forsyth County, NC and surrounding regions (NCT03430427). Participants were excluded from the study if they were a single or double lower extremity amputee, had musculoskeletal impairments severe enough to impede functional testing (e.g., joint replacements), or dependency on a walker or another person to ambulate. The participants were also excluded if they had a history of any of the following: surgery or hospitalization within the past 6 months, serious or uncontrolled chronic disease (e.g., stage 3 or 4 cancer, stage 3 or 4 heart failure, liver failure or cirrhosis of the liver, uncontrolled angina, respiratory disease requiring the use of oxygen, renal failure requiring dialysis, diagnosis of schizophrenia, bipolar, or other psychotic disorders, or alcoholism (>21 drink per week)), clinical manifestation of a neurologic disease affecting mobility, prior traumatic brain injury with residual deficits, brain tumors, seizures within the last year, and major uncorrected hearing or vision problems. In addition, they were excluded if they reported plans to relocate within the next 2 years, were participating in a behavioral intervention trial, or had evidence of impaired cognitive function. Cognitive impairment was defined based on scores on the Montreal Cognitive Assessment (MoCA). MoCA scores of 20 or lower on the MoCA were considered ineligible. The full complement of cognitive tests in those with scores between 21 and 25 was reviewed by the study neuropsychologist, and those with a pattern consistent with MCI were excluded. Each participant signed a written informed consent form and the Institutional Review Board (IRB) of the Wake Forest School of Medicine approved the study.

Cognitive function testing

MoCA

The MoCA is a brief cognitive screening tool for global cognition and is scored out of a possible total score of 30 points, with higher scores indicating better cognitive performance. It assesses different cognitive domains including attention and concentration, memory, language, conceptual thinking, calculations, and orientation (Nasreddine et al., 2005; Freitas et al., 2013). The overall MoCA score was evaluated in this study.

Semantic fluency

Semantic fluency is a measure of speeded word retrieval and executive function. The participant is asked to name various items of a given semantic category (animals or vegetables), and the number of unique responses named is scored. Participants are given 60 s to generate as many distinct responses as they can, with a higher score indicating better performance. The individual score for animals or vegetables was evaluated in this study.

Verbal fluency

Verbal Fluency is a measure of speeded word retrieval and executive function. The participant is asked to name items that begin with a certain letter of the alphabet (F or L). The number of unique responses named is scored. Participants are given 60 s to generate as many distinct responses as they can, with a higher score indicating better performance. The individual score for F or L was evaluated.

Craft story

The Craft Story 21 Recall (Immediate) assesses the ability to recall a short story. The study staff reads a short story and immediately after hearing the story, the participant is asked to retell the story from memory. Points are given for correct recall of details from the story. After approximately a 20-min delay, the participant is asked to repeat the story and scored for correct recall of details from the story, with

higher scores indicating better performance. The immediate and delayed scores were each assessed in this study.

Digit symbol coding

The Digit symbol coding (DSC) assesses processing speed. The participant is asked to translate numbers (1–9) to symbols using a key provided at the top of the test form. The outcome included here is the total number of correct responses within 90 s, with higher scores indicating better performance.

Auditory verbal learning test

The Auditory verbal learning test (AVLT) is a 15-word, six trial list learning task with immediate and delayed recall conditions. Fifteen words are read aloud and then the participant must recall the words from the list. Correct words recalled after each trial are awarded 1 point. After a 20- to 30-min delay, the participant is asked to recall the same words from the list again (Schmidt, 1996). The Delayed Recall score is the mean number of words correctly recalled across all six trials, and the Short Delay Recall (Trial 6) reflects the raw number of words recalled after an interference trial, with higher scores indicating better performance. The short and delayed recall scores were considered in this analysis.

Trail making A and B

The Trail making (TMT) includes Parts A and B. Part A requires participants to connect a series of circles numbered 1 to 25, and it assesses visual scanning, sequencing, and psychomotor speed. Part B adds a set shifting element by requiring the participant to switch between numbers and letters. The maximum time in seconds is 150 for Part A and 300 for Part B, with higher number of seconds indicating worse performance. TMT A and TMT B scores were each analyzed in this study.

Flanker

A computerized assessment of executive function and response inhibition administered using the EPRIME software 2.0 (Psychology Software Tools, Inc.). The Flanker task required participants to indicate the direction, by button press, of a central target arrow flanked by congruent or incongruent arrows. Accuracy and response times were recorded with the differenced in response time between the congruent and incongruent conditions being the summary score (Sanders et al., 2018). Higher difference scores are considered poorer performance. For this analysis, the log of the ratio of median response times was used.

Mobility function testing

Grip strength

Grip strength (kg) was measured using a Jaymar handheld dynamometer. Three trials were performed and the maximum was taken across the 3 trials of the dominant hand, with larger values representing better performance.

Postural sway

Postural sway was assessed using Center-of-Pressure (COP) trajectory data collected at 100 Hz using an Advanced Mechanical Technology Incorporated (AMTI) AccuSway biomechanics force platform. Participants were barefoot in an upright closed stance and asked to stand comfortably on the platform for a series of five, 30-s trials. Postural sway was measured using a standard firm force plate as well as a foam force plate. For both plates, the area (in.^{2}) within the 95% confidence ellipse path around the center of pressure was used to represent performance, with higher values representing worse performance.

Expanded short physical performance battery

The expanded Short Physical Performance Battery (eSPPB) was adapted from the test described by Guralnik et al. (1994) in order to address ceiling effects that could limit the value of the traditional SPPB in a well-functioning cohort such as BNET. The eSPPB increases the challenge to participants' physical function assessments for balance and gait. Participants are asked to hold a side-by-side posture for 10 s, and the semi-tandem, tandem, and one-leg position for 30 s each. If participants are unable to hold the semi-tandem stand for 30 s, then they are requested to hold a short tandem stand for 10 s instead of 30 s. In addition to the usual 4-m gait speed (m/s), a narrow walking pace is also assessed over 4 m wherein participants are required to keep their steps in between 2 parallel lines marked 20 cm apart. The number of times a participant can stand up from a seated position, or chair pace, is also measured during a 5 s period. Scores for each subcomponent are then calculated based on the proportion of the best possible score (a continuous measure), not according to ranges of performance (a categorical measure). The resulting overall eSPPB score ranges from 0–4, rather than the traditional 12-point right-skewed categorical score distribution of the SPPB. The higher values represent better performance.

400-m walk test

Participants completed the fast-paced 400-m walk protocol developed by the Health Aging and Body Composition study, which has been shown to predict future mobility disability and mortality (Newman et al., 2006). The 400-m gait speed in m/s was analyzed in this study.

Dual task

During the Dual Task, participants completed 4 trials of walking over the 4-m GaitRITE Mat while saying the alphabet but skipping every other letter (e.g., B D F H J, etc.). The gait velocity was measured in cm/s and converted to m/s for the purpose of analysis.

Statistical methods

Means (SD) and proportions were calculated for descriptive statistics and Spearman correlations were calculated between all cognitive and physical function variables. The distributions of variables were examined, and log transformation was performed for postural sway, 400-m walk pace, Trails A and B. For the main analysis, a canonical correlation analysis (Mielke et al., 2013) (CCA) was used to relate the 12 cognition measures to the 6 physical function measures (see Table 1 for a listing of cognition and physical function variables) after adjusting for sex and years of education (i.e., the CCA was run on the residuals for each variable after removing the sex and education effect). Sex was included as an adjustment factor due to significant associations of sex with strength, especially grip strength, and education was adjusted for since it can affect cognitive performance. This CCA analysis creates linear functions of the two groups of variables that maximize the correlation between the synthetic variables (e.g., one for cognition and one for physical function) formed by those linear functions, with the number of pairs of synthetic variables being equal to the lower number of variables within a group (6 physical function measures in our case). Each synthetic variable is mathematically constructed so that it is

TABLE 1 Descriptive statistics from participants at baseline in the BNET study.

	Overall (*N*=192)
	Mean (SD); range
Age	76.43 (4.72); 70 to 90
Sex	
Women	108 (56.2)
Men	84 (43.8)
Race/Ethnicity	
Caucasian or White/Non-Hispanic	171 (89.1)
African American or Black/Non-Hispanic	18 (9.4)
Caucasian or White/Hispanic	2 (1.0)
Asian/Non-Hispanic	1 (0.5)
BMI	28.39 (5.63); 15.7 to 59.8
Years of education	15.68 (2.45); 12 to 25
Cognitive measures	
MoCA adjusted score	25.64 (2.20); 21 to 30
Semantic fluency: Animals (no. in 60 s)	18.78 (4.82); 7 to 34
Semantic fluency: Vegetables (no. in 60 s)	13.26 (3.87); 0 to 26
Verbal Fluency: F words (no. in 60 s)	12.33 (3.94); 3 to 26
Verbal Fluency: L words (no. in 60 s)	13.23 (4.02); 4 to 28
Craft immediate recall (no.)	21.03 (5.99); 7 to 35
Craft delayed recall (no.)	18.67 (5.74); 7 to 34
DSC (no. in 90 s)	55.18 (12.20); 21 to 87
AVLT short delay recall, Trial 6 (no.)	8.37 (3.20); 0 to 15
AVLT delayed recall (no.)	7.94 (3.46); 0 to 15
TMT A (sec)	36.75 (11.15); 18 to 89
TMT B (sec) (*N*=191)	98.70 (43.96); 36 to 300
Flanker (log of ratio of medians) (*N*=189)	0.11 (0.08); −0.03 to 0.39
Physical function measures	
Maximum grip strength (kg) (*N*=189)	28.80 (9.78); 8 to 52
Force plate postural sway 95% area (in.^{2}) - Firm (*N*=188)	0.37 (0.34); 0.07 to 2.40
Force plate postural sway 95% area (in.^{2}) – Foam (*N*=188)	1.18 (0.82); 0.34 to 8.68
eSPPB score (*N*=190)	2.00 (0.52); 0.48 to 3.26
400-m walk pace (m/s)	1.27 (0.43); 0.31 to 4.17
Dual Task pace (m/s) (*N*=186)	1.07 (0.21);0.55 to 1.67

MoCA, Montreal Cognitive Assessment; DSC, Digit Symbol Coding; AVLT, Auditory Verbal Learning Test; TMT, Trail Making Test.

uncorrelated with the other synthetic variables, and the canonical correlation R_c is the Pearson correlation between these linear functions. The square of this value represents the proportion of variance shared between the cognition and physical function variables, after accounting for all previous pairs of synthetic variables. This technique accounts for the correlation structures among the cognitive and physical variables to help elucidate shared aspects of physical and cognitive measures. An advantage of this technique is that it provides this information in a single analysis, reducing concerns over multiple testing that one might have if comparing sets of cognitive and physical measures in a pairwise fashion.

As suggested by Sherry and Henson (2005) we used both the magnitude of the standardized canonical function coefficients and the structure coefficients (r_s) to inform interpretation of the synthetic variables. Structure coefficients measure the bivariate correlation between an observed individual variable and the synthetic variable that incorporates that measure. The square of the structure coefficients (r_s^2) measures the proportion of variance shared by the observed variable and the created synthetic variable. The communality coefficient (h^2) measures the proportion of variance that each observed measure shares with the solution across the selected functions, is equal to the sum of the structure coefficients, and is informative as to the importance of the individual variable across the selected functions. The Wilks lambda criterion was used to test the full model and perform hierarchal tests of groups of functions. We followed the recommendations of Sherry and Henson in our presentation of CCA results.

Results

Descriptive statistics for demographic characteristics, cognitive measures, and physical function measures are presented in Table 1. To explore the multivariate shared relationship between cognition and physical function, the CCA was conducted using data from 174 participants with complete data for the 12 cognition variables and the 6 physical function variables. Twenty participants did not have complete data and therefore were excluded from the main analyses. Six functions were obtained with squared canonical correlations of 0.263, 0.195, 0.133, 0.098, 0.053, 0.012 for each, respectively. We found that the full model incorporating all six functions was statistically significant with Wilks's $\lambda = 0.434$, F (78, 838.7) = 1.76, and $p = 0.0001$. Moreover, the full model explained 57% ($1-\lambda \times 100$) of the shared variance between the variable sets. In contrast, hierarchal tests for functions 2–6 had $p = 0.021$, functions 3–6 had $p = 0.25$, and all remaining hierarchal groups had $p \geq 0.62$. Function 1 explained 26.3% of the shared variability between the cognition and physical function variables, whereas Function 2 explained 19.5% of the remaining variance in the variable sets after accounting for the variability explained by the first function. All remaining functions each explained ~13% or less of the remaining variance. We focused our results presentation on the first two functions.

Standardized canonical function coefficients, structure coefficients (r_s), squared structure coefficients (r_s^2) and communalities (h^2) are presented in Table 2 for Functions 1 and 2. Function 1 was labeled as a "cognitive and physical speed" variable because the primary cognitive and physical measures in this canonical correlation reflected speed of performance. Inspection of the coefficients for Function 1 revealed that the important physical function variables were primarily eSPPB score, log transformed 400-m walk speed, and the Dual Task pace. These variables had the largest squared structure coefficients (all ≥43.2). Note that the sex- and education-adjusted, Pearson correlation coefficients between the eSPPB and the log transformed 400-m walk speed ($r = 0.58$), and Dual Task ($r = 0.62$) were fairly large (Supplementary Table S1).

Focusing on the cognitive variable set in Function 1, we found that semantic fluency (animals), DSC total score, and log transformed TMT B cognitive measures were the primary measures that contributed to the linear synthetic variable. Because the DSC and animals scores were inversely related to TMT B, the structure coefficient for TMT B was negative.

TABLE 2 Canonical correlation analysis results adjusted for sex (n=174).

	Function 1			Function 2			h^2 (%)
	Standardized coefficient	r_s	r_s^2 (%)	Standardized coefficient	r_s	r_s^2 (%)	
Physical function measures							
Grip strength (kg)	−0.151	0.127	1.61	−0.276	−0.147	2.16	3.77
Log transformed force plate postural sway 95% area (in.^{2}) - Firm	−0.072	−0.233	5.41	0.926	0.227	5.17	10.58
Log transformed force plate postural sway 95% Area (in.^{2}) - Foam	0.306	−0.239	5.72	−1.051	−0.454	20.63	26.36
eSPPB	0.896	0.948	89.82	−0.376	0.074	0.54	90.36
Log transformed 400-m walk pace (m/s)	0.126	0.657	43.17	−0.221	−0.098	0.96	44.13
Dual task pace (m/s)	0.207	0.694	48.14	0.722	0.384	14.78	62.92
Canonical correlation (R_c)			0.51			0.44	
Squared canonical correlation [R_c^2(%)]			26.31			19.52	
Cognitive measures							
MoCA Adjusted Score	−0.048	0.091	0.82	0.205	0.381	14.55	15.37
Semantic fluency animals (no. in 60 s)	0.531	0.497	24.72	−0.318	−0.071	0.50	25.22
Semantic fluency vegetables (no. in 60 s)	−0.080	0.203	4.12	−0.199	−0.080	0.64	4.76
Verbal fluency (L words) (no. in 60 s)	0.045	0.105	1.11	0.720	0.536	28.73	29.84
Verbal fluency (F words) (no. in 60 s)	−0.281	−0.149	2.23	−0.318	0.164	2.69	4.93
Craft immediate recall (no.)	−0.546	−0.209	4.37	0.426	0.547	29.92	34.30
Craft delayed recall (no.)	0.347	−0.102	1.05	0.072	0.458	21.01	22.05
DSC (no. in 90 s)	0.493	0.625	39.09	0.142	0.318	10.09	49.19
AVLT short delay recall, Trial 6 (no.)	0.121	−0.044	0.19	−0.587	0.162	2.63	2.82
AVLT delayed recall (no.)	−0.322	−0.151	2.29	0.627	0.322	10.34	12.64
Log transformed TMT A (sec)	0.423	−0.187	3.50	−0.190	−0.296	8.78	12.28
Log transformed TMT B (sec)	−0.527	−0.571	32.63	−0.160	−0.456	20.80	53.43
Flanker (log of ratio of medians (sec))	−0.217	−0.265	7.02	−0.025	−0.107	1.14	8.16

Underlined effects have $r_s^2 > \sim 15\%$; Hierarchical Tests of canonical correlations (1–6: $p = 0.0001$; 2–6: $p = 0.0211$; 3–6: $p = 0.2545$; 4–6: $p = 0.6252$; 5–6: $p = 0.9125$; 6: $p = 0.9832$). The standardized function coefficients (Std. Coef.) define the linear combinations used to construct each synthetic variable. The structure coefficients (r_s) measure the bivariate correlation between an observed individual variable and the synthetic variable that incorporates that measure. The square of the structure coefficients × 100 (r_s^2) measures the proportion of variance shared by the observed variable and the created synthetic variable. The communality coefficient × 100 (h^2) measures the proportion of variance that each observed measure shares with the solution across the selected functions, is equal to the sum of the structure coefficients, and is informative as to the importance of the individual variable across the selected functions. The canonical correlation (R_c) is the Pearson correlation between the linear functions for the physical and cognitive measures. The square of this value represents the proportion of variance shared between the cognition and physical function variables, after accounting for all previous pairs of synthetic variables.

The 2nd function explained 19.5% of the remaining shared variance after accounting for the first function. The coefficients in Table 2 for this function suggested that this function primarily relates a synthetic cognition variable with primary contributions of the MoCA adjusted score, Verbal Fluency L words, Craft story immediate and delayed recall measures, and log transformed TMT B to the log transformed

foam-based force plate postural sway time and the Dual Task. We labeled this function as "complex motor tasks and complex cognitive tasks" many of which provided an additional challenge to executive function and cognitive attention. Because software performing valid missing data imputation and analysis methods appropriate for CCA are very limited, we performed a sensitivity analysis to increase our sample size. This was done by dropping the grip strength and flanker variables to gain data from 4 participants, bringing the analytical sample with complete data to 93% of the baseline sample ($n = 176$). There were no substantial changes to the results.

Discussion

There is a growing body of literature suggesting a relationship between gait speed and cognition, and moreover that dysfunction in both domains may predict onset of dementia (Inzitari et al., 2007; Clouston et al., 2013; Chou et al., 2019; Jayakody et al., 2019, 2021). However, which types of cognitive measures are associated with gait speed has varied across studies (Morris et al., 2016) and there are more limited analyses relating other measures of physical performance to specific tests of cognitive performance. This study is the first to apply CCA to 18 tests of cognitive and physical performance to determine whether there are any important underlying synthetic functions relating these assessments in cognitively healthy older adults. The first function explained a large proportion (26.3%) of the joint variability between these sets of variables and included tests of cognitive and physical speed. The second function explained 19.5% of the remaining variance and included complex motor tasks and challenges to cognitive function including executive function and cognitive attention. The relative grouping of these measures may suggest the involvement of shared underlying neurophysiologic pathways required to accomplish those tasks.

Slowed gait speed has been previously shown to predict decline in processing speed as measured by the Symbol Search and DSC (Inzitari et al., 2007; Chou et al., 2019; Jayakody et al., 2019). Similarly, in our study, multiple timed assessments that included gait speed were associated with several timed assessments of cognition related to processing speed in Function 1. The eSPPB included both usual 4-m gait speed and narrow walking pace, and the eSPPB score was highly correlated with the 400-m walking pace. The Dual Task also measured walking pace on the GaitRITE mat while completing a cognitive verbal task. All three of the correlated cognitive tasks were also timed assessments that partially capture processing speed: semantic fluency (naming animals), DSC, and TMT B. Participants in BNET were cognitively intact at baseline, so the underlying association observed between these measures of gait speed and cognitive speed may be intrinsic rather than due to impairment in cognition and could suggest a common shared neurophysiologic pathway related to speed. Moreover, injury to such a pathway could result in dual impairments in gait speed and cognitive processing. Concurrent declines in gait speed and cognition could place those individuals at significantly greater risk of incident dementia compared to those who decline in gait speed or cognitive function alone (Collyer et al., 2022). Study of the neuropathophysiology underlying these associations will be an important next step toward identification of potential upstream targets that could be intervened upon to prevent cognitive disability.

As one ages, gait also increasingly relies on higher order executive function, which may explain why performing a cognitive verbal dual task while walking was not only associated with processing speed (Function 1) but also executive function and cognitive attention (Function 2; Ezzati et al., 2015). For example, dual task was related to cognitive tasks like semantic fluency and verbal fluency that draw on both speed and executive function. A recent study by Holtzer and colleagues used principal components analysis to determine cognitive factors, and then used multiple regression analyses to examine the relationship between the cognition factors and gait velocity with and without interference by dual task in a cohort of cognitively normal older adults (Holtzer et al., 2006). Most notably, they found that speed/executive attention and memory both predicted gait velocity not only under usual conditions but also whenever there was interference by introduction of a secondary verbal task (i.e., dual task). A recent meta-analysis also found strong evidence that mild cognitive impairment was associated with impaired gait in particular during dual task conditions (Bahureksa et al., 2017), which may suggest a stronger association between early cognitive dysfunction and gait dysfunction under conditions that make competing demands on attention or that challenge both physical and cognitive reserve. Older adults with slower gait speed, particularly during dual task, are also at particularly higher risk of incident falls (Verghese et al., 2002). Similarly, cognitive impairment may increase one's risk for falls but which specific domains are responsible for falls is not known (Shaw, 2002; Allali et al., 2017). The relationship between cognition, gait speed, and falls is complex and multifactorial. Future studies should consider if concurrent decrements in dual task gait speed and cognitive tests that challenge speed and executive function may help to identify a subgroup of older adults at substantially greater risk of not only cognitive impairment but also mobility disability, including falls.

The predominant complex motor task in the second function was maintaining postural stability on the foam-based force plate. Similar to the dual task, which provided an additional cognitive challenge while walking, standing on the foam rather than firm surface provided an additional stress to cognitive attention which is otherwise known to decline with age (Craik and Byrd, 1982). This may explain why postural sway on the foam surface was associated with cognitive assessments of executive function such as verbal fluency and log transformed TMT B. Older adults have been shown to have significantly worse postural control on compliant, unstable surfaces (e.g., foam) relative to younger adults (Hsiao et al., 2020). Moreover, in one study, the association between poor executive function and falls was mediated by postural sway (Taylor et al., 2017), which may correspond to the connection between postural sway and executive function observed in Function 2 in our study. More global cognitive (e.g., MOCA) and memory tasks were also associated, possibly due to the complex nature of these assessments, but further research is needed to elucidate what neurophysiologic pathways may relate these measures.

Although the underlying neuropathophysiology connecting the physical and cognitive measures in Functions 1 or 2 cannot be directly ascertained by CCA, the groupings of particular measures with gait speed or complex motor tasks like postural sway on a foam surface may suggest future directions for further exploration on neuroimaging. A growing body of literature has examined whether associations between mobility, especially gait speed, and brain structure are explained by cognitive measures (Wilson et al., 2019). In some cases, adjusting for cognition attenuated the relationship between gait velocity and specific regions of the brain (Wilson et al., 2019) or other structural imaging measures such as beta amyloid burden (Nadkarni et al., 2017). For example, the relationship between gait and hippocampal volume was

attenuated after adjustment for verbal memory (Ezzati et al., 2015). Similarly, after adjustment for MMSE there was no association of gait speed with frontal and parietal lobe gray matter volume, but there was a persistent relationship with sensorimotor cortex, insula, thalamus, basal ganglia, and caudate nucleus volumes (Dumurgier et al., 2012). Additional adjustment for TMT-A also had little impact on the association of gait speed with subcortical volumes of the caudate nucleus and basal ganglia. In the Health, Aging and Body Composition study, larger cognitive cerebellar gray matter volume were associated with faster gait speed but this was not independent of DSC scores, and larger sensorimotor cerebellar volume was also associated with higher DSC but not gait (Nadkarni et al., 2014). Meanwhile vestibular volumes were associated with neither gait nor DSC. The authors concluded that information processing speed may influence the association between gait speed and cerebellar gray matter volumes, especially in the cognitive sub-region. These findings track well with our finding of a correlation between cognitive measures of processing speed and gait speed in Function 1.

Similarly, older adults are known to experience decrements in postural and volitional balance control (Kanekar and Aruin, 2014) that are more pronounced in those with mild cognitive impairment (Bahureksa et al., 2017). Reduced gray matter volumes in the brainstem and cerebellum have been significantly associated with reduced postural control (Kannan et al., 2022). Compared to cognitively normal older adults, those with mild cognitive impairment and Alzheimer's dementia have also been shown to have more vestibular impairment, which in turn was associated with lower hippocampal volumes (Cohen et al., 2022). One limitation of the current literature is that most of the imaging methodologies applied in the context of mobility and cognition have examined structural rather than functional metrics. Exploration of particular pathways *via* network science, however, may provide better insight into how and why specific aspects of gait speed, balance, and cognition are functionally related, and will be the focus of future analyses.

Limitations

A notable limitation of this study was the exclusion of participants who had evidence of substantial cognitive impairment (i.e., MOCA scores 21–25 who were deemed ineligible by a neuropsychologist or MOCA scores of 20 or lower). Similarly, potential participants were excluded if they had substantial mobility restrictions due to prior amputations or joint replacement, or if they depended on a walker or another person to ambulate. Since all included participants had higher cognitive and physical function at baseline, this likely restricted our ability to detect correlations between very poor cognitive and physical performance on these tests. However, it is possible that older adults with substantial physical or cognitive impairment would not have been able to complete these complex motor and cognitive tasks. Moreover, our findings highlight that there is correlation between these cognitive and physical measures even when assessed in a cohort of highly functional older adults. Thus, these early markers of dysfunction may be preclinical and hence upstream of disability, suggesting a possible point of intervention for future work. The reasons that particular tests grouped into Function 1 versus 2 are likely multifactorial and may not be fully explained by the more general names we ascribed to these functions. While some common themes were noted, such as the importance of speed to the tests of Function 1, there were also timed cognitive assessments that did not group into Function 1. Similarly, executive function was not exclusively important to the tests in Function 2 and why certain assessments were not highly correlated with one of the functions is not well understood but should be further investigated. Whether common neurologic pathways may underlie these groups of functions will be a focus of future study.

Conclusion

In summary, we applied CCA to identify two connected groups of cognitive and physical function tasks in a cross-sectional cohort of cognitively intact, healthy older adults. The predominant function included speed related tasks in gait and cognition, while the second function included complex motor and cognitive tests. Future studies should investigate whether common underlying neurologic pathways are shared by these functions and may provide a point of intervention to prevent downstream disability.

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 Wake Forest Baptist Health Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SK, MM, and EH: conceptualization. MM, EH, HC, and AT: methodology. MM, SK, CH, PL, HC, and AT: validation. MM, EH, AT, PL, SK, and CH: investigation. AT, MM, and EH: writing. AT, MM, EH, HC, CH, PL, and SK: editing manuscript. SK and PL: funding acquisition. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

AT is a consultant for Topcon Medical Inc. which had no relationship to this study.

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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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2023.1090641/full#supplementary-material

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Corrigendum: Examining the intersection of cognitive and physical function measures: Results from the brain networks and mobility (B-NET) study

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A corrigendum on
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In the published article, there was an error in Table 1 as published. Two participants were miscategorized as American Indian or Alaskan Native and should have been categorized as Caucasian or White race with Hispanic ethnicity. In addition, the standard deviation for age was incorrectly written as 4.74 and should have been 4.72. The corrected Table 1 appears below and includes updated race/ethnicity variable labels.

The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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TABLE 1 Descriptive statistics from participants at baseline in the BNET study.

	Overall ($N = 192$) Mean (SD); range
Age	76.43 (4.72); 70 to 90
Sex	
Women	108 (56.2)
Men	84 (43.8)
Race/Ethnicity	
Caucasian or White/Non-Hispanic	171 (89.1)
African American or Black/Non-Hispanic	18 (9.4)
Caucasian or White/Hispanic	2 (1.0)
Asian/Non-Hispanic	1 (0.5)
BMI	28.39 (5.63); 15.7 to 59.8
Years of education	15.68 (2.45); 12 to 25
Cognitive measures	
MoCA adjusted score	25.64 (2.20); 21 to 30
Semantic fluency: Animals (no. in 60 s)	18.78 (4.82); 7 to 34
Semantic fluency: Vegetables (no. in 60 s)	13.26 (3.87); 0 to 26
Verbal fluency: F words (no. in 60 s)	12.33 (3.94); 3 to 26
Verbal fluency: L words (no. in 60 s)	13.23 (4.02); 4 to 28
CRAFT immediate recall (no.)	21.03 (5.99); 7 to 35
CRAFT delayed recall (no.)	18.67 (5.74); 7 to 34
DSC (no. in 90 s)	55.18 (12.20); 21 to 87
AVLT short delay recall, Trial 6 (no.)	8.37 (3.20); 0 to 15
AVLT delayed recall (no.)	7.94 (3.46); 0 to 15
TMT A (sec)	36.75 (11.15); 18 to 89
TMT B (sec) ($N = 191$)	98.70 (43.96); 36 to 300
Flanker (log of ratio of medians) ($N = 189$)	0.11 (0.08); −0.03 to 0.39
Physical function measures	
Maximum grip strength (kg) ($N = 189$)	28.80 (9.78); 8 to 52
Force plate postural sway 95% Area ($in.^2$) – Firm ($N = 188$)	0.37 (0.34); 0.07 to 2.40
Force plate postural sway 95% Area ($in.^2$) – Foam ($N = 188$)	1.18 (0.82); 0.34 to 8.68
eSPPB score ($N = 190$)	2.00 (0.52); 0.48 to 3.26
400 m walk pace (m/s)	1.27 (0.43); 0.31 to 4.17
Dual Task pace (m/s) ($N = 186$)	1.07 (0.21); 0.55 to 1.67

MoCA, Montreal cognitive assessment; DSC, Digit symbol coding; AVLT, Auditory verbal learning test; TMT, Trail making test.

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Predictors of cognitive and physical decline: Results from the Health Aging and Body Composition Study

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Background: Risk factors for cognitive decline and physical decline have been studied independently, however older adults might experience decline in both areas i.e., dual decline. Risk factors associated with dual decline are largely unknown and have significant implications on health outcomes. The aim of this study is to explore risk factors associated with dual decline.

Methods: Using data from the Health, Aging and Body Composition (Health ABC) study, a longitudinal prospective cohort study, we examined trajectories of decline based on repeated measures of the Modified Mini-Mental State Exam (3MSE) and the Short Physical Performance Battery (SPPB) across 6 years (n=1,552). We calculated four mutually exclusive trajectories of decline and explored predictors of decline: cognitive decline (n = 306) = lowest quartile of slope on the 3MSE or 1.5 SD below mean at baseline, physical decline (n = 231) = lowest quartile of slope on the SPPB or 1.5 SD below mean at baseline, dual decline (n = 110) = lowest quartile in both measures or 1.5 SD below mean in both measures at baseline. Individuals who did not meet criteria for one of the decline groups were classified as the reference group. (n= 905).

Results: Multinomial logistic regression tested the association of 17 baseline risk factors with decline. Odds of dual decline where significantly higher for individuals at baseline with depressive symptoms (CES-D >16) (Odds Ratio (OR)=2.49, 95% Confidence Interval (CI): 1.05-6.29), *ApoE-ε4* carrier (OR= 2.09, 95% CI: 1.06-1.95), or if individuals had lost 5+lbs in past year (OR=1.79, 95% CI: 1.13-2.84). Odds were significantly lower for individuals with a higher score on the Digit Symbol Substitution Test per standard deviation (OR per SD: 0.47, 95% CI 0.36-0.62) and faster 400-meter gait (OR per SD= 0.49, 95% CI: 0.37-0.64).

Conclusion: Among predictors, depressive symptoms at baseline significantly increased the odds of developing dual decline but was not associated with decline in the exclusively cognitive or physical decline groups. *APOE-ε4* status increased the odds for cognitive decline and dual decline but not physical decline. More research on dual decline is needed because this group represents a high risk, vulnerable subset of older adults.

KEYWORDS

cognitive decline, physical decline, aging, risk factors, depressive symptoms, dual decline

1. Introduction

Declines in cognitive and physical function are major concerns for older adults, and can result in loss of independence, higher health care utilization, and increased risk for dementia (Verghese et al., 2002; Hardy et al., 2011). The research community has commonly viewed these two abilities as independent trajectories, although emerging research is beginning to show a consensus that cognitive abilities and physical abilities are correlated, dynamic, and bidirectional (Tabbarah et al., 2002; Atkinson et al., 2007, 2010; Fitzpatrick et al., 2007; Inzitari et al., 2007; Rosano et al., 2008; Soumare et al., 2009; Watson et al., 2010; Mielke et al., 2013; Gothe et al., 2014; Krall et al., 2014; Best et al., 2016; Finkel et al., 2016; Montero-Odasso et al., 2019; Okley and Ian, 2020). A meta-analysis by Clouston and colleagues (Clouston et al., 2013) found evidence from 36 longitudinal studies consistently showing a correlation between physical function and cognitive function, although the strength of the association varied depending on assessment type. For example, grip strength was associated with changes in global cognition, while walking speed was correlated with changes in fluid cognition. Few studies have modeled changes in cognitive function and physical function together as a dual process longitudinally, i.e., dual decline. In prior studies examining combined decline (Montero-Odasso et al., 2020; Tian et al., 2020; Collyer et al., 2022) the authors primarily investigated dual decline as a predictor for dementia, which all three studies found significant associations. Additionally, each of those studies used scores from gait speed only and cognition/memory to define dual decline. In the current study, we seek to define dual decline by using a variety of physical function tests that represent different domains of function including balance, sit to stand, and walk speed.

What has not been well characterized are if there are certain predictors that predispose an individual for dual decline. The first study to examine predictors of dual decline was published in 2005 and identified smoking and low hemoglobin as significant predictors (Atkinson et al., 2005), albeit the sample only included 522 older women. Since then, little work has been conducted on risk factors of decline and thus a gap in the literature exists.

The purpose of this study is to (a) define four mutually exclusive groups (dual decline, cognitive decline only, physical decline only, and a reference group) and (b) explore predictors that may have a particularly strong association with dual decline. Determining predictors and modeling dual decline may help in early identification of a high-risk group of older adults and potentially develop interventions in order to prevent poor health outcomes in the future.

2. Materials and methods

Our study includes information from over 1,500 older adults from the Health, Aging and Body Composition (Health ABC) study, a longitudinal prospective cohort study of well-functioning, community dwelling older adults with a comprehensive examination of physical function, cognitive function, health data, and biomarkers. Health ABC recruited 3,075 men and women aged 70–79 years from a random sample of White and Black Medicare eligible residents in the Pittsburgh, PA, and Memphis, TN, metropolitan areas between April 1997 and June 1998 (51.5% female, 41.7% African American). Participants were eligible if they reported no difficulty walking ¼ mile, climbing 10 steps, or performing basic activities of daily living.

2.1. Subject selection

For this project, we examined previously collected data across 6 years (1997/1998–2002/2003). We considered baseline to be inclusive of data through the 36-month visit (to include certain biomarkers not collected at month 0). All participants were free of mobility and cognitive impairments at baseline per self-report. Trajectories of decline were evaluated from three timepoints across 6 years. Participants who completed the Modified Mini-Mental State Exam (3MSE) and Short Physical Performance Battery (SPPB) at baseline with at least one successive measure after baseline were included in the analysis to calculate the slope. The SPPB was collected at the 0-, 48-, and 72-month follow-up visits and the 3MSE was collected at 0-, 36-, and 60-month follow-up visits.

Participants were excluded if they had a previous stroke ($n = 88$), Parkinson's Disease ($n = 21$), or died before the 72-month visit ($n = 384$). Participants with only one measure of 3MSE or SPPB were excluded from analyses ($n = 329$). Complete case analysis was used and participants with missing baseline variables were excluded ($n = 701$). The final sample size was 1,552.

2.2. Risk factors at baseline

Selection of risk factors in this study were based upon previous research in this area (Atkinson et al., 2005) and we hypothesized that poor metabolic health (i.e., diabetes, hypertension, current smoker, alcohol drinker, high body mass index, and low hemoglobin) would be a particularly potent set of risk factors for those with dual decline.

2.3. Demographic variables

Demographic information and health questions were collected from self-report and included: age, sex, years of education completed, marital status, race (black, white), weight history, and self-reported health (poor, fair, good, very good, excellent). Participants were asked about smoking (are you a current smoker), and alcohol intake (do you currently drink alcohol, and how much per day). Participants were asked if they had fallen in the past 12 months (dichotomized to ≤ 1 time or 2 + times) and/or hospitalizations in the past 12 months (Yes or No). Disease status for diabetes and hypertension was ascertained from the question at baseline, "Has a doctor ever told you that you have…." Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D 20; Radloff, 1977). A score of 16 is the screening cut-off for risk of clinical depression.

2.4. Functional variables

Objective measures of functioning were also collected at an in-person clinic visit. Body mass index was calculated as weight/height $(m)^2$ (Fitzpatrick et al., 2007). Lung function was measured as the percent predicted forced expiratory volume in 1 s (pFEV1). A value of less than 80 was used to indicate poor lung function. Hand grip strength was calculated as the average of two trials in the right hand using an adjustable grip strength dynamometer. Grip strength was adjusted for gender and body weight. Participants also completed a 400-m walk at baseline. Executive function was measured using the Digit Symbol Substitution Test (DSST; Wechsler, 1997).

2.5. Biomarker variables

Blood samples were collected *via* a venipuncture during an in-person baseline assessment. The biomarkers chosen for this project included: total cholesterol (mg/dL), hemoglobin (g/dL), serum albumin (g/dL), and serum vitamin D (25-hydroxyvitamin D; ng/mL) deficient (< 20 ng/ml), and at least one Apolipoprotein ε4 allele (*APOE*-ε4). These biomarkers were selected based upon previous studies (Atkinson et al., 2005, 2007) and are known to influence physical function and cognitive function. All biomarkers were collected at month 0 with the exception of hemoglobin (values were from the 36-month visit because it was not collected at month 0, and serum vitamin D is from the 24-month visit).

2.6. Outcome variables

Physical function was measured using the SPPB (Guralnik et al., 1994). The SPPB is composed of three physical function domains: a balance test, an 8-m walk, and a timed chair sit to stand. Scores from each domain were summed to create a composite score which ranges from 0 to 12 with higher scores indicating better performance. Cognitive function was measured using the 3MSE (Teng and Chui, 1987). The 3MSE includes tests of orientation, registration, attention, calculation, recall, and visual–spatial skills. Scores can range from 0 to 100 points, with higher scores indicating better performance.

Four trajectory groups were defined by a decline in the slope across 6 years (0–72 months) using repeated measures from participant-specific slopes of 3MSE and SPPB scores. Those with a predicted slope in the lowest quartile or 1.5 SD below the mean at baseline, exclusively in cognition or physical function were classified as "cognitive decline" only or "physical decline" only. Those who met the same criteria for both cognitive and physical decline were classified as "dual decline." Individuals who did not meet criteria for one of the decline groups were classified as the reference group.

2.7. Analytic approach

The four trajectory groups were defined based upon participant-specific slopes of 3MSE and SPPB scores from 0 to 72 months. Cognitive decline = lowest quartile of 3MSE slope or 1.5 SD below the mean at month 0, physical decline = lowest quartile of SPPB or 1.5 SD below the mean at month 0, and dual decline = lowest slope quartiles of 3MSE and SPPB or 1.5 SD below the mean in both domains at month 0. Participants who did not meet criteria for one of the decline groups were categorized as the reference group. Descriptive statistics were used to describe group characteristics with baseline predictors (Chi-square for proportions, and ANOVA for continuous variables). Next, a risk profile was constructed to identify which variables from baseline were associated with membership of each prospective decline category. Multinomial logistic regression was performed to model decline category with significant baseline variables as predictors. Hemoglobin g/dL, serum albumin g/dL, grip strength kg, DSST, and 400 m walk m/s were converted to z-scores for ease of interpretation. Odds Ratios and 95% confidence intervals (95% CI) are presented. All analyses were conducted using SAS 9.4.

3. Results

Characteristics of the four trajectory groups are presented in Table 1. The cognitive decline group ($n = 306$) had an average 3MSE score of 88.8 at baseline and decreased on average 1.1 points per year. The physical decline group ($n = 231$) had an average SPPB score of 10.2 at baseline decreased by 0.55 points per year. The dual decline group ($n = 110$) had an average 3MSE score of 89 and SPPB score of 10.0 at baseline and decreased by 2.40 points on the 3MSE and 0.76 points on the SPPB per year. The dual decline group was significantly older, included more women and those who were less educated, black, and those less likely to be married, and more likely to self-report having lost 5 or more pounds in the past year. They also had more depressive symptoms, poorer self-rated health, and were less likely to be a current alcohol drinker compared to the reference group. The dual decline group also had significantly lower grip strength, lower hemoglobin (g/dL), albumin (g/dL), were more likely to be deficient in serum vitamin D (25-hydroxyvitamin D; < 20 ng/ml ng/mL), and to have at least one *APOE*-ε4 allele.

When significant variables from baseline were entered into a multinomial logistic regression model, significant risk factors of cognitive decline were higher age (OR = 1.05, 95% CI: 1.00–1.11), low education (≤ high school; OR = 1.46, 95% CI: 1.07–1.98), poor self-rated health (OR = 1.78, 95% CI: 1.16–2.71) and *APOE*-ε4 (OR = 1.44, 95% CI: 1.06–1.95). Higher serum albumin (OR per standard deviation (SD) = 0.81, 95% CI: 0.95–0.98), higher DSST score (OR per SD: 0.57, 95% CI: 0.48–0.68), and faster 400 m walk (OR per SD 0.81, 95% CI: 0.68–0.96) were significantly associated with lower odds of cognitive decline (Figure 1). Physical decline predictors are depicted in Figure 2. Higher age (OR = 1.07, 95% CI: 1.01–1.13) increased the odds, while serum albumin (OR per SD = 0.85, 95% CI 0.72–0.99) and 400 m (OR per SD = 0.67, 95% CI: 0.56–0.81) decreased the odds.

Risk factors for dual decline included: age (OR = 1.13, 95% CI: 1.04–1.22), lost 5 + lbs. in past year (OR = 1.79, 95% CI: 1.13–2.84), depressive symptoms (OR = 2.49, 95% CI: 1.05–5.91), and *APOE*-ε4 (OR = 2.09, 95% CI: 1.33–3.28). Higher scores on the DSST and faster 400 m walking speed were significantly related to lower odds of dual decline (OR per SD = 0.47, 95% CI: 0.36–0.62; OR per SD = 0.49, 95% CI 0.37–0.64), respectively (Figure 3). OR and 95% CIs for all groups are presented in Table 2.

4. Discussion

Across the four decline categories, different patterns of risk factors emerged. Having less than a high school education and poor self-rated health were significantly related to higher odds of cognitive decline but were not related to physical decline or dual decline. Losing weight and depressive symptoms were significant risk factors for dual decline, but not related to the other categories. *APOE*-ε4 and DSST were significant predictors of cognitive decline and dual decline, and 400 m walk was significant across all three groups.

Evidence from large epidemiological studies have consistently shown that educational attainment influences rates of cognitive decline and risk of dementia (Stern et al., 1994). The association between self-rated health and cognitive decline is more novel, although it can be postulated that self-report engages a mental representation of personal history that consists of semantic and episodic knowledge (Jylha, 2009). This may provide rationale that self-rated health has a

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TABLE 1 Descriptive characteristics at baseline across four groups of decline, data from the Health, Aging and Body Composition (Health ABC) Study (*n*=1,552).

	Reference group (*n* =905)	Cognitive decline (*n* =306)	Physical decline (*n* =231)	Dual decline (*n* =110)	Value of *p*
Baseline characteristics:					
Health					
Age, mean (SD)	73.1 (2.7)	73.6 (3.0)	73.7 (2.9)	74.4 (3.0)	<0.001
Women, *n* (%)	428 (47.3)	148 (48.3)	141 (61.0)	67 (60.9)	<0.001
Education, *n* (%)					
≤ High school	399 (44.1)	202 (66.0)	116 (50.2)	77 (70.0)	<0.001
Race, *n* (%)					
White	677 (74.8)	160 (52.3)	164 (71.0)	55 (50.0)	<0.001
Black	228 (25.2)	146 (47.7)	67 (29.0)	55 (50.0)	
BMI, mean (SD)	26.9 (4.1)	27.2 (4.3)	27.7 (5.1)	27.4 (5.6)	0.047
Not Married, *n* (%)	387 (42.7)	133 (43.5)	123 (53.3)	61 (55.5)	0.004
Weight history					
Gained 5 + lbs. in past year	273 (31.0)	103 (34.6)	78 (34.2)	31 (29.0)	0.523
Lost 5 + lbs. in past year	260 (28.7)	103 (33.7)	85 (36.8)	47 (42.7)	0.004
Self-rated health, poor, *n* (%)	66 (7.3)	59 (19.3)	25 (10.8)	23 (20.9)	<0.001
Lifestyle *n*, %					
Current smoker	61 (6.7)	25 (8.2)	17 (7.4)	11 (10.0)	0.587
Smoked 100 + cigarettes	501 (55.4)	152 (49.7)	120 (52.0)	57 (51.8)	0.649
Current alcohol drinker	516 (57.0)	135 (44.1)	124 (53.7)	40 (36.4)	<0.001
Depressive symptoms, %	24 (2.7)	8 (2.6)	6 (2.6)	11 (10.0)	<0.001
Grip Strength (kg), mean (SE)	31.6 (0.3)	32.4 (0.6)	28.3 (0.7)	28.8 (0.9)	<0.001
Walk > 150 min a week	297 (33.0)	85 (28.2)	74 (32.0)	36 (32.7)	0.138
PFEV1 < 80%	196 (21.7)	73 (23.9)	53 (22.9)	22 (20.0)	0.796
Fallen in past year	202 (22.4)	54 (17.7)	50 (21.8)	23 (21.1)	0.386
Two or more times	42 (4.7)	12 (3.9)	17 (7.4)	7 (6.4)	0.250
Been hospitalized in past year	102 (11.3)	31 (10.1)	26 (11.3)	13 (11.8)	0.944
Two or more times	16 (1.8)	4 (1.3)	3 (1.3)	1 (0.9)	0.851
Biomarkers, mean (SD)					
Total cholesterol (mg/dL)	204.1 (38.3)	201.5 (36.7)	200.2 (36.0)	205.1 (35.3)	0.410
Hemoglobin (g/dL)	13.8 (1.2)	13.6 (1.4)	13.6 (1.3)	13.3 (1.3)	<0.001
Serum albumin (g/dL)	4.0 (0.3)	3.9 (0.3)	4.0 (0.3)	3.9 (0.3)	<0.001
Serum Vitamin D (25-hydroxyvitamin D) (ng/mL)	27.9 (10.1)	25.2 (10.3)	26.2 (11.7)	26.2 (10.0)	<0.001
Deficient (< 20 ng/ml), *n* (%)	212 (23.4)	100 (32.7)	77 (33.3)	34 (30.0)	0.001
ApoE-4 +	219 (24.2)	101 (33.0)	46 (19.9)	45 (40.9)	<0.001
Chronic disease, *n* (%)					
Hypertension	404 (44.6)	136 (44.4)	120 (52.0)	58 (52.7)	0.102
Diabetes	96 (10.6)	36 (11.8)	31 (13.4)	18 (16.4)	0.258
Other, mean (SD)					
3MSE	93.0 (4.8)	88.8 (9.4)	93.0 (4.8)	89.0 (7.9)	<0.001
SPPB	10.5 (1.1)	10.3 (1.2)	10.2 (1.8)	10.0 (1.6)	0.001
DSST	42.1 (11.7)	32.9 (13.2)	39.3 (13.0)	30.4 (12.7)	<0.001
400 m gait speed, m/s (SD)	1.3 (0.2)	1.2 (0.2)	1.2 (0.2)	1.1 (0.2)	<0.001

BMI = body mass index, PFEV1 = predicted forced expiratory volume in 1 s, Depressive symptoms = score of > 16 on the Center for Epidemiologic Studies Depression Scale (CES-D-20), ApoE-4 + = Apolipoprotein e4 +, 3MSE = Modified Mini Mental Status Exam, SPPB = Short Physical Performance Battery, DSST = Digit Symbol Substitution Test.

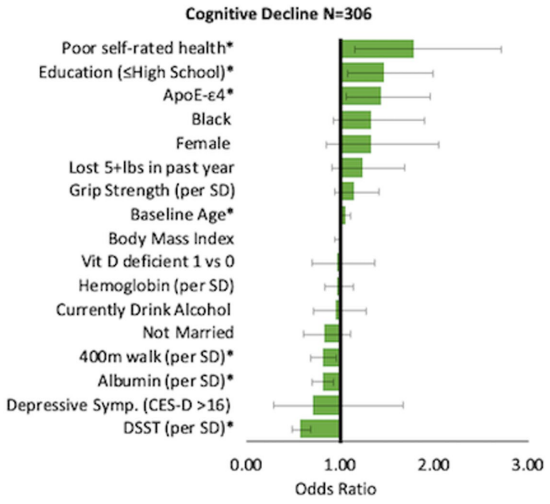

FIGURE 1
Correlates of cognitive decline. Odds Ratio [95% CI] compared to the reference group.

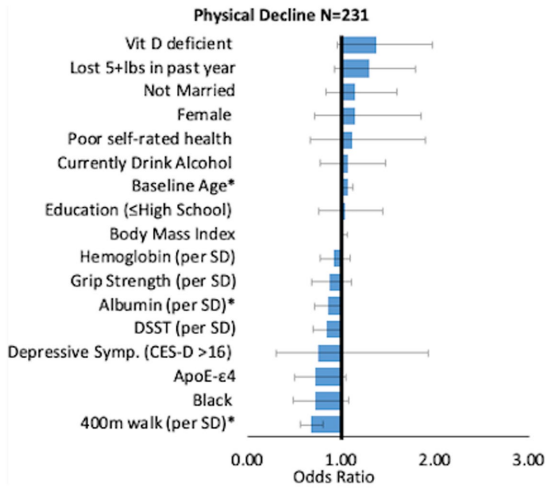

FIGURE 2
Correlates of physical decline. Odds Ratio [95% CI] compared to the reference group.

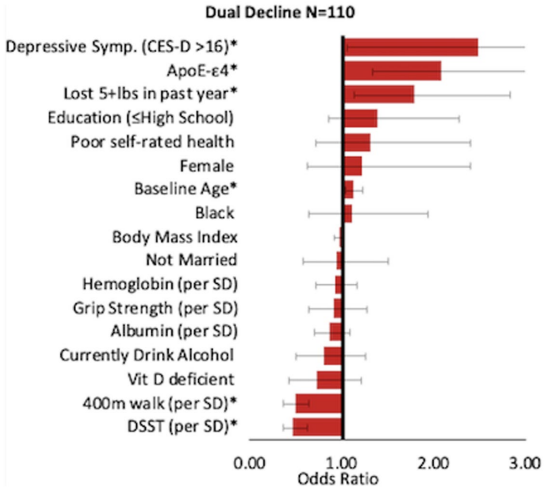

FIGURE 3
Correlates of dual decline. Odds Ratio [95% CI] compared to the reference group.

cognitive underpinning which we were able to detect as a significant predictor of subsequent cognitive decline.

Our results also showed that *APOE*-ε4 was a significant risk factor for cognitive decline and dual decline. *APOE*-ε4 has been widely shown to be a significant risk factor for Alzheimer's disease and dementia (Corder et al., 1993). Less is known about *APOE*-ε4 and the association with physical decline, however in a recent study, Stringa et al. (2020) examined the modulation of *APOE*-ε4 on cognition including an interaction with self-reported physical activity in three longitudinal cohort studies: Longitudinal Aging Study Amsterdam, InCHIANTI, and Rotterdam Study. *APOE*-ε4 carriers had higher odds of cognitive decline in these cohorts, although there was no significant interaction between self-reported physical activity, *APOE*-ε4, and cognitive decline. This supports our finding that *APOE*-ε4 increases the risk of cognitive decline, however we also found a significant association between *APOE*-ε4 and dual decline. It may be that the association between *APOE*–ε4 and dual decline was simply driven by the cognitive portion of dual decline. Physical function was measured objectively in the Health ABC study using the 400 m walk and we found that faster 400 m walk time was related to lower odds of cognitive, physical, and dual decline.

Depressive symptoms and weight loss were uniquely related to dual decline. Depressive symptoms increased the odds by nearly 2.5-fold that a person would develop dual decline. Major depressive disorder is a common mental health problem for older adults and has been correlated with increased risk of falls (Kvelde et al., 2013), slower gait (Brandler et al., 2012), and increased executive dysfunction (Koenig et al., 2014). A systematic review examining this "triad" of physical function decline, cognitive decline, and depression was supported by 12 out of 15 studies suggesting a linkage among these factors (Patience et al., 2019). The basis for this connection is not fully understood, but this may be an important area of research in the future. To note, the number of participants with depressive symptoms was 3% (49/115) which may limit the generalizability of our study. In the cognitive decline and physical decline groups, depressive symptoms was not significant although the OR's appear to look protective. This could be due to fact that those with depressive symptoms tended to be grouped into dual decline as opposed to only a single decline. Depression represents a potent modifiable risk factor and more research is needed to understand the consequences associated with cognitive and physical decline.

The first study examining predictors of dual decline and using a four group trajectory model (Atkinson et al., 2005) found smoking (OR = 5.66, 95% CI 1.49–21.54) and low hemoglobin (OR 0.68, 95% CI 0.47–0.98) to be unique predictors of dual decline in older women from the Women's Health and Aging Study. Our results did not confirm those results, but our sample was more diverse including both men and women, and different methods were used to construct our definition of dual decline.

Strengths of this study include a longitudinal, well-described sample of over 1,500 older adults. The key strengths of Health ABC are the in-depth health, physical function, and clinical examinations administered

TABLE 2 Odds ratios [95% CI] with all significant predictors from regression analyses with comparison to the reference group.

	Cognitive decline (*n*=306)			Physical decline (*n*=231)			Dual decline (*n*=110)		
	OR	95% CI		OR	95% CI		OR	95% CI	
Health									
Age	**1.05**	1.00	1.11	**1.07**	1.01	1.13	**1.13**	1.04	1.22
Female	1.32	0.85	2.05	1.14	0.71	1.85	1.22	0.62	2.40
Education (≤High School)	**1.46**	1.07	1.98	1.04	0.76	1.44	1.39	0.85	2.27
Race (Black)	1.33	0.93	1.90	0.72	0.48	1.08	1.11	0.64	1.94
Body Mass Index	0.98	0.94	1.01	1.02	0.98	1.06	0.97	0.92	1.01
Not married	0.82	0.60	1.11	1.15	0.84	1.59	0.94	0.58	1.51
Lost 5+lbs. in past year	1.24	0.91	1.68	1.29	0.93	1.79	**1.79**	1.13	2.84
Self-rated health, fair or poor	**1.78**	1.16	2.71	1.12	0.67	1.89	1.31	0.72	2.40
Current alcohol drinker	0.95	0.71	1.27	1.07	0.78	1.47	0.80	0.50	1.26
Depressive symptoms, (CES-D>16)	0.70	0.29	1.67	0.75	0.30	1.92	**2.49**	1.05	5.91
Grip Strength (per SD)	1.15	0.94	1.41	0.87	0.68	1.10	0.91	0.64	1.28
Biomarkers									
Hemoglobin (per SD)	0.97	0.83	1.14	0.92	0.78	1.09	0.92	0.72	1.17
Serum Albumin (per SD)	**0.81**	0.70	0.93	**0.85**	0.72	0.99	0.87	0.70	1.09
Serum Vitamin D, Deficient (<20 ng/ml)	0.97	0.70	1.36	1.38	0.96	1.97	0.72	0.43	1.21
ApoE-e4+	**1.44**	1.06	1.95	0.72	0.50	1.05	**2.09**	1.33	3.28
Other									
DSST (per SD)	**0.57**	0.48	0.68	0.84	0.70	1.01	**0.47**	0.36	0.62
400 m gait speed (per SD)	**0.81**	0.68	0.96	**0.67**	0.56	0.81	**0.49**	0.37	0.64
Sensitivity analysis									
**CES-D>10*	1.00	0.62	1.62	0.94	0.56	1.57	1.58	0.85	2.95

SD = Standard Deviation, Depressive symptoms = score of > 16 on the Center for Epidemiologic Studies Depression Scale (CES-D-20), APOE-4+ = Apolipoprotein e4+, DSST = Digit Symbol Substitution Test. Bold text means significant value.

annually or bi-annually in a healthy, well-functioning sample of older adults. Our study used the SPPB, as opposed to gait speed alone, which provides more information about function and included measures of gait speed, chair stand, and balance. This is the first study to use this approach as well as 17 different predictors. We chose to use a prospective longitudinal approach because participants at baseline reported no difficulty with physical function or cognitive impairment, and in this presumably healthy sample we could evaluate subsequent decline.

Our study has limitations, particularly since it used secondary data. The baseline age range of 70–79 and a presumably healthy cohort (i.e., self-reported no difficulties in cognition or physical function at baseline) was criterion for the Health ABC Study. We acknowledge that using self-reported cognitive status as a criterion for inclusion or exclusion in Health ABC is a limitation, but concerns are mitigated by the fact that these participants were able to complete procedures and participate in the study for a minimum of 4 years. Another weakness is that our results only included those with complete data, therefore individuals with missing data were not captured. The group size, specifically for dual decline, was slightly underpowered to detect meaningful differences. Since the study was exploratory in nature, we believe that our results contribute to an important emerging topic and warrants replication in a larger sample. The use of a global measure of cognition, the 3MSE, is a weakness because it is a single general test of cognition and not as comprehensive as a full neuropsychological battery. Also, predictors such as weight loss, depression, and alcohol drinking were from one visit at baseline, and we are unable to determine if these conditions were acute vs. chronic/habitual. In the future, it would be interesting to compare short term vs. long term predictors of decline.

More research is needed to further explore the mechanisms and the connection between cognitive health and physical health. Many have posited the role of the central nervous system and the hippocampus as being an important contributor to decline (Sorond et al., 2015). Of note, imaging measures were not available on our sample of participants. However, given the role of psychosocial factors (i.e., depression, walking speed) these factors are more easily measurable and can provide valuable information about a person's cognitive and physical function.

5. Conclusion

Our study provides a longitudinal assessment of cognitive, physical, and dual decline among older adults providing new evidence for risk factors of decline. Future research should examine the role of psychosocial factors as they relate to cognitive and physical function and specifically target modifiable factors which may help reduce the burden of cognitive and physical decline among older adults.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: https://healthabc.nia.nih.gov/.

Author contributions

EH, SK, KH, and XL: conceptualization, methodology, and editing manuscript. EH: writing. SK and EH: funding acquisition. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Visual-somatosensory integration (VSI) as a novel marker of Alzheimer's disease: A comprehensive overview of the VSI study

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Identification of novel, non-invasive, non-cognitive based markers of Alzheimer's disease (AD) and related dementias are a global priority. Growing evidence suggests that Alzheimer's pathology manifests in sensory association areas well before appearing in neural regions involved in higher-order cognitive functions, such as memory. Previous investigations have not comprehensively examined the interplay of sensory, cognitive, and motor dysfunction with relation to AD progression. The ability to successfully integrate multisensory information across multiple sensory modalities is a vital aspect of everyday functioning and mobility. Our research suggests that multisensory integration, specifically visual-somatosensory integration (VSI), could be used as a novel marker for preclinical AD given previously reported associations with important motor (balance, gait, and falls) and cognitive (attention) outcomes in aging. While the adverse effect of dementia and cognitive impairment on the relationship between multisensory functioning and motor outcomes has been highlighted, the underlying functional and neuroanatomical networks are still unknown. In what follows we detail the protocol for our study, named The VSI Study, which is strategically designed to determine whether preclinical AD is associated with neural disruptions in subcortical and cortical areas that concurrently modulate multisensory, cognitive, and motor functions resulting in mobility decline. In this longitudinal observational study, a total of 208 community-dwelling older

adults with and without preclinical AD will be recruited and monitored yearly. Our experimental design affords assessment of multisensory integration as a new behavioral marker for preclinical AD; identification of functional neural networks involved in the intersection of sensory, motor, and cognitive functioning; and determination of the impact of early AD on future mobility declines, including incident falls. Results of The VSI Study will guide future development of innovative multisensory-based interventions aimed at preventing disability and optimizing independence in pathological aging.

KEYWORDS

multisensory integration, sensory processing, mobility, cognition, Alzheimer's disease

Introduction

Alzheimer's disease (AD) affects over 6 million Americans and is the most-common cause of dementia (Alzheimer's Association, 2022). AD follows a prolonged, progressive disease course that begins with pathophysiological changes affecting individuals' brains years before any clinical manifestations are observed (Jack et al., 2013). The notion that Alzheimer's modifies sensory processing is in its very early stages (Albers et al., 2015). Yet, this supposition is supported by evidence demonstrating that amyloid-beta (Aβ) protein accumulates in sensory-association areas of the brain well before higher-order cognitive areas like the prefrontal cortex (PFC; Thal et al., 2002). While it is well known that mobility impairments are common in mild cognitive impairment and AD (Beauchet et al., 2008; Verghese et al., 2008a), the National Institute on Aging (NIA) has recognized that functional changes in sensory and motor systems also modulate the progression of AD. Thus, the NIA is supportive of new initiatives aimed at discovering novel, non-cognitive and non-invasive biomarkers for early detection of Alzheimer's disease, and this is directly in line with the research priorities of our division.

There is a well-established association of higher-order cognitive processes including attention and executive functioning with balance (Woollacott and Shumway-Cook, 2002; Zettel-Watson et al., 2015), gait (Verghese et al., 2007b, 2008a; Holtzer et al., 2012; Groeger et al., 2022) and falls (Hausdorff and Yogev, 2006; Holtzer et al., 2007) in healthy, as well as cognitively impaired older adults. In fact, the PFC has been found to play a critical role in successful gait and cognition (Beauchet et al., 2016). Work from our division has linked gait to discrete brain structures such as cerebellar, precuneus, supplementary motor, insular, and PFC (Blumen et al., 2019). Additionally, we have found: (1) associations between walking performance and functional connectivity in sensory-motor and fronto-parietal resting-state networks (Yuan et al., 2015); (2) links between gray matter volume in areas involved in multisensory integration (including superior temporal sulcus and superior temporal gyrus) with aspects of gait and gait control (Tripathi et al., 2022); and (3) significant associations between gait and visual somatosensory integration (VSI) processes (Mahoney and Verghese, 2018, 2020). However, the interplay of multisensory, cognitive, and motor processes and the underlying functional neural networks involved remain largely undefined in healthy and pathological aging.

Sensory inputs emanating from a device like a cell phone (that simultaneously lights up, vibrates, and plays a ringtone) combine in the brain to yield faster responses than responses to individual unisensory components, thereby decreasing the time it takes to answer the phone. The *magnitude of multisensory integration* can be quantified using established probabilistic modeling procedures of behavioral performance, such as reaction time (RT) and accuracy (Mahoney and Verghese, 2019). *Magnitude of multisensory integration* is operationalized as the area-under-the-curve of the difference between actual and predicted cumulative probability distribution functions during a pre-identified portion of the difference waveform. For example, **Figure 1** depicts cumulative probability difference values (*y*-axis) between actual and predicted distribution functions from our latest study for percentile binned RT responses ranging from 0.0 to 1.0 in 5% increments (Mahoney and Verghese, 2020).

The combined study cohort (n = 345; dashed trace) reveals successful multisensory integration processes (i.e., positive cumulative probability difference values) during the fastest tenth (0.0–0.1) of RTs. Here, the area under the curve during the 0.0–0.1 percentiles (gray shaded box) is operationalized as the *magnitude of multisensory integration* (a continuous measure). Higher values indicate superior ability to integrate visual-somatosensory information (i.e., benefit from multisensory inputs), whereas lower and negative values indicate inability to integrate or to benefit from multisensory inputs. Stratifying the overall group based on cognitive status assigned during consensus case conference procedures [normal cognition (n = 293) – solid light gray trace; mild cognitive impairment (MCI; n = 40) – solid dark gray trace; and dementia (n = 12) – solid black trace] revealed that *magnitude of multisensory integration* is significantly reduced for individuals with MCI or dementia. Further, cognitive status significantly mediated the relationship between *magnitude of multisensory integration* and measures of mobility, such that older adults with cognitive impairments demonstrated impaired multisensory integration and significantly slower gait, as well as poorer balance compared to older adults without cognitive impairments (Mahoney and Verghese, 2020). Our findings further revealed that VSI is also correlated with attention-based performance measures (Mahoney et al., 2012; Mahoney and Verghese, 2020) that may target PFC

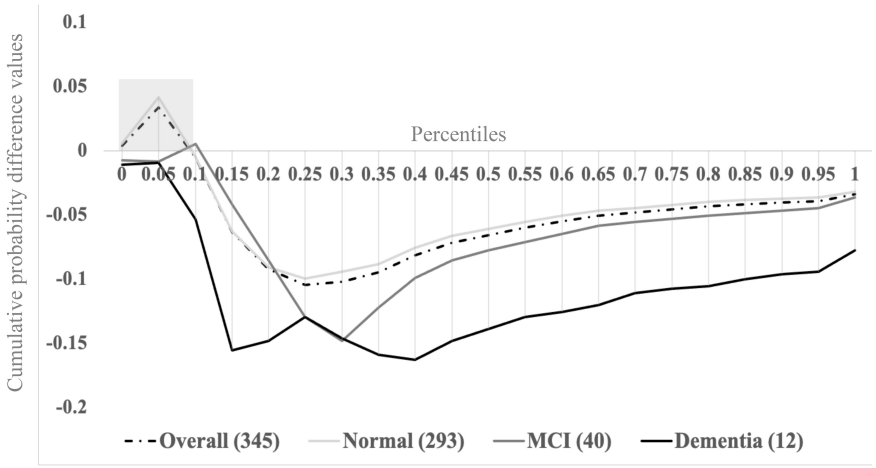

FIGURE 1
Visual-somatosensory integration (VSI) cumulative probability difference waves overall and by cognitive status (normal, mild cognitive impairment, or dementia). Adapted from Mahoney and Verghese (2022). Reprinted by permission of Oxford University Press on behalf of The Gerontological Society of America.

regions known to be compromised in AD. Consequently, we argue that multisensory integration has potential utility in early AD detection, though further work is needed to uncover the exact structural and functional neural correlates of VSI.

Significance

Balance requires efficient interactions between musculoskeletal and sensory systems (Shumway-Cook and Woollacott, 2012), which are compromised in aging (Lord et al., 2007). Poor balance is a major predictor of falls, a leading cause of injury and death in older Americans. Our research reveals that better *magnitude of VS integration*, is associated with better balance and gait, as well as decreased risk of falls (Mahoney et al., 2019). Our previous investigations, however, did not determine the association of impaired VSI with early dementia stages, nor its contribution to mobility decline.

Impairments in cognition could adversely affect the association between *magnitude of multisensory integration* and mobility measures because: (1) multisensory processing appears to be regulated by PFC (Jones and Powell, 1970; Cao et al., 2019); (2) selective attention modulates multisensory integration in aging (Hugenschmidt et al., 2009; Mozolic et al., 2012); and (3) disruptions in executive attention and cognition in aging compromise multisensory integration and mobility processes (Yogev-Seligmann et al., 2008; Holtzer et al., 2012; Mahoney and Verghese, 2020). Although our preliminary findings are encouraging and of high public health significance, we believe that we are only scratching the surface for a much-needed larger multisensory investigation. The proposed study, from here on referred to as The VSI Study, is significant as it will identify the functional neural correlates of VSI, while also determining whether Alzheimer pathology concurrently impacts sensory integration and motor processes. The goal of The VSI Study is to determine the combined influence of multisensory, cognitive and motor changes in early Alzheimer's disease in an effort to shape the development of future innovative multisensory-based interventions, prognostic tools, and new research-driven therapies aimed at preventing disability and optimizing independence in pathological aging.

Specific aims

The VSI Study seeks to achieve three main specific aims denoted as stars in **Figure 2**. In this conceptual model, cognitive, motor, and (multi) sensory functioning are depicted as individual gears that must work together to transmit a behavioral response. However, the impact of preclinical AD on each of the individual gears, as well as on the overall system (requiring successful interactions across all functions) requires systematic examination. Thus, our three main study aims are as follows:

Identify baseline structural and functional neural correlates of VSI in preclinical AD

Results from The VSI Study employing multimodal neuroimaging procedures will provide a deeper understanding of the structural and functional neural correlates of VSI in older adults with normal and preclinical AD. Here, preclinical AD will be defined as manifesting impaired cognitive performance [performance worse than 1.5 standard deviations from the mean on standardized neuropsychological tests] and presence of elevated Aß in plasma at baseline using established cut scores (Bateman et al., 2019). We hypothesize that the *magnitude of VSI* will be correlated with gray matter volume, cortical thickness, and blood-oxygen-level-dependent (BOLD) signal activation in *subcortical* and *cortical* regions of interest including dorsal lateral prefrontal cortex (DLPFC), rostral middle frontal, and superior frontal gyrus at study baseline (Year 1). We predict that older adults with preclinical AD will manifest reduced *magnitude of VSI* (worse), decreased cortical volumetrics, decreased functional connectivity, and lower BOLD responses when compared to older adults with normal cognition.

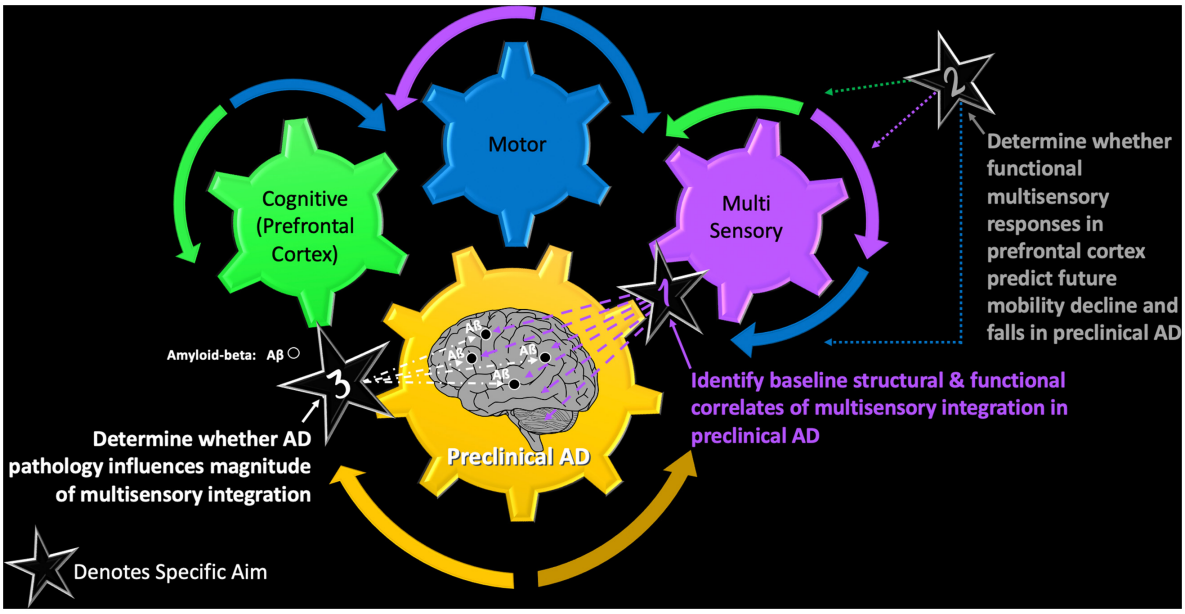

FIGURE 2
The VSI Study – a conceptual model of the main objectives of the VSI Study and how each afford examination of the intersection of cognitive, motor, and multisensory functioning in healthy and pathological aging.

Determine whether VSI task-related BOLD activation in prefrontal cortex predicts future mobility decline and falls

Individuals with Alzheimer's disease are at greater risks for falls and mobility disability, but specific causes of AD and the temporal onset of functional changes across systems are currently not known. We have shown a mediating effect of dementia and mild cognitive impairment on the relationship between VSI and motor outcomes (Mahoney and Verghese, 2018; Mahoney et al., 2019). These results suggested that individuals with cognitive impairments manifested poor VSI and poor balance/slow gait. Using an fMRI task where participants are asked to respond as quickly as possible to unisensory visual, unisensory somatosensory and combined visual-somatosensory stimuli in a 3-Tesla (3T) magnet, our second specific aim will determine whether visual-somatosensory task-related BOLD activation in the prefrontal cortex at baseline predicts future mobility (gait) declines and risk of incident falls. We hypothesize that preclinical AD causes disruptions in subcortical and cortical (multisensory, motor, and cognitive) regions that modulate multisensory, motor, and cognitive functions necessary for efficient mobility.

Assess the validity of VSI as a novel Alzheimer's behavioral marker

The validity of VSI as a novel marker for AD will be established by correlating the *magnitude of VSI* with presence of Aβ using plasma-based measures at baseline. In Year 2, positron emission tomography (PET) measures affording localization of Aβ deposits (Piramal Imaging) to estimate Aβ neuritic plaque density will also be examined in relation to *magnitude of VSI*. Aβ protein deposition has been documented in both sensory and cognitive areas (Thal et al., 2002; Jack et al., 2018, 2019; Bateman et al., 2019). Therefore, we hypothesize that increased Aβ accumulation in sensory and cognitive areas, areas related to increased AD pathology, will be associated with decreased *magnitude of VSI*.

In keeping with the NIA-AA research framework (Jack et al., 2018), our innovative and timely project will distinguish AD symptomology (presence of mild cognitive impairment) from AD pathology (Aβ accumulation), while also applying the AT (N) classification system [Aβ (A), tau (T), and neurodegeneration (N)] to attain more direct assessment of neuropathologic changes. More specifically, and in keeping with the goals of establishing whether *magnitude of VSI* is a novel and early biomarker of AD, associations of VSI with plasma-based total and phosphorylated Tau, neurofilament (NfL), ApoE, and multimodal neuroimaging measures of Neurodegeneration will also be examined for study completeness.

Innovation

Multisensory integration is not well-understood in aging and its relation to cognitive and motor functioning is recognized as a major knowledge gap in the field (Meyer and Noppeney, 2011; Wallace, 2012; Mahoney and Barnett-Cowan, 2019; Campos et al., 2022). The NIA recognizes that functional changes in sensory and motor (i.e., non-cognitive) systems have an impact on the development and progression of AD and requests identification of novel, non-cognitive non-invasive predictors to aid in early AD detection. Our multisensory integration research meets this request, while also addressing the knowledge gap and providing significant public health implications. We are recognized as the first group to have established the clinical utility of *magnitude of VSI* in aging by linking it to poor motor outcomes including loss of balance, falls, and gait decline.

Additional innovation highlights of the VSI Study include: (1) access to established research infrastructure and existing collaborations; (2) cost and time-efficient design affording access to *a priori* identified participants with and without preclinical AD; (3) longitudinal design affording comprehensive examination of systemic changes (and their interactions) over time on the progression of AD and its subsequent link to mobility declines; (4) novel project with comprehensive multimodal neuroimaging approach providing clear clinical application of results; and (5) identification of a novel, non-cognitive behavioral marker that simultaneously taps multiple integrative systems that have not been systematically examined in previous AD investigations.

The current study also provides innovation beyond its specific aims as it affords: (1) a deeper investigation of the onset of functional systemic changes over time; (2) comprehensive investigation of the neurobiological consequences of AD and its links to medical co-morbidities in relation to VSI processes given previously reported diminished multisensory integration in older adults with diabetes (Mahoney et al., 2021); (3) enhancement of multisensory digital health tools like CatchU® used to screen and prevent falls for older adults in clinical settings (Mahoney et al., 2022); and (4) development of future multisensory-based interventions that will further enhance quality of life for seniors.

Methods

Study design

We propose a longitudinal study of older adults with (n = 104) and without (n = 104) preclinical AD; participants meeting criteria for dementia or AD will be excluded. In accordance with the NIA-AA research framework (Jack et al., 2018) and as stated earlier, our innovative project will allow us to disentangle differences in outcomes related to Alzheimer's symptomatology [mere presence of mild cognitive impairment syndrome at established clinical case conference (Holtzer et al., 2008)] from those related to Alzheimer's pathology (Aβ accumulation). Based on our previous studies (Mahoney and Verghese, 2020), we expect our preclinical AD group will include older adults with varying levels of cognitive impairment, ranging from amnestic and mixed MCI to preclinical AD. Sub-groupings of MCI and mild stage AD will afford *post hoc* analyses aimed at examining the impact of cognitive impairment syndromes on multisensory integration processes.

Interested participants will undergo extensive neuropsychological, sensory, physical functioning (mobility), neuroimaging, and blood testing, though we recognize that participants may decline participation in some procedures. The VSI Study includes three study sessions in Year 1 with subsequent follow-up calls every 2 months (to monitor falls) and yearly in-house visits in study Years 2 and 3. Initial enrollment of all 208 participants will be staggered across study Years 1–3, with follow-up visits conducted during study Years 2–5. Baseline sessions, designed using established divisional research studies as a model, aim to minimize fatigue and maximize effort by spreading test procedures out over three study sessions, each lasting about 3–4 h in duration (see **Figure 3** for overview of study procedures by session). Based on our experience with previous and currently NIH-funded divisional studies that have similar protocols, we estimate a 90% completion rate for this protocol.

Recruitment and study criteria

Participant recruitment for this project will be strategic. We will utilize existing infrastructure, recruitment methods, and available registration lists over 600 eligible and interested participants from previously funded divisional studies (R01AG036921, R01AG044007, and 1R01AG050448; and K01AG049813) for enrollment in the VSI Study. Adults aged 65 and older living in the NY metropolitan area may also be contacted using a commercially available third-party list. We have used these and other lists to recruit over 1,000 participants for various aging studies over the past 12 years. Identification of older adults with preclinical Alzheimer's disease will be supplemented by clinical recommendations from neurologists and neuropsychologists (Drs. Verghese, Weiss, and Zwerling), as well as clinical patient lists from Montefiore's Center of Excellence for Alzheimer's disease (CEAD), including both the Center for the Aging Brain (CAB) and the Memory Disorders Center. Since the VSI Study builds on existing research infrastructure, we will ensure similar distributions of age, gender, and ethnicity for older adults with and without preclinical Alzheimer's disease by monitoring demographic and clinical parameters and adjusting as needed as we accrue our sample.

In terms of our recruitment procedures, we will first mail letters to participants explaining the VSI Study. Then, the research team will follow-up by telephone and inquire whether the letter was received. If the participant received the letter, the research assistant will conduct standardized telephone recruitment interview procedures. If a letter was not received, the participant's name and mailing address will be verified by the research team and a new letter will be mailed out, which will be followed by a telephone interview call. Interested participants meeting study eligibility criteria (see **Table 1** for detailed inclusion and exclusion criteria) will be scheduled to come to the Albert Einstein College of Medicine, Division of Cognitive and Motor Aging, Sensorimotor Integration in Aging Lab for all in-house study sessions. After baseline study procedures are completed, the VSI Study case consensus team will convene and provide clinical diagnoses based on neuropsychological performance, neurological exam, medical history, and Aβ plasma results. Study group assignment will be determined during Year 1 case-conferences, and monitored every study year.

Study measures

A comprehensive list of established assessment measures is delineated in **Table 2** by domain and session. The variables of interest and their applications will be explained in detail below as they relate to each specific aim. Note that additional measures (i.e., pilot measures) unrelated to the study's specific aims may be included in the protocol but are not listed here. Variables and test measures labeled in green will be used as covariates in certain statistical models, depending on the specific research aim. As noted earlier, our central hypothesis is that preclinical AD is associated

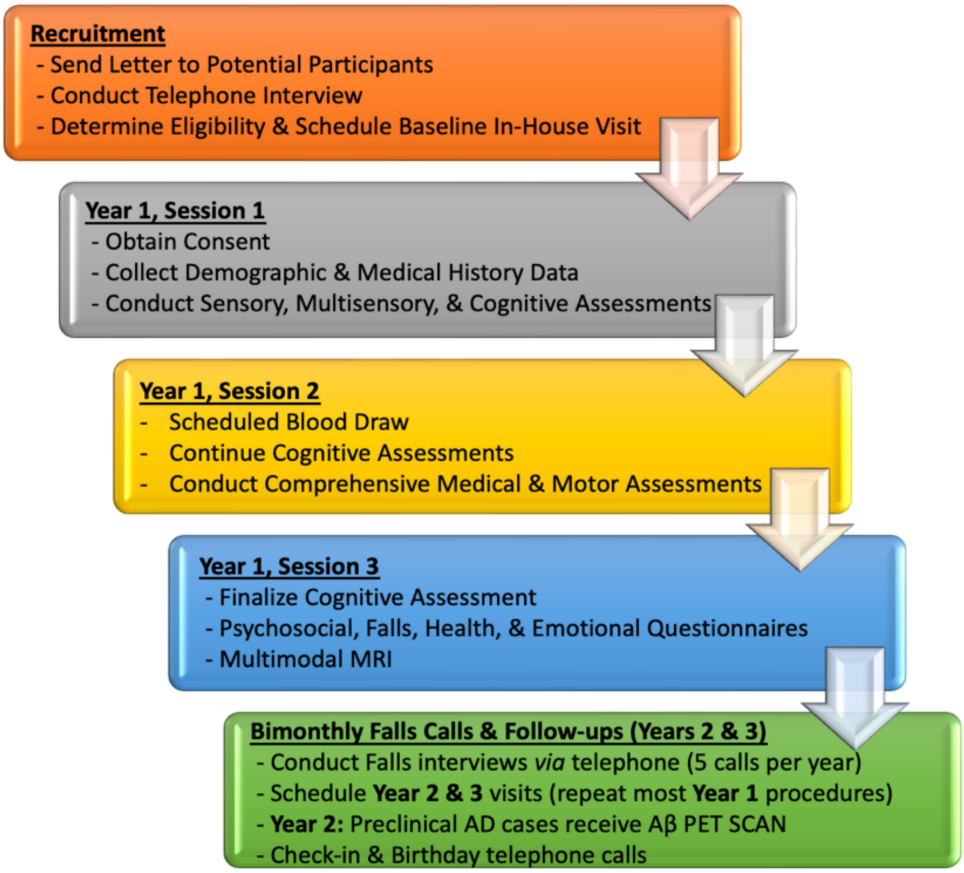

FIGURE 3
VSI Study flow by Year with high-level overview of targeted domains by baseline (Year 1) and follow-up sessions.

with neural disruptions in subcortical and cortical areas that concurrently modulate sensory, motor, and cognitive functions, resulting in mobility decline. Therefore, our study strategically includes a wide array of test measures in each domain.

Our independent variable is *magnitude of VSI* derived from our established VSI test (Mahoney and Verghese, 2019), and our dependent variables include neuroimaging measures of functional integrity (BOLD signal and resting state functional connectivity), motor outcomes (balance, gait, and falls), and Alzheimer pathology (Aß presence and accumulation). Comprehensive screening measures, neuropsychological and neurological/medical history assessments will be used to ensure study appropriateness, characterize our cohort, as well as aid in determination of cognitive status and study group enrollment. Additional psychosocial, social, emotional, and personality measures are included for study completeness as they will foster future research initiatives.

Primary research outcomes and statistical plan by aim

As stated earlier, our group has linked the *magnitude of VSI* to important cognitive and motor outcomes (Mahoney et al., 2014; Mahoney and Verghese, 2018, 2020; Mahoney et al., 2019). Furthermore, we highlighted the adverse effect of dementia and mild cognitive impairments on these outcomes (Mahoney and Verghese, 2020). However, the functional neural substrates of VSI have not been identified in healthy or cognitively impaired adults. The justification for identifying associated functional neural networks of multisensory integration will allow us to design novel multisensory-based interventions to complement existing interventions that demonstrate some fall reduction. The VSI Study will employ a theoretical and empirical approach to determine whether VSI is indeed a novel non-cognitive, non-invasive predictor of early Alzheimer's disease and specifically, address the following research aims:

Identify baseline structural and functional neural correlates of VSI in preclinical AD

Participants will complete a simple reaction time (RT) test employing three bilaterally presented conditions (visual, somatosensory, and multisensory visual-somatosensory) and a control (i.e., "catch") condition where no stimulation is presented, and no response is expected. The four stimulus conditions will be randomly presented with equal frequency (15 trials per condition per block, 3 blocks, yielding a total of 180 trials). The addition of "catch" trials and variable inter-stimulus-interval (ranging from 1–3 s) impedes anticipatory effects (see Mahoney and Verghese, 2018; Mahoney and Verghese, 2019, 2020; Mahoney et al., 2019; for details). Participants will be instructed to respond to all stimuli

TABLE 1 VSI Study eligibility criteria.

A	General inclusion criteria
1	Adults aged 65 and older, residing in New York Metropolitan area who plan to be in area for next three or more years.
2	Able to speak English at a level sufficient to undergo our cognitive assessment battery.
3	Ambulatory. Participants are classified as "non-ambulatory" if they are unable to leave the confines of their home and attend a clinic visit. Participants who require walking aids to walk outside but are able to complete our mobility protocols without an assistive device or the assistance of another person will not be excluded.
B	**General exclusion criteria (one or more criteria)**
1	Presence of dementia [Telephone based Memory Impairment Screen score (T-MIS) of < 5, Alzheimer's disease 8 (AD8) ≥ 2, or dementia diagnosed by study clinician at initial visit].
2	Serious chronic or acute illness such as cancer (late stage, metastatic, or on active treatment), chronic pulmonary disease on ventilator or continuous oxygen therapy or active liver disease. Individuals with recent cardiovascular or cerebrovascular event (MI, PTCA, CABG, or stroke) will not be excluded if they meet above inclusion criteria.
3	Mobility limitations solely due to musculoskeletal limitation or pain (e.g., severe osteoarthritis) that prevent participants from completing mobility tests. Mere presence of disease will not be used to exclude participants if they can complete the mobility tasks.
4	Any medical condition or chronic medication use (e.g., neuroleptics) in the judgment of the screening clinician that will compromise safety or affect cognitive functioning or terminal illness with life expectancy less than 12 months.
5	Progressive, degenerative neurologic disease (e.g., Parkinson's disease or ALS) diagnosed by study clinician and as per medical history.
6	Presence of clinical disorders that overtly alter attention like delirium.
7	Hospitalized in the past 6 months for severe illness or surgery that specifically affects mobility (e.g., hip or knee replacement) and that prevent participants from completing mobility tests or plans for surgery affecting mobility in the next 6 months.
8	Severe auditory, visual, or somatosensory impairments: Vision is screened using a Snellen chart – significant loss of vision is defined as corrected vision less than 20/400 on the Snellen chart with both eyes. Hearing is initially evaluated as part of the screening telephone interview. Participants will be excluded only if they are unable to follow questions asked in a loud voice during in-house sessions. Somatosensory functioning will be measured using quantitative sensory threshold protocols and presence of neuropathy will be assessed using the Michigan Neuropathy Screening Instrument.
9	Active psychoses or psychiatric symptoms (such as agitation) noted during the clinic visit that will prevent completion of study protocols. Past history of these symptoms or presence of psychiatric illness not used as exclusion criteria.
10	Living in nursing home.
11	Participation in intervention trial. Participants can participate in other observational studies.

as quickly as possible. Performance accuracy will be defined as the number of accurate stimulus detections divided by 45 trials per condition. Using our established methodology, robust probability (P) models that compare the cumulative distribution function (CDF) of combined unisensory visual (V) and unisensory somatosensory (S) reaction times with an upper limit of 1 min [P ($RT_V \leq t$) + P ($RT_S \leq t$), 1] to the CDF of multisensory visual-somatosensory (VS) reaction times [P ($RT_{VS} \leq$ t)] will be implemented. For any latency t, the inequality holds when the CDF of the actual multisensory VS condition [P ($RT_{VS} \leq t$)] is less than or equal to the predicted CDF {min [P ($RT_V \leq t$) + P ($RT_S \leq t$), 1]}. When the actual CDF is greater than the predicted CDF (i.e., positive value), the model is violated, and the RT facilitation is the result of multisensory interactions that allow signals from redundant information to integrate or combine non-linearly. Predicted CDF will be subtracted from the actual CDF to form a difference curve. *The area-under-the-curve of the group-level violated portion of the difference curve will serve as the continuous measure of magnitude of VSI.*

All neuroimaging procedures will be conducted at the Gruss Magnetic Resonance Research (MRRC) Center at Albert Einstein College of Medicine under the direction of Dr. Lipton. The MRRC offers state-of-the-art multimodal neuroimaging on Philips whole-body Ingenia Elition 3.0 Tesla Magnetic Resonance Imaging (MRI) scanner equipped with 32-channel head coil. Multimodal MRIs will be captured at baseline (i.e., study Year 1) and processed by our neuroimaging team consisting of Drs. Blumen, Fleysher, and Hoptman. Our non-invasive multimodal MRI imaging techniques are reliable and have been used extensively in both healthy aging and dementia studies in our division/department. For the VSI Study, specific MRI outcome measures are listed by modality in **Table 3**. Structural MRI (sMRI; ∼5 min) will be acquired using high-resolution T1-weighted whole head structural imaging using axial 3D-MP-RAGE acquisition over a 240 mm field of view (FOV) with 1.0 mm isotropic resolution. TE = 4.6 ms, TR = 9.9 ms, $\alpha = 8°$, and SENSE factor = 2.6 (left-right) x 2 (head-foot). Functional MRI (∼10 min total) will be acquired using whole brain T2* weighted images with echo planar weighted images with echo planar imaging over a 224 mm FOV on a 112 × 112 acquisition matrix, 3 mm slice thickness (no gap); TE = 30 ms, TR = 2,000 ms, flip angle = 90°, SENSE factor = 2 and 42 trans-axial slices per volume. The fMRI procedures will measure BOLD activation (outcome measure) during the VSI task. This event-related design emulates our established psychophysical protocol where 60 trials of visual alone, somatosensory alone, multisensory visual-somatosensory (VS; Mahoney and Verghese, 2019) will be presented in the scanner, but will also include the above-mentioned "catch" trials (60 trials). The visual (V) stimulus will be bilateral asterisks presented for 100 ms on a VisuaStim digital visor (Resonance Technology, Inc., Northridge, CA, USA).

TABLE 2 Assessment measures by domain and session.

Domain	Session	Assessment measures
Screening	Telephone Interview	Demographic (including age, gender, ethnicity and education level)/Health screen/Telephone memory impairment screen (Lipton et al., 2003); AD8 dementia screening interview (Galvin et al., 2005); life space assessment scale (Baker et al., 2003)
Sensory	Years 1–3	Visual sensory screen (Snellen test); Shoebox auditory testing; Vibratron (Shy et al., 2003); Michigan neuropathy screening instrument (Feldman et al., 1994; Lunetta et al., 1998); Simple reaction time test; Odor identification test (NIH Toolbox)
Multisensory	Years 1–3	Visual-somatosensory integration test (Mahoney et al., 2019); CatchU® (Mahoney and Verghese, 2022)
Neuropsychological	Years 1–3	MoCA (Nasreddine et al., 2005); WRAT-3 (Ashendorf et al., 2009); WAIS-IV (Wechsler, 2008; Processing speed index score); Trails A&B (Lezak et al., 2004); Golden stroop (Golden, 1978); Wisconsin card sorting test (WCST-64; Heaton, 1981; Greve, 2001); Conner's continuous performance test –3 (CPT-3; Conners, 2014); Flanker test (Fan et al., 2002); Boston naming test (Kaplan et al., 1983); Free-cued selective reminding test (FCSRT; Grober et al., 1988); Control oral word association test (Benton, 1968); MINT (Gollan et al., 2012); Benson complex figure (Possin et al., 2011); Craft story (Craft et al., 1996); Judgment of line orientation test (SF-12 item); Established clinical case conference
Neurological/ Medical History/ Physiological/Other	Years 1–3	Neurological exam; CDR; Medical history interview (medical comorbidities, including CVD); Medication/Polypharmacy list; Height/Weight/Blood pressure/Pulse; AD family history questionnaire; TBI history intake; History of COVID; SF-12 (Ware et al., 1996); Brief fatigue inventory (Shahid et al., 2011); Smoking/Alcohol consumption intake; Pittsburgh sleep quality index (Buysse et al., 1989); STOP-BANG (Chung et al., 2008); MOS pain (de Mos et al., 2007)
Gait/Mobility	Years 1–3	Quantitative gait assessment (Verghese et al., 2002b, 2007a, 2009); Normal pace walking/Walking while talking protocol (Holtzer et al., 2011) and Primary gait screen (Protokinetics); General mobility questionnaire
Balance/Physical Performance/Leisure	Years 1–3	Unipedal stance test (Hurvitz et al., 2000, 2001); Berg balance test (Berg et al., 1992); Biodex sensory organization test; ABC scale (Powell and Myers, 1995); Short physical performance test (SPPB; Guralnik et al., 1994); Stair climbing; Grip strength (Guralnik et al., 1994); Functional reach (Duncan et al., 1990); Purdue pegboard (Tiffin and Asher, 1948); Maze (Sanders et al., 2008); Leisure scale (Verghese et al., 2003)
Falls	Years 1–3	Baseline and bimonthly fall interviews (Verghese et al., 2004; Verghese et al., 2008b, 2009); Falls self-efficacy scale (Tinetti et al., 1990)
Activities of Daily Living		4 ADLs; Instrumental ADLs (Lawton and Brody, 1970); Bathing scale
Psychosocial/Personality	Years 1–3	Geriatric depression scale (Brink et al., 1982); Beck anxiety inventory (Beck et al., 1988); Big-5 inventory (Barrick and Mount, 1991)
Social Support/Loneliness	Years 1–3	Social network index; MOS social support survey (Sherbourne and Stewart, 1991); UCLA loneliness index-3 (Russell, 1996).
Multimodal Neuroimaging	Year 1	Structural MRI (s-MRI) including total intracranial volume; Functional MRI (fMRI: task-based VSI test and resting state fMRI (Yuan et al., 2015; Pillemer et al., 2017), FLAIR (3D); DTI/NODDI; Pseudo-continuous arterial spin labeling (pc-ASL); Susceptibility weighted imaging (SWI) – (see Table 3 for more details)
Blood and Plasma	Year 1	Basic chemistry; Lipid panel; Glucose/A1C; IL-6; CRP; Aβ/ApoE/pTau/Neurofilament (Bateman et al., 2019)
Amyloid Imaging	Year 2*	Fluorine-18 florbetaben (Neuraceq) PET scan in individuals with preclinical AD [*case confirmed→ Aß + plasma test and confirmed poor neuropsychological performance]

Established study procedures labeled in green for use as covariate in statistical models.

The somatosensory (S) stimulus will be bilateral pneumatic pulses presented for 100 ms through the Somatosensory Stimulus Generator system (4-D Neuroimaging) which is compatible in the MRI scanner. These stimuli will be presented alone and concurrently in the case of the concurrent VS stimulus. The critical contrast here will examine differences in BOLD activation between the multisensory VS condition *vs.* the sum of the two unisensory conditions (V + S). Resting-state (rs)-fMRI (10 min) will also be captured while participant lay still and relax (i.e., a passive no-task condition) with their eyes open. Fluid Attenuated Inversion Recovery (FLAIR; ∼5 min total) will account for white matter hyperintensities (WHI) indicative of small vessel disease. FLAIR will be acquired using whole head imaging sagittal 3D-TSE-IR acquisition over a 250 mm FOV with 1 mm isotropic resolution. TE = 338 ms, TR = 4,800 ms, TI = 1,650 ms TSE Factor = 182, compressed SENSE acceleration factor 3.5. FLAIR results will account for presence/absence of small vessel disease and will be considered as a covariate. Additional multimodal neuroimaging procedures to be included for study completeness, beyond the scope of the specific aims include: Susceptibility Weighting Imaging (SWI); Pseudo-Continuous Arterial spin labeling (pc-ASL); and Neurite orientation and dispersion density imaging (NODDI) – see **Table 3** for details.

In terms of our statistical approach for Aim 1, the *magnitude of VSI* (independent variable) will be analyzed and quantified using established probabilistic modeling procedures (Mahoney and Verghese, 2019). The dependent measures of structural and functional neural integrity include: (1) cortical thickness:

TABLE 3 List of Magnetic Resonance Imaging (MRI) procedures.

MRI measures	Modality	Outcome measure(s)
Structural	Structural MRI	Cortical thickness and gray matter volume
	3D FLAIR	Presence of white matter hyperintensities and lacunes
	Susceptibility Weighting Imaging (SWI)	Presence of microbleeds
	Pseudo-continuous arterial spin labeling (pc-ASL)	Quantitatively measures tissue perfusion, or cerebral blood flow (CBF)
	Neurite orientation and dispersion density imaging (NODDI)	A diffusion imaging technique to detect cortical and corticospinal tract neurodegeneration (N)
Functional	Functional MRI (fMRI)	BOLD response (beta) during VSI task
	Resting state fMRI	Fisher *z*-transformed Resting state functional connectivity

(2) volumetric measures for regions of interest extracted from structural MRI; (3) Beta-weights for the multisensory contrasts for each region of interest extracted from task-based fMRI; and (4) Fisher *z*-transformed resting-state functional connectivities between pairs of regions extracted from resting-state fMRI.

Covariates identified in our prior studies (Holtzer et al., 2007; Verghese et al., 2007b, 2008a; Mahoney and Verghese, 2018, 2019, 2020), including but not limited to age, gender, ethnicity, medical comorbidities (including cardiovascular disease), total intracranial volume, and attentional capacity will be selected to account for their influence on VSI and association with outcomes. Participants will be categorized into two groups based on preclinical AD diagnosis at baseline. All statistical approaches will be supervised by our study statistician, Dr. Wang.

SAS 9.4 (Cary, NC) will be used for the analyses. We will conduct multivariate mixed effects models for imaging outcomes for the following *a priori* selected regions of interest including: dorsal lateral PFC, rostral middle frontal, and superior frontal gyrus regions, superior temporal sulcus, motor cortex, thalamus, basal ganglia, hippocampal, and cerebellum (one per outcome, with group factors as necessary). These regions are selected based on preliminary findings in 100 older adults (*unpublished data*) which reveal significant ($p < 0.05$) associations between magnitude of VSI and measures of structural integrity (defined here as either volume or cortical thickness) in the following regions: parahippocampal (memory); caudal middle-frontal dorsal lateral prefrontal cortex (DLPFC: cognitive functions - especially executive & attention); superior temporal sulcus (STS; multisensory); precentral (motor), postcentral (somatosensory), and lateral occipital (visual). Preliminary fMRI findings in 56 healthy older adults (ages 65–92; *unpublished data*) further supports inclusion of these regions given significant associations between VSI magnitude and blood-oxygen-level-dependent (BOLD) responses in known multisensory (middle temporal), motor (basal ganglia), and cognitive areas (PFC including DLPFC). The outcomes in these models include measures of neural integrity, structural (volume and thickness), and/or functional (BOLD) activation isolated by region, and the predictor of interest is the *magnitude of VSI*. Additional models will further include cognitive status (normal or preclinical AD) and its interaction with *magnitude of VSI*. The effect of cognitive status (normal or preclinical AD) on *magnitude of VSI* will be evaluated using similar mixed effects models. The hypothesis-driven analyses will be limited to BOLD activation in the aforementioned regions of interest. Models will be run unadjusted and then adjusted for confounders.

Determine whether VSI task-related BOLD activation in prefrontal cortex predicts future mobility decline and falls in preclinical AD

Here, we propose that reduced VSI activation in specific regions of PFC (fMRI BOLD responses), will be associated with worse balance (unipedal stance), slower gait (worse Pace scores), and increased risk of incident falls. Additionally, we propose that preclinical AD will reduce VSI activation in PFC regions of interest, which will in turn adversely affect mobility measures. Our longitudinal design will allow us to identify the impact of functional changes in (multi)sensory, motor, and cognitive processes (and their interactions) on the progression of AD that result in mobility decline.

The VSI task and multimodal neuroimaging procedures for this aim have been described above in Aim 1. For Aim 2, the VSI task will be run in the magnet to obtain fMRI task-related BOLD responses with concurrent psychophysical data. The following aim-related mobility procedures [established tests that have been validated and utilized in our center for over two decades (Verghese et al., 2002a, 2007b, 2008a, 2009, 2012; Holtzer et al., 2007, 2012, 2014; Verghese and Xue, 2010, 2011; Ayers and Verghese, 2014; Mahoney et al., 2014, 2017, Holtzer et al., 2014; Mahoney and Verghese, 2018, 2020)] will be included in Aim 2:

Balance (~2 min) will be assessed using unipedal stance time, which requires individuals to balance their body weight with foot on the ground for a maximum of 30 s (Hurvitz et al., 2000, 2001). Unipedal stance time is a widely used clinical test that is listed under NIH's toolbox. Poor scores on this test have been associated with presence of neuropathy (Hurvitz et al., 2001), and predict falls in older adults (Hurvitz et al., 2000). This test will be administered twice during each study visit and maximum unipedal stance time (sec) will serve as the outcome measure.

Quantitative Gait (~5 min) will be assessed on a 28-foot instrumented walkway (PKMAS system; Zenometrics LLC) with embedded pressure sensors that provides spatial and temporal gait parameters including: gait velocity, stride length, percentage of double support, stride time, stance time, cadence, stride length variability, and swing time variability. Participants will be assessed twice while walking on the mat at their everyday pace. Gait velocity, as well as the Pace Factor score comprised of gait velocity, stride length and percentage of double support, will serve as dependent measures.

History of falls (~5 min) in the past 1 year, number of incident falls over a 3 year longitudinal study-period, and fall information such as type, injury and location will be tracked at yearly in-house interviews and during bimonthly telephone interviews using established criteria and standardized questionnaires (Tinetti et al., 1994). Falls are defined as sudden, unintentional, unprovoked changes in body posture, not due to a major intrinsic event (stroke) or overwhelming hazard. Dichotomous ratings of fall-history over

the past 1 year (0, 1), presence of incident fall over study period (0, 1) and time to fall/censor will serve as outcome measures.

The association of functional VSI activation in specific PFC regions of interest with mobility measures of balance and quantitative gait will be examined cross-sectionally at baseline (Year 1), using linear regression models. Linear mixed effects models (LMEM) will be used to examine the association of baseline functional VSI activation in the PFC on the changes in the longitudinal balance and quantitative gait performance. The predictors will be examined as continuous variables to facilitate clinical translation of results. Adjustments for multiple comparisons will be made. Additional LMEMs will be employed to examine interplay and time course of multisensory, cognitive, and motor functioning. Cox proportional hazard model will be used to evaluate the association of *magnitude of VSI* with the risk of incident falls (Mahoney et al., 2019) and hazard ratios (HR) with 95% confidence intervals (CI) will be reported. Time to fall will be recorded as number of days from baseline study date to the interview date when the fall was recorded. If the participant does not report a fall, the follow-up time will be defined as the number of days from the baseline in-house visit to the last date of contact. Repeated incident falls will be examined using Andersen-Gil extension of Cox model (Anderson and Gill, 1982) and Poisson models. Robust sandwich covariance estimates account for correlations among multiple events within the same participant. Cox models will be adjusted for potential confounders. Proportional hazards assumptions of all models will be tested graphically and analytically. We will also apply mediation analysis using product of coefficients methods to evaluate whether cognitive status (normal vs. preclinical AD; independent variable) causes variation in PFC-related VSI activation (mediator), which in turn causes variation in specific mobility measures (dependent variables) using separate mediation models (balance and pace). Mediation analyses will be run using IBM's Statistical Package for the Social Sciences (SPSS-28) and Hayes' PROCESS package (Hayes, 2018). Confidence intervals that do not include 0 for the mediator will be defined as mediation.

Assess the validity of VSI as a novel Alzheimer's behavioral marker

Alzheimer's disease is associated with build-up of specific proteins (i.e., biological markers) in the brain, namely Amyloid-βeta (Aβ) in the form of plaques (Thal et al., 2002) and tau (T) in the form of neurofibrillary tangles. Common brain imaging techniques such as MRI or Computerized Tomography (CT) do not afford assessment of amyloid plaques and neurofibrillary tangles. However, molecular imaging procedures like Positron Emission Tomography (PET) imaging directly visualize these characteristic features of Alzheimer's disease. Aβ accumulates in sensory association areas well before higher-order cognitive areas like the PFC (Thal et al., 2002). In Aim 3, we predict that AD pathology (i.e., accumulation of Aβ) will be associated with decreased *magnitude of VSI* in preclinical Alzheimer's disease participants. Here, presence of Aβ will be measured in blood at baseline using plasma-based assays and established cut-scores (Bateman et al., 2019). Individuals that are Aβ+ on plasma-based tests at baseline, will receive amyloid PET imaging in study year 2. The combined use of conventional MRI with these techniques will also contribute to the early identification of Alzheimer's disease.

The experimental design for this aim has been described above. Beyond the VSI task the following specific Aβ procedures will be implemented to determine its association with *magnitude of VSI,* and ultimately its use as a novel and early biomarker for preclinical AD.

Plasma-Based Blood Testing will be conducted during baseline visits for each participant. Aβ (40 and 42) and Apolipoprotein E (ApoE) will be assessed by C_2N Diagnostics lab using novel multiplexed assays (Jack et al., 2018). PrecivityAD^{TM} accuracy for determining amyloid positive versus negative status was 86%. Blood samples will be collected and placed in Einstein's biorepository. Frozen samples will be subsequently shipped to C_2N Diagnostics to be processed. Results from plasma-based testing conducted on bloods drawn at baseline, in conjunction with neuropsychological performance, will be critical for study group assignment, as well as disentangling AD symptomology from AD pathology.

Amyloid PET Imaging will only be conducted in study Year 2 for participants enrolled in the preclinical AD group (n = 104). All PET scans will be conducted at Montefiore Medical Center by Dr. Valdivia and her team. Positron emission tomography (PET) is expensive and involves the use of an imaging device (scanner) and a radiotracer that is injected into the patient's bloodstream. The radiotracer used to estimate Aβ neuritic plaque density for this specific aim is called Neuraceq (florbetaben F-18) and is manufactured by Piramal Imaging. PET imaging after the radiotracer is injected, will afford quantification of the distribution of Aβ in the brain, where affected brain regions containing Aβ will be tabulated.

The association of *magnitude of VSI* with presence of Aβ protein levels in both plasma-based Aβ levels (continuous measure) and amyloid PET scans (dichotomous ± rating by brain region) will be examined using logistic and linear regression models, respectively, while adjusting for potential confounders.

Discussion

In summary, we propose to recruit 208 community-dwelling older adults with and without preclinical AD for a three-year longitudinal study. Our central hypothesis is that preclinical Alzheimer's disease is associated with neural disruptions in subcortical and cortical areas that concurrently modulate sensory, cognitive, and motor functions, resulting in mobility decline. Our project seeks to address a NIH-identified high-priority research topic, where the interplay of multisensory integration with cognitive and mobility outcomes will be extensively studied in individuals with and without preclinical Alzheimer's disease. A deeper understanding of the underlying neural correlates of VSI and their association with cognitive and motor outcomes will support the advance of novel, non-invasive, and non-cognitive AD markers, as well as foster the development of novel multisensory interventions designed to target specific neural derailments, while significantly augmenting existing interventions to prevent disability and optimize independence.

As with any study, there are potential pitfalls and limitations that should be discussed, along with strategies to mitigate any potential shortcomings. Missing data is a concern of any longitudinal study; to reduce the likelihood of missing data, we will reschedule study visits that are missed and update participant

contact information annually. Though not a main objective, diffusion tensor imaging data will be collected and analyzed using FSL software to provide a measure of functional anisotropy. Further examination of multimodal neuroimaging relationships will be computed using probabilistic tractography between regions of interest (ROIs). Neuroimaging data access can enable investigations of additional cortical pathways not identified in our proposed neural circuit; our approach here, however, is to focus on theory-based predictions. We recognize that biomarkers, including the AT (N) classification system [Aβ (A), tau (T), and neurodegeneration (N)] recently developed the NIA-AA task-force, affords a more direct assessment of neuropathologic changes (Jack et al., 2019). In an effort to determine whether magnitude of VSI is a novel and early biomarker of mild stage Alzheimer's disease, the current study will also assess plasma-based total and phosphorylated Tau, neurofilament (NfL) and (ApoE).

In line with current preventative approaches, results from The VSI Study will provide insight into the neurobiology of early AD and aid the development of novel prognostic tools and therapeutic interventions. The primary focus of this project will guide strategic design of new multisensory-based interventions for non-cognitive outcomes like falls. Although not a specific aim of the current study, development of future multisensory-based interventions in high-risk patients requires identification of the structural and functional neural networks involved in multisensory integration processes, as well as understanding of the impact of early AD on these networks and systems. Such knowledge will be essential to designing future remediation trials that target key PFC and other regions involved in multisensory integration to induce neural plasticity that will be associated with improvements in sensory, cognitive, and mobility outcomes for older adults with and without pre-existing cognitive impairments.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board at the Albert Einstein College of Medicine. All participants provided written informed consent to participate in this study.

Author contributions

JRM wrote the manuscript. All authors reviewed, revised, and approved the final manuscript before submission.

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Conflict of interest

JRM has a financial interest in JET Worldwide Enterprises Inc., a digital health startup spun out of research conducted at Albert Einstein College of Medicine. MH reports financial support was provided by American Foundation for Suicide Prevention and also relationship with Kessler Research Foundation that includes consulting or advisory and serves on the Editorial board of Brain Sciences and is an Associate Editor for Frontiers of Psychiatry - Schizophrenia Section.

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.

Publisher's note

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Dual-task gait and white matter hyperintensities in Lewy body diseases: An exploratory analysis

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Background: Parkinson's disease (PD) and dementia with Lewy bodies (DLB) are part of a spectrum of Lewy body disorders, who exhibit a range of cognitive and gait impairments. Cognitive-motor interactions can be examined by performing a cognitive task while walking and quantified by a dual task cost (DTC). White matter hyperintensities (WMH) on magnetic resonance imaging have also been associated with both gait and cognition. Our goal was to examine the relationship between DTC and WMH in the Lewy body spectrum, hypothesizing DTC would be associated with increased WMH volume.

Methods: Seventy-eight participants with PD, PD with mild cognitive impairment (PD-MCI), PD with dementia or DLB (PDD/DLB), and 20 cognitively unimpaired participants were examined in a multi-site study. Gait was measured on an electronic walkway during usual gait, counting backward, animal fluency, and subtracting sevens. WMH were quantified from magnetic resonance imaging using an automated pipeline and visual rating. A median split based on DTC was performed. Models included age as well as measures of global cognition and cardiovascular risk.

Results: Compared to cognitively unimpaired participants, usual gait speed was lower and DTC was higher in PD-MCI and PDD/DLB. Low DTC participants had higher usual gait speed. WMH burden was greater in high counting DTC

participants. Frontal WMH burden remained significant after adjusting for age, cardiovascular risk and global cognition.

Conclusion: Increased DTC was associated with higher frontal WMH burden in Lewy body disorders after adjusting for age, cardiovascular risk, and global cognition. Higher DTC was associated with age.

KEYWORDS

dual task, gait, white matter hyperintensities, cognition, Lewy body disease, Parkinson's disease

Introduction

Lewy body disorders (LBD) represent a spectrum of disorders, characterized by the over-accumulation of alpha-synuclein in the brain, leading to the formation of Lewy bodies, which are associated with neuronal loss (Galasko, 2017; Kouli et al., 2018). Neuronal loss progression in subcortical and cortical brain regions results in increasing motor (including gait) and cognitive impairment (Galasko, 2017; Mirelman et al., 2019, 2021). Consequently, diagnoses range from Parkinson's disease (PD) with intact cognition, PD with mild cognitive impairment (PD-MCI) to PD with dementia (PDD) and dementia with Lewy bodies (DLB) (grouped as PDD/DLB).

Gait slowing in aging, especially while performing a simultaneous cognitive task (dual task), is thought to be an early predictor of significant cognitive decline (Mielke et al., 2012; Montero-Odasso et al., 2012a). The extent of slowing can be quantified by dual task cost (DTC), which indicated slowing during a secondary task, relative to the participant's usual task gait speed (Montero-Odasso et al., 2012b). Essentially, DTC reflects cognitive-motor reserve. While it is clear that gait is affected by dual tasks in healthy older adults (Smith et al., 2017), patients with LBD (Raffegeau et al., 2019), and older people with cognitive decline (Montero-Odasso et al., 2017) associated brain imaging correlates are not well established (Veldkamp et al., 2021).

White matter lesions presenting as white matter hyperintensities (WMH) on magnetic resonance imaging (MRI) have also been related to cognitive and gait deficits in healthy aging (Crockett et al., 2022), cerebral small vessel disease (Sharma et al., 2022), and PD (Toda et al., 2019; Dadar et al., 2020). Some studies have found participants with PDD may have greater WMH volumes than controls and PD with intact cognition (Butt et al., 2021).

Overall, the relationship between dual task gait change and WMH in the Lewy body spectrum is not well understood. To address this gap, we explored the association between white matter changes and DTC across the Lewy body spectrum. We hypothesized that WMH would be associated with DTC, regardless of the secondary task.

Materials and methods

Participants were enrolled in the multi-center Canadian Consortium on Neurodegeneration in Aging's (CCNA), Comprehensive Assessment of Neurodegeneration and Dementia (COMPASS-ND) study (Chertkow et al., 2019) and the Functional Assessment and Vascular Reactivity (FAVR)-II study (Beaudin et al., 2022). The COMPASS-ND was approved by the research ethics boards of all the involved institutions while FAVR-II was approved at the University of Alberta and University of Calgary. Both studies were carried out in accordance with the Code of Ethics of the World Medical Association. Participants provided their written informed consent to participate.

Participants

Participants were recruited from movement disorder and cognitive clinics as well as referrals from community physicians and community advertisements. Three COMPASS-ND study sites (University of Alberta, University of Calgary, and the Sunnybrook Research Institute in Toronto) completed assessments with electronic walkways. Cognitively unimpaired (CU) participants from FAVR-II, which is harmonized with COMPASS-ND, were recruited at the University of Alberta and University of Calgary. Sequential male and female participants from the recruiting sites were included. All met published criteria for a LBD or were CU as outlined previously (Chertkow et al., 2019; Pieruccini-Faria et al., 2021). Patients with severe cognitive impairment (MoCA <13), active neuro-psychiatric problems or immobility were not included.

Eighty-two participants diagnosed with PD or DLB were included from the COMPASS-ND cohort: 42 had PD without cognitive impairment (PD), 20 had PD-MCI, 9 had PDD, and 11 were diagnosed with DLB. Initial diagnosis criteria included Montreal Cognitive Assessment (MoCA) score (range 0–30, higher score represents better cognition) where a score ≤ 24 indicated PD-MCI or PDD/DLB. The PDD/DLB group had sufficient cognitive impairment to interfere with independent function. A MoCA score between 8 and 20 inclusive was considered indicative of dementia. Final diagnosis was based on further evaluation by an experienced neurologist (RC/ES/MM/SEB) using established criteria as previously described (Pieruccini-Faria et al., 2021). Given the small number of participants and that PDD and DLB are both Lewy body dementias with overlapping pathological features (Galasko, 2017), the PDD and DLB groups were combined for statistical analysis (PDD/DLB). CU participants were included, with 13 from COMPASS-ND and 7 from FAVR-II. Four participants were unable to undergo MRI and subsequently

excluded. The final number of participants for analysis was 20 CU, 41 PD, 17 PD-MCI, and 20 PDD/DLB.

Clinical assessment

Demographic descriptors included age, sex, and years of education. Global cognition was measured using MoCA. Cardiovascular health was summarized using the Framingham cardiovascular risk score (D'Agostino et al., 2008), which includes age, sex, diabetes, current smoking status, systolic blood pressure, treatment for hypertension, and body mass index. Patients were characterized by disease duration, levodopa equivalent daily dose (LEDD) (Tomlinson et al., 2010), and Movement Disorder Society-Unified Parkinson's Disease Rating Scale Part 3 (MDS-UPDRS III) (range 0–132, higher score indicates greater severity) (Goetz et al., 2008). The patients were in the ON state when their gait was tested if they were on dopaminergic medications. They were tested at a time they were comfortable with doing the walking task. While dyskinesia were present in some patients these did not interfere with the walking tasks. Self-reported gait freezing was assessed using the Freezing of Gait Questionnaire (range 0–24, higher score indicates greater severity of gait impairment) (Giladi et al., 2000).

Gait measurement and analysis

Gait was evaluated according to the standardized COMPASS-ND protocol (Cullen et al., 2018). A ProtoKinetics Zeno Walkway (Edmonton and Calgary) or a GAITRite (Sunnybrook) walkway

TABLE 1 Demographics and DTC variables for all groups.

	CU	PD	PD-MCI	PDD/DLB	*p*
N	20	41	17	20	–
Age (years)	68.7 ± 5.8	66.7 ± 7.2	70.5 ± 8.0	72.9 ± 8.5	**0.02**
Females, *N* (%)	15 (75.0)	22 (53.7)	3 (17.6)	2 (10.0)	**<0.001**
Education (years)	16.1 ± 2.9	15.8 ± 3.0	15.6 ± 3.3	16.2 ± 5.0	1
FCRS† (%)	18.9 ± 14.6	19.3 ± 14.4	30.0 ± 11.7	28.7 ± 14.0	**0.01**
MoCA	27.5 ± 1.8	27.9 ± 1.4	22.4 ± 4.3	18.70 ± 4.4	**<0.001**
Disease duration (years)	–	6.4 ± 3.7	8.0 ± 5.9	7.8 ± 5.8	0.4
MDS-UPDRS III	–	21.2 ± 10.7	26.2 ± 12.5	29.0 ± 19.0	0.1
LED (mg)	–	640 ± 375	852 ± 477	469 ± 531	0.1
FOG-Q	–	3.4 ± 3.6	5.1 ± 5.4	7.0 ± 6.3	**0.03**
Baseline gait speed (cm/s)	141.1 ± 16.2	132.6 ± 23.9	119.3 ± 22.5	104.5 ± 23.1	**<0.001**
Counting					
DTC (%)	1.4 ± 4.5	3.5 ± 6.6	7.6 ± 6.3	14.0 ± 16.8	**<0.001**
Correct subtractions	6.8 ± 1.8	8.3 ± 2.3	8.4 ± 2.3	7.8 ± 3.9	0.2
Fluency					
DTC (%)	5.2 ± 7.3	7.1 ± 9.0	15.2 ± 9.8	19.1 ± 11.4	**<0.001**
Number named	6.0 ± 1.0	6.6 ± 1.6	5.6 ± 1.3	4.8 ± 1.7	**<0.001**
Serial 7s					
DTC (%)	9.6 ± 10.1	11.6 ± 12.5	23.0 ± 12.1	20.4 ± 14.5	**0.001**
Correct subtractions	2.8 ± 1.7	3.8 ± 1.9	2.5 ± 1.6	2.0 ± 1.9	**0.001**
Raw WMH volume (mm^3)*					
Total	6,210 ± 4,833	8,790 ± 11,543	14,541 ± 15,566	20,581 ± 16,742	**0.001**
Frontal lobe	3,207 ± 2,757	43,89 ± 5,842	7,051 ± 7,397	8,912 ± 6,562	**0.008**
Temporal lobe	730 ± 575	968 ± 990	1,575 ± 1,417	2,341 ± 2,607	**0.002**
Parietal lobe	1,406 ± 1,440	2,315 ± 4,409	4,234 ± 5,949	6,573 ± 6,821	**0.004**
Occipital lobe	864 ± 596	1,111 ± 1,103	1,658 ± 1,271	2,747 ± 2,026	**< 0.001**
Fazekas score#					
Total	1.50 ± 1.10	2.22 ± 1.30	2.65 ± 1.27	2.90 ± 1.21	**0.003**
Periventricular	0.60 ± 0.60	1.10 ± 0.70	1.35 ± 0.70	1.80 ± 0.83	**<0.001**
Subcortical	0.90 ± 0.72	1.12 ± 78	1.29 ± 0.69	1.10 ± 0.55	0.4

PD, Parkinson's disease; PD-MCI, Parkinson's disease with mild cognitive impairment; PDD, Parkinson's disease with dementia; DLB, dementia with Lewy bodies; FCRS, Framingham cardiovascular risk score; MoCA, Montreal Cognitive Assessment; MDS-UPDRS III, Movement Disorders Society-Unified Parkinson's Disease Rating Scale; FOG-Q, Freezing of Gait Questionnaire; LED, levodopa equivalent dose; DTC, dual task cost; WMH, white matter hyperintensities. †Missing for one participant. *Not significant after for correction for age and sex, except for occipital WMH. *p*-Values for raw comparisons are shown. #Significant for total and periventricular scores after correction for age and sex. *p*-Values for raw comparisons are shown. Bold values represent the statistically significant.

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was used to measure gait parameters from 6 m walks (Cullen et al., 2018). To ensure steady gait speed on the walkway and minimum acceleration and deceleration effects, walks commenced 1 m before and ended 1 m after the gait mat. Usual gait was measured while participants walked at a comfortable pace. Three trials were performed to calculate average usual gait. Participants were then instructed to walk while simultaneously engaging in the following verbal tasks in a fixed order: (1) counting backward by 1s starting from 100 ("counting"), (2) naming as many animals as possible without repetition ("fluency"), and (3) counting backward by 7s starting from 100 ("serial 7s"). Performance on the verbal tasks were measured by the number of correct subtractions for counting and serial 7s, and the number of unique animals named for fluency. The cognitive task performance was recorded but cognitive task costs were not analyzed.

The following formula was used to calculate the DTC on gait speed for each condition (Montero-Odasso et al., 2012b):

$$DTC = \left(\frac{[usual\ gait\ speed - dual\ gait\ speed]}{usual\ gait\ speed}\right) \times 100$$

Evaluation of WMH on MRI

All MRI scans were completed on a Siemens Prisma 3.0 T system (Edmonton and Sunnybrook) or 3.0 T GE Discovery MR750 (Calgary), according to the Canadian Dementia Imaging Protocol (Duchesne et al., 2018). T1-weighted, T2-weighted, and fluid-attenuated inversion recovery images were used to measure WMH volumes with an automated tool (Dadar et al., 2017). Total WMH volume was normalized for intracranial volume and $\log_{10}$ transformed to obtain a normal distribution. Additionally, the presence and severity of WMH was rated qualitatively using Fazekas Visual Rating Scale (Fazekas et al., 1987). Illustrative images and technical details are published (Dadar et al., 2022).

Statistical analysis

Data was analyzed using SPSS (Version 26, IBM Corporation, Armonk, NY, USA). One-way analysis of variance (ANOVA) was used for continuous variables and Chi-squared test for categorical variables. Two analyses were performed, (1) across the groups (CU, PD-MCI, and PDD/DLB) where we looked at overall group comparisons and pair wise comparisons between the groups. The Sidak correction for multiple corrections was used for *post-hoc* pairwise comparisons between the groups, and (2) high vs. low DTC groups within the Lewy body spectrum.

First, clinical characteristics, gait and dual task gait were compared across groups for each task separately using ANOVAs or ANCOVAs. For all three dual task conditions, DTC was not normally distributed and attempts to normalize with commonly used transformations such as $\log_{10}$, various functions (powers, exponential, and arcsinh), and a Box Cox transformation failed. Consequently, and based on the observation that some participants show no DTC, while others showed a range of increased cost, a median split of DTC for each task within the Lewy body group, excluding CU, was used to convert DTC into a categorical variable.

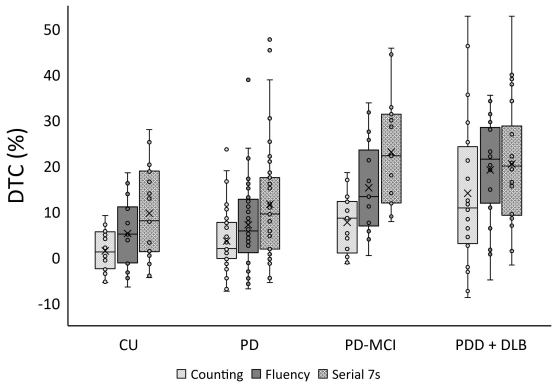

FIGURE 1
Boxplot of dual task cost (DTC) % for cognitively unimpaired health participants (CU), Parkinson's disease (PD), Parkinson's disease with mild cognitive impairment (PD-MCI), and a combined group of participants with either Parkinson's disease with dementia (PDD) or Dementia with Lewy Bodies (DLB).

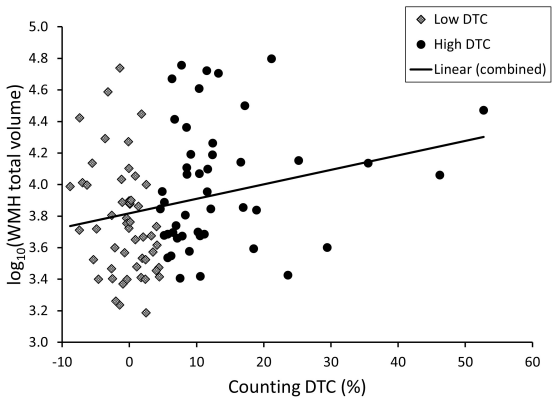

FIGURE 2
Scatterplot of total white matter hyperintensity (WMH) volume and dual task cost (DTC) under the counting condition for patients with Lewy body disorders with high vs. low DTC (median split).

Differences in WMH volumes between the high and low DTC groups were modeled to explore contributions from covariates. An ANOVA model was first used to compare $\log_{10}$ transformed WMH volumes between high and low DTC groups across the Lewy body spectrum (model 1). Subsequent analysis of covariance (ANCOVA) was performed with age as a covariate (model 2) due to its potential association with gait, cognition, and white matter changes. Cardiovascular risk (FCRS) was added (model 3) due to the established relationship with WMH (Moroni et al., 2018). The impact of global cognition was evaluated by including MoCA (model 4). While MDS-UPRDS III did not differ significantly between the high and low DTC group, it has been shown to correlate with WMH volumes (Chen et al., 2021; Jeong et al., 2021); hence, supplementary modeling was performed with it as a covariate.

Estimated marginal means ± standard deviations are reported for the ANOVAs and ANCOVAs. A threshold of $p < 0.05$ was considered statistically significant. With the exception of multiple pair wise comparisons across study groups, multiple

comparisons corrections were not performed, given the exploratory nature of the study.

Results

Controls and Lewy body spectrum groups

Differences in age and sex proportion of the four study groups (CU, PD, PD-MCI, and PDD/DLB) were statistically significant (Table 1). Global cognition, as assessed by MoCA, was significantly different between groups ($p < 0.001$) as expected. Education did not differ significantly between groups ($p = 0.99$). Framingham cardiovascular risk score differed significantly between groups ($p = 0.01$) and was highest in PD-MCI and PDD/DLB groups (*post-hoc* CU vs. PD: $p = 0.9$, CU vs. PD-MCI: $p = 0.02$, CU vs. PDD/DLB: $p = 0.03$). The groups did not differ significantly with respect to disease duration ($p = 0.4$) or MDS-UPDRS III ($p = 0.1$). LEDD significantly differed between the groups ($p = 0.04$); PD-MCI had higher LEDD than PDD/ DLB (*post-hoc* $p = 0.03$). Self-reported gait freezing differed between the PD groups ($p = 0.03$) with the PDD/ DLB group reporting greater freezing than PD (*post-hoc* $p = 0.009$) while the PD and PD-MCI groups were similar (*post-hoc* $p = 0.2$). Baseline gait speed significantly differed between groups ($p < 0.001$) with both the PD-MCI and PDD/DLB groups being slower than the CU and PD groups (*post-hoc* CU vs. PD-MCI: $p = 0.004$, CU vs. PDD/DLB: $p < 0.001$, CU vs. PD, $p = 0.2$). The DTC for counting, fluency, and serial 7s were all significantly different between groups ($p < 0.001$ for counting and fluency, $p = 0.001$ for serial 7s). For all tasks, PD-MCI and PDD/DLB participants had significantly higher DTC compared to CU (*post-hoc* CU vs. PD-MCI: $p = 0.04$ for counting, $p = 0.002$ for fluency and serial 7s; CU vs. PDD/DLB: $p < 0.001$ for counting and fluency, $p = 0.007$ for serial 7s). Cognitive task performance was similar in all groups for counting ($p = 0.2$); but differed for fluency ($p < 0.001$), where the PDD/DLB group performed worse than CU (*post-hoc* $p = 0.02$), and for serial 7s (*post-hoc* $p = 0.001$), where the PD group performed better than the other groups (*post-hoc* PD vs. CU: $p = 0.05$, PD vs. PD-MCI: $p = 0.01$, PD vs. PDD/DLB: $p < 0.001$). We show DTC by group, including the control group in Figure 1.

White matter hyperintensities volume was significantly different across groups for total volume ($p = 0.001$) as well as each lobe (frontal: $p = 0.008$, temporal: $p = 0.002$, parietal, $p = 0.004$, occipital: $p < 0.001$), though this was not significant after correction for age and sex except for the occipital lobe. In uncorrected post hoc comparisons, the PDD/DLB group was significantly different from CU and PD but not PD-MCI with respect to total WMH volume (*post-hoc* CU vs. PDD/DLB: $p = 0.003$, PD vs. PDD/DLB: $p = 0.005$) as well as all lobes (*post-hoc* CU vs. PDD/DLB: frontal $p = 0.02$, temporal $p = 0.005$, parietal $p = 0.001$, occipital $p < 0.001$; PD vs. PDD/DLB: frontal $p = 0.03$, temporal $p = 0.006$, parietal $p = 0.002$, occipital $p < 0.001$). The differences in WMH burden were also evident qualitatively *via* Fazekas score, where total score ($p = 0.003$) and periventricular score ($p < 0.001$) were significantly different between groups, and remained significant after correction for age and sex; the total Fazekas score was greater in PD-MCI and PDD/DLB compared to CU (*post-hoc* CU vs. PD-MCI: $p = 0.03$, CU vs. PDD/DLB: $p = 0.003$) and the periventricular score was greater in all three PD groups vs. CU (*post-hoc* CU vs. PD: $p = 0.04$, CU vs. PD-MCI: $p = 0.005$, CU vs. PDD/DLB: $p = 0.001$). In addition, the PDD/DLB had a higher periventricular score than the PD group (*post-hoc* $p = 0.001$). We show the association between DTC and WMH in Figure 2. We show the difference in total and frontal WMH for each dual task divided by median split in Figure 3.

High vs. low DTC groups

The DTC medians for the Lewy body spectrum were 4.5% for counting, 10.9% for fluency, and 14.5% for serial 7s. After median splitting the Lewy body spectrum participants by DTC, the difference in age was statistically significant in all dual task conditions (Table 2), with the low DTC group being younger (counting: $p = 0.04$, fluency: $p = 0.03$, serial 7s: $p = 0.03$). Sex, years of education, Framingham cardiovascular risk score, disease duration, and LEDD did not significantly differ between the low and high DTC groups across conditions. For all conditions, MoCA was significantly different, with the low DTC group performing better than the high DTC group (counting: $p = 0.01$, fluency: $p < 0.001$, serial 7s: $p = 0.001$). The proportion of patients with freezing of gait only differed between the high and low serial 7s DTC groups ($p = 0.008$), with the high DTC group reporting significantly greater gait freezing. A higher proportion of PD participants were in the low DTC groups, and the majority of PD-MCI and PDD/DLB participants were in the high DTC groups for all conditions (counting: $p = 0.01$, fluency: $p < 0.001$, serial 7s: $p = 0.01$).

As expected, mean DTC and baseline gait speed differed significantly between the low and high DTC groups for all conditions (counting: $p = 0.006$, fluency: $p = 0.001$, serial 7s: $p < 0.001$). Mean DTC for the low DTC groups was significantly lower than the mean for the high group ($p < 0.001$ for all conditions). For usual gait speed, the low DTC group was consistently faster than the high DTC group (counting: $p = 0.006$, fluency: $p = 0.001$, serial 7s: $p < 0.001$). Performance on the cognitive task did not differ between high and low DTC groups for counting ($p = 0.3$) or fluency ($p = 0.5$); however, for serial 7s, the low DTC had more correct subtractions than the high DTC group ($p < 0.001$). Total WMH volume was significantly different between high and low DTC groups for counting only ($p = 0.02$), with the differences predominantly in the frontal ($p = 0.01$) and parietal ($p = 0.03$) lobes. For fluency and serial 7s, the differences in total and lobar WMH volumes were not significantly different between the high and low DTC groups. Similar trends were observed with Fazekas scoring, where the high and low DTC groups for counting differed in total score ($p = 0.03$) and periventricular score ($p = 0.01$), but not for fluency or serial 7s.

Counting dual task cost

Boxplots of $\log_{10}$ transformed WMH volumes are shown in Figures 3A, D for the counting condition. The low DTC group had lower WMH burden which was statistically significant in three

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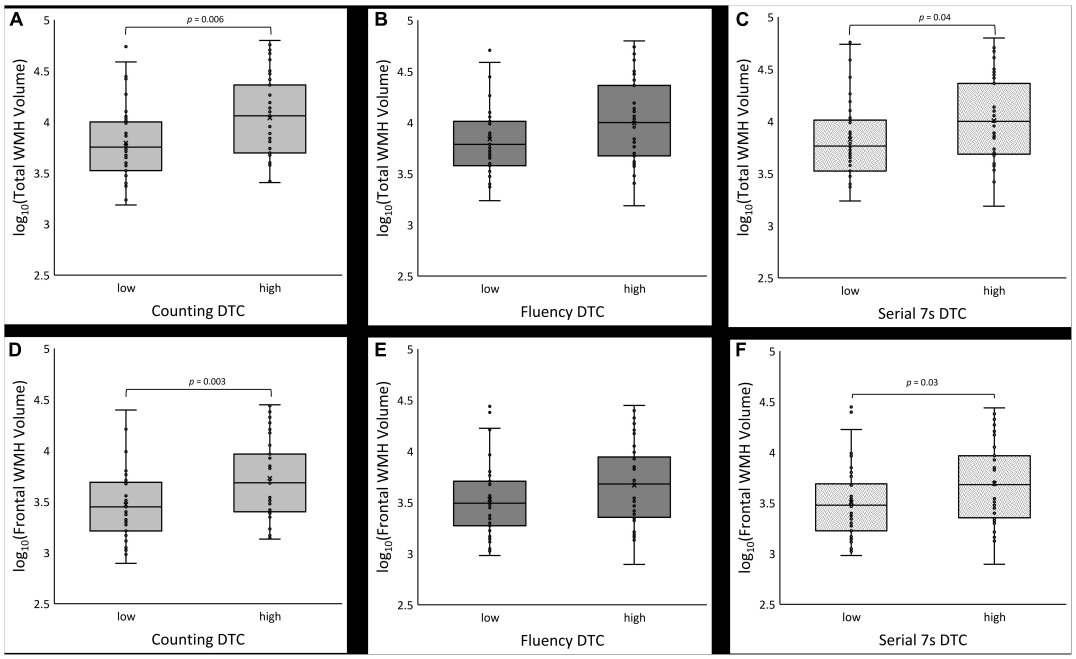

FIGURE 3
Boxplots of $\log_{10}$-transformed total white matter hyperintensity (WMH) volume **(A–C)** and frontal lobe WMH volume **(D–F)** for low vs. high dual task cost (DTC) under counting, fluency and serial 7s conditions, respectively.

of the four models (Table 3). Without covariates (model 1), the estimated difference in the $\log_{10}$ transformed total WMH volume between the low vs. high DTC group was 0.245 (p = 0.006). The frontal, parietal, and occipital lobes had greater WMH burden in the high DTC group compared to the low DTC group (difference = 0.259, p = 0.003 for frontal, difference = 0.319, p = 0.008 for parietal, and difference = 0.177, p = 0.04 for occipital).

For the second model, with age included, the estimated difference in $\log_{10}$ transformed total WMH volumes between the low and high DTC group was 0.133 but was no longer statistically significant (p = 0.07); however, the adjusted R^2 value increased from 0.083 with no covariates to 0.413 for total WMH, with similar trends for all lobes, suggesting age significantly improved the model. While the difference in WMH in the frontal lobe remained significant (difference = 0.154, p = 0.03), the parietal and occipital lobes no longer differed between the low vs. high DTC group for counting.

Including the Framingham cardiovascular risk score as a covariate (model 3) resulted in an estimated difference in $\log_{10}$ transformed total WMH volumes of 0.163 (p = 0.03) between the low and high DTC group. The adjusted R^2 value increased slightly to from 0.413 to 0.428 for total WMH. In this model, the frontal and parietal $\log_{10}$ transformed WMH volumes were greater in the high DTC group (difference = 0.174, p = 0.02 for frontal, difference = 0.213, p = 0.03 for parietal).

In the fourth model, which included age, cardiovascular risk, and MoCA as covariates, the estimated difference between the $\log_{10}$ transformed total WMH volumes of the low and high DTC groups was 0.150 but was not statistically significant (p = 0.053). For total WMH, the adjusted R^2 value slightly decreased to 0.423 from 0.428 with the addition of MoCA. Frontal lobe WMH, however, remained significantly different between the high and low DTC groups (difference = 0.166, p = 0.03). Additional modeling with MDS-UPDRS III as a covariate did not substantially change the above results (see Supplementary material).

Fluency dual task cost

For all models, the difference in the $\log_{10}$ transformed WMH volumes were not significantly different between the low vs. high DTC with the exception of the occipital lobe using the model with no covariates (difference = 0.177, p = 0.04). Similar to counting DTC, adding age improved the model with the adjusted R^2 increasing from 0.026 to 0.388 for total WMH burden with similar changes for all lobes; however, WMH burden was not significantly different between the low and high DTC groups for either the total or any of the lobes. The addition of the Framingham cardiovascular risk and MoCA, as well as additional modeling with MDS-UPDRS III (see Supplementary material), did not alter the results.

Serial 7s dual task cost

In the model with no covariates (Table 3), the $\log_{10}$ transformed WMH volume between low and high DTC groups was significantly different for total volume (difference = 0.181, p = 0.04) as well as in the frontal (difference = 0.180, p = 0.03) and occipital lobes (difference = 0.177, p = 0.04). After controlling for age (model 2), the estimated differences in $\log_{10}$ transformed total or lobar WMH volumes were no longer significant. The adjusted R^2 value for total WMH burden increased from 0.040 from the first model to 0.400 for the second model; again; suggesting the addition of age significantly improved the model. Modeling with the Framingham cardiovascular risk and MoCA did not alter this result (Table 3), nor did the addition of MDS-UPDRS III as a covariate (Supplementary material).

TABLE 2 Demographics and dual task cost (DTC) variables for median split data without cognitively unimpaired healthy participants.

	Low DTC	High DTC	*p*
Counting DTC			
Age (years)	68.2 ± 8.2	71.0 ± 7.6	**0.04**
Females, *N* (%)	13 (33.3)	14 (35.9)	0.8
Education (years)	15.9 ± 2.9	15.9 ± 4.3	1
FCRS (%)	25.6 ± 16.7	22.4 ± 11.9	0.3
MoCA	25.8 ± 4.0	22.9 ± 5.6	**0.01**
Disease duration (years)	6.9 ± 4.4	7.3 ± 5.2	0.7
MDS-UPDRS III	23.1 ± 13.7	25.4 ± 14.1	0.5
LED (mg)	580 ± 366	706 ± 527	0.2
FOG-Q	4.6 ± 5.0	4.7 ± 5.0	0.9
Baseline gait speed (cm/s)	130.5 ± 21.4	114.51 ± 27.88	**0.006**
DTC (%)	−0.5 ± 3.5	14.7 ± 10.6	<**0.001**
Correct on cognitive task	8.6 ± 2.0	8.0 ± 3.4	0.3
Raw WMH volume (mm^3)			
Total	9,261 ± 10,779	16,873 ± 16,939	**0.02**
Frontal lobe	4,279 ± 4,898	7,978 ± 7,564	**0.01**
Temporal lobe	1,144 ± 1,050	1,760 ± 2,157	0.1
Parietal lobe	2,414 ± 3,776	5,236 ± 6,840	**0.03**
Occipital lobe	1,412 ± 1,630	1,887 ± 1,478	0.2
Fazekas score			
Total	2.2 ± 1.1	2.8 ± 1.4	**0.03**
Periventricular	1.1 ± 0.6	1.5 ± 0.8	**0.01**
Subcortical	1.1 ± 0.6	1.3 ± 0.8	0.2
PD/PD-MCI/PDD/DLB (%)	70/15/15	36/28/36	**0.01**
Fluency DTC			
Age (years)	67.1 ± 7.5	71.1 ± 8.2	**0.03**
Females, *N* (%)	15 (38.5)	12 (30.8)	0.5
Education (years)	16.0 ± 2.6	15.8 ± 4.5	0.8
FCRS (%)	22.6 ± 15.2	25.4 ± 13.7	0.4
MoCA	26.2 ± 4.1	22.4 ± 5.2	<**0.001**
Duration of disease (years)	7.3 ± 4.9	7.0 ± 4.8	0.8
MDS-UPDRS III	22.2 ± 3.2	26.3 ± 14.4	0.2
LED (mg)	656 ± 442	630 ± 471	0.8
FOG-Q	4.5 ± 4.7	4.9 ± 5.3	0.7
Baseline gait speed (cm/s)	131.9 ± 22.5	113.1 ± 26.1	**0.001**
DTC (%)	3.0 ± 4.8	20.9 ± 7.8	<**0.001**
Correct on cognitive task	6.1 ± 1.7	5.8 ± 1.8	0.5
Raw WMH volume (mm^3)			
Total	103,712 ± 12,160	15,762 ± 16,434	0.1
Frontal lobe	5,130 ± 6,060	7,127 ± 7,066	0.2
Temporal lobe	1,100 ± 1,003	1,803 ± 2,166	0.07
Parietal lobe	2,769 ± 4,603	4,881 ± 6,455	1.0
Occipital lobe	1,364 ± 1,489	1,934 ± 1,605	1.0
Fazekas score			
Total	2.3 ± 1.3	2.6 ± 1.3	0.3
Periventricular	1.2 ± 0.6	1.5 ± 0.8	0.06
Subcortical	1.2 ± 0.8	1.2 ± 0.6	1
PD/PD-MCI/PDD/DLB (%)	74/13/13	31/31/38	<**0.001**
Serial 7s DTC			
Age (years)	67.7 ± 7.2	70.5 ± 8.8	**0.03**
Females, *N* (%)	15 (38.5)	12 (30.8)	0.5
Education (years)	16.0 ± 3.8	15.7 ± 3.4	0.7
FCRS (%)	23.6 ± 16.0	24.3 ± 12.9	0.8
MoCA	26.1 ± 4.1	22.5 ± 5.3	**0.001**
Duration of disease (years)	6.2 ± 3.8	8.0 ± 5.5	0.09
MDS-UPDRS III	22.5 ± 12.5	26.0 ± 15.1	0.3
LED (mg)	560 ± 391	686 ± 514	0.4
FOG-Q	3.2 ± 3.6	6.2 ± 5.7	**0.008**
Baseline gait speed (cm/s)	132.2 ± 20.0	112.8 ± 27.9	<**0.001**
DTC (%)	5.4 ± 5.4	27.2 ± 10.6	<**0.001**
Correct on cognitive task	3.8 ± 2.1	2.32 ± 1.7	<**0.001**
Raw WMH volume (mm^3)			
Total	1,0434 ± 2,951	15,700 ± 5,840	0.1
Frontal lobe	4,830 ± 5,946	7,427 ± 7,029	0.08
Temporal lobe	1,203 ± 1,269	1,701 ± 2,053	0.2
Parietal lobe	2,868 ± 4,699	4,783 ± 6,416	0.1
Occipital lobe	1,516 ± 1,658	1,780 ± 1,476	0.5
Fazekas score			
Total	2.3 ± 1.2	2.7 ± 1.4	0.2
Periventricular	1.2 ± 0.6	1.4 ± 0.8	0.2
Subcortical	1.1 ± 0.7	1.2 ± 0.7	0.3
PD/PD-MCI/PDD/DLB (%)	70/15/15	36/28/36	**0.01**

DTC, dual task cost; FCRS, framingham cardiovascular risk score; MoCA, Montreal Cognitive Assessment; MDS-UPDRS III, Movement Disorders Society-Unified Parkinson's Disease Rating Scale; LED, levodopa equivalent dose; FOG-Q, Freezing of Gait Questionnaire; WMH, white matter hyperintensities; PD, Parkinson's disease; PD-MCI, Parkinson's disease with mild cognitive impairment; PDD, Parkinson's disease with dementia; DLB, dementia with Lewy bodies. Bold values represent the statistically significant.

Discussion

The goal of this study was to assess the relationship between WMH burden and DTC across the spectrum of Lewy body related diseases. Baseline gait speed differed between the LBD groups, decreasing with increasing cognitive impairment (Table 1) and consistent with other studies (Mielke et al., 2012; Doi et al., 2014;

Stegemöller et al., 2014). Similarly, WMH increased with increasing cognitive impairment. Under all conditions, the low DTC group was younger, had faster usual gait speed, was less cognitively impaired, and had lower WMH burden corresponding (**Figure 1**). Consistent with studies showing frontal brain areas are relevant for dual task walking performance (Kim and Fraser, 2022), dual task gait costs were associated with increased global WMH volume and most consistently with greater frontal WMH volume in the simplest counting backward task. We conclude that DTC may differ based on the secondary task and that WMH are associated with DTC. Age was a significant covariate. The associations were not statistically significant for the other dual task conditions after adjusting for covariates. The influence of different dual tasks on gait may differ between different patient populations (Smith et al., 2017; Raffegeau et al., 2019).

In a CU elderly population, increased volume of deep WMH was associated with slower walking speed under dual task conditions (Ghanavati et al., 2018). A study of patients with dementia showed white matter tract integrity was associated with lower speed under dual task conditions supporting an association between white matter changes and dual task gait performance (Hairu et al., 2021). Toda et al. (2019) concluded that higher WMH burden, measured with Scheltens visual rating scale, was associated with slower speed under dual task conditions in PD.

The overall model between median split DTC and $\log_{10}$ transformed WMH volume was statistically significant for the counting and serial 7s DTC conditions, but not for fluency DTC, without covariates (**Table 3**). Low or high DTC group membership may explain a statistically significant portion of the variance in the total WMH burden. It is not clear why results were only significant after age-adjustment for the counting DTC, but not the other tasks given that some studies suggests that DTC does not depend on the secondary task. One possibility is that there are differences in the impact of different DTCs in the population studied. Alternatively, participants may not have persisted in performing the secondary task. Adding age to the model significantly increased the adjusted R^2 values for the whole model for all conditions, indicating age is an important factor that is associated with WMH and dual task gait (**Table 3**). The literature parallels this finding showing DTC increases and overall cognitive ability decreases, while WMH burden increases, with age (Murman, 2015; Sartor et al., 2017; Garnier-Crussard et al., 2020). Future studies should examine age-related imaging changes, such as brain atrophy and structural and functional connectivity.

Adding cardiovascular risk and MoCA did not significantly increase the adjusted R^2 values (**Table 3**; Moroni et al., 2018). In a study of individuals with severe cerebral small vessel disease, in a younger population, single task and dual task gait performance was relatively preserved and showed little decline compared to healthy controls (Finsterwalder et al., 2019). In our sample WMH increased with cognitive impairment raising the possibility of a neurodegenerative contribution to white matter changes (Dadar et al., 2022). Although a positive correlation between cognitive function and gait speed under normal and dual task conditions has been shown (Chen et al., 2021), the lack of effect seen when MoCA is added to the model suggests that the relationship between DTC and WMH is not solely driven by global cognitive ability. In contrast, Ghanavati et al. (2018) found the relationship between deep WMH and dual task gait was not statistically significant after controlling for global cognition or executive function; however, the participants were cognitively normal community dwelling individuals.

One concern regarding the current study is data collection across multiple sites; however, this was mitigated with harmonized gait and imaging protocols. Furthermore, by using speed measures from electronic walkways (vs. stopwatch) and automated WMH volume measurements, variability and subjectivity was minimized. A major limitation of this study is sample size. Expanding the study to the rest of the COMPASS-ND cohort, which has stopwatch gait data for all participants could address this or examining other cohorts that include the spectrum of LBD (Montero-Odasso et al., 2020). Another limitation is that we did not examine the patients prior to and following taking medications, and hence cannot comment on the impact of medications on DTC and its associations. While many patients had a history of freezing of gait this did not interfere with gait performance, consistent with the patients being in an ON state (Camicioli et al., 1998). We provide the average freezing of gait score for descriptive purposes, but did not specifically examine differences in DTC between patients with or without freezing of gait.

The Lewy body group was treated as a continuous group, given that Lewy body pathology defines the population; but it is possible that other pathologies, particular Alzheimer pathology (Dadar et al., 2021), in addition to vascular pathology are present. Mixed pathology or misdiagnosis could influence the results.

Given sample size, associations between specific cognitive subdomains, dual task gait, and WHM were not examined. In a study of mild cognitive impairment, Alzheimer's disease, and cognitively normal individuals, the visuospatial domain of the MoCA was independently associated with dual task gait measures (Ansai et al., 2017). Another study – of active cognitively normal elderly individuals – also found an association between dual task and the visuospatial/executive domains of the MoCA and Mini-Mental State Exam (Lima et al., 2015). The lack of change observed when MoCA was included in present analyses, could be due to a specific aspect of cognition driving the relationship rather than global cognition. A future direction could be to use MoCA domains or other domain-specific neuropsychological tests to determine which are related to DTC in the Lewy body spectrum and other neurodegenerative disorders with different cognitive profiles, given that stop-watch based DTCs will be available in COMPASS-ND (Montero-Odasso et al., 2020).

Future work could also include a more extensive analysis of dual task gait parameters. Dual task costs could be calculated for gait measures other than speed, like stride length or other specific gait domains, as they may show distinct relationships with specific regional brain changes (Murray et al., 2010; Lord et al., 2012; Pieruccini-Faria et al., 2021).

Some participants may have given up on the verbal tasks midway, as suggested by lower performance in the fluency and serial 7s tasks in the cognitively impaired groups. Such behaviors would not be adequately represented by measures that are averaged over the walking distance, and may account for the lack of statistically significant associations in these models. Additionally,

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TABLE 3 Models of linear univariate analysis with estimated marginal means.

Condition	Lobe	Log_{10} (WMH volume)		Estimated difference	*p*-value	Adjusted R^2
		Low DTC	High DTC			
MODEL # 1: no covariates						
Counting DTC	Total	3.80 ± 0.38	4.04 ± 0.38	0.245	**0.006**	0.083
	Frontal	3.47 ± 0.37	3.73 ± 0.37	0.259	**0.003**	0.100
	Temporal	2.90 ± 0.39	3.04 ± 0.39	0.143	0.1	0.02
	Parietal	3.08 ± 0.52	3.40 ± 0.52	0.319	**0.008**	0.078
	Occipital	2.97 ± 0.37	3.15 ± 0.37	0.177	**0.04**	0.044
Fluency DTC	Total	3.84 ± 0.39	4.00 ± 0.39	0.156	0.08	0.026
	Frontal	3.53 ± 0.39	3.67 ± 0.39	0.138	0.1	0.019
	Temporal	2.89 ± 0.39	3.05 ± 0.39	0.154	0.09	0.025
	Parietal	3.13 ± 0.53	3.35 ± 0.53	0.222	0.07	0.031
	Occipital	2.97 ± 0.37	3.15 ± 0.37	0.177	**0.04**	0.043
Serial 7s DTC	Total	3.83 ± 0.39	4.01 ± 0.39	0.181	**0.04**	0.040
	Frontal	3.51 ± 0.38	3.69 ± 0.38	0.180	**0.03**	0.054
	Temporal	2.89 ± 0.39	3.04 ± 0.39	0.150	0.1	0.023
	Parietal	3.12 ± 0.52	3.35 ± 0.52	0.230	0.06	0.034
	Occipital	2.97 ± 0.37	3.15 ± 0.37	0.177	**0.04**	0.043
MODEL #2: age						
Counting DTC	Total	3.85 ± 0.31	3.98 ± 0.31	0.133	0.07	0.413
	Frontal	3.52 ± 0.31	3.68 ± 0.31	0.154	**0.03**	0.409
	Temporal	2.95 ± 0.34	2.99 ± 0.34	0.040	0.6	0.313
	Parietal	3.15 ± 0.42	3.32 ± 0.42	0.169	0.08	0.406
	Occipital	3.01 ± 0.33	3.11 ± 0.33	0.100	0.2	0.253
Fluency DTC	Total	3.90 ± 0.32	3.93 ± 0.32	0.035	0.6	0.388
	Frontal	3.59 ± 0.31	3.61 ± 0.31	0.020	0.8	0.372
	Temporal	2.95 ± 0.34	2.99 ± 0.34	0.045	0.6	0.314
	Parietal	3.21 ± 0.42	3.27 ± 0.42	0.061	0.5	0.384
	Occipital	3.02 ± 0.33	3.11 ± 0.33	0.090	0.2	0.252
Serial 7s DTC	Total	3.87 ± 0.32	3.96 ± 0.32	0.094	0.2	0.400
	Frontal	3.55 ± 0.31	3.65 ± 0.31	0.103	0.1	0.389
	Temporal	2.93 ± 0.33	3.00 ± 0.33	0.072	0.3	0.319
	Parietal	3.18 ± 0.42	3.29 ± 0.42	0.114	0.2	0.392
	Occipital	3.03 ± 0.33	3.09 ± 0.33	0.060	0.5	0.243
MODEL #3: age and FCRS†						
Counting DTC	Total	3.84 ± 0.31	4.00 ± 0.31	0.163	**0.03**	0.428
	Frontal	3.52 ± 0.31	3.69 ± 0.31	0.174	**0.02**	0.414
	Temporal	2.93 ± 0.33	3.01 ± 0.33	0.080	0.3	0.351
	Parietal	3.13 ± 0.42	3.35 ± 0.42	0.213	**0.03**	0.428
	Occipital	3.00 ± 0.34	3.12 ± 0.33	0.121	0.1	0.266
Fluency DTC	Total	3.90 ± 0.31	3.94 ± 0.32	0.039	0.6	0.391
	Frontal	3.59 ± 0.32	3.62 ± 0.32	0.024	0.7	0.369
	Temporal	2.95 ± 0.33	3.00 ± 0.33	0.049	0.5	0.344
	Parietal	3.21 ± 0.43	3.28 ± 0.42	0.068	0.5	0.395
	Occipital	3.02 ± 0.34	3.11 ± 0.33	0.094	0.2	0.257

(Continued)

TABLE 3 (Continued)

Condition	Lobe	Log_{10} (WMH volume)		Estimated difference	*p*-value	Adjusted R^2
		Low DTC	High DTC			
Serial 7s DTC	Total	3.88 ± 0.31	3.97 ± 0.31	0.091	0.2	0.401
	Frontal	3.56 ± 0.31	3.65 ± 0.32	0.096	0.2	0.382
	Temporal	2.93 ± 0.33	3.01 ± 0.33	0.078	0.3	0.350
	Parietal	3.19 ± 0.42	3.29 ± 0.43	0.105	0.3	0.400
	Occipital	3.04 ± 0.34	3.09 ± 0.34	0.040	0.5	0.246
MODEL #4: age, FCRS, and MoCA[†]						
Counting DTC	Total	3.85 ± 0.32	4.00 ± 0.32	0.150	0.053	0.423
	Frontal	3.52 ± 0.32	3.68 ± 0.32	0.166	**0.03**	0.407
	Temporal	2.93 ± 0.34	3.02 ± 0.34	0.088	0.3	0.342
	Parietal	3.15 ± 0.44	3.33 ± 0.43	0.187	0.07	0.427
	Occipital	3.02 ± 0.34	3.10 ± 0.34	0.080	0.3	0.288
Fluency DTC	Total	3.92 ± 0.33	4.00 ± 0.32	0.012	0.9	0.392
	Frontal	3.60 ± 0.32	3.60 ± 0.33	0.000	1	0.368
	Temporal	2.95 ± 0.34	3.00 ± 0.34	0.050	0.5	0.335
	Parietal	3.23 ± 0.44	3.25 ± 0.44	0.023	0.8	0.401
	Occipital	3.04 ± 0.34	3.08 ± 0.34	0.045	0.6	0.281
Serial 7s DTC	Total	3.89 ± 0.32	3.96 ± 0.33	0.071	0.4	0.399
	Frontal	3.56 ± 0.32	3.64 ± 0.32	0.081	0.3	0.377
	Temporal	2.93 ± 0.34	3.02 ± 0.34	0.083	0.3	0.341
	Parietal	3.21 ± 0.43	3.28 ± 0.44	0.067	0.5	0.404
	Occipital	3.06 ± 0.33	3.06 ± 0.33	0.000	1	0.378

[†]One participant was missing data needed to calculate FCRS thus is not included in analysis for Models #3 and 4. WMH, white matter hyperintensity; DTC, dual task cost; FCRS, framingham cardiovascular risk score. Bold values represent the statistically significant.

the analysis did not control for the possibility of a cueing effect, whereby participants walk faster while completing a rhythmic task like counting.

Conclusion

In this study, higher dual task gait cost with counting backward was associated with increased frontal WMH burden in participants across the spectrum of LBD, independent of age, vascular risk and MoCA score. However, the relationship appears to be strongly influenced by age. The impact of age-related neurodegeneration should be examined in future analyses and specific interventions, such as dual task training, should be examined to improve DTC. The study provides support for using the counting DTC as a practical task and motivates further examination of the neural substrates of DTC.

Data availability statement

The datasets presented in this article are not readily available because data will become publicly available after the data acquisition phase of the COMPASS-ND study is completed and 1 year has passed. Requests to access the datasets should be directed to randi.pilon@ladydavis.ca.

Ethics statement

The studies involving human participants were reviewed and approved by the University of Alberta Health Ethics Research Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

IF drafted the manuscript with MG, KN, and RC. MG, KN, BS, MM, SB, ES, FP-F, and MM-O contributed to acquisition of data. IF, MG, FB, MD, SD, BS, MM, SB, ES, QA, and FP-F contributed to data analysis. RC provided the overall project oversight. All authors contributed to conceptualization of the project and reviewed the 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.

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Supplementary material

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Does bimanual coordination training benefit inhibitory function in older adults?

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Introduction: Whether complex movement training benefits inhibitory functions and transfers the effects to non-practiced motor and cognitive tasks is still unknown. The present experiment addressed this issue using a bimanual coordination paradigm. The main hypothesis was that bimanual coordination training allows for improving the involved cognitive (i.e., inhibition) mechanisms and then, transferring to non-practiced cognitive and motor tasks, that share common processes.

Methods: 17 older participants (72.1 ± 4.0 years) underwent 2 training and 3 test sessions (pre, post, and retention one week after) over three weeks. Training included maintaining bimanual coordination anti-phase pattern (AP) at high frequency while inhibiting the in-phase pattern (IP). During the test sessions, participants performed two bimanual coordination tasks and two cognitive tasks involving inhibition mechanisms. Transfer benefits of training on reaction time (RT), and total switching time (TST) were measured. In the cognitive tasks (i.e., the Colour Word Stroop Task (CWST) and the Motor and Perceptual Inhibition Test (MAPIT)), transfer effects were measured on response times and error rates. Repeated one-way measures ANOVAs and mediation analyses were conducted.

Results: Results confirmed that training was effective on the trained task and delayed the spontaneous transition frequency. Moreover, it transferred the benefits to untrained bimanual coordination and cognitive tasks that also involve inhibition functions. Mediation analyses confirmed that the improvement of inhibitory functions mediated the transfer of training in both the motor and cognitive tasks.

Discussion: This study confirmed that bimanual coordination practice can transfer training benefits to non-practiced cognitive and motor tasks since presumably they all share the same cognitive processes.

KEYWORDS

bimanual coordination training aging, cognition, inhibition function, cognitive-motor training, bimanual coordination

1. Introduction

As we age, cognitive functions undergo a decline that is often considered a forerunner of neurodegeneration and loss of behavioral adaptability in everyday tasks. It is now widely admitted that these alterations can be attenuated or delayed in healthy older adults by cognitively and physically enriched life habits. Therefore, understanding how effective training protocols can prevent cognitive decline in healthy older adults is a major challenge for the aging research community (Erickson et al., 2013; Voss and Jain, 2022).

For a long time, age-related alterations in cognitive and motor domains have been considered separately (Zapparoli and Mariano, 2022). Accordingly, cognitive training was hypothesized to be the only means to improve cognitive functioning. By demonstrating the benefits of aerobic exercise on cognition, Colcombe and Kramer (2003) played a pivoting role in the Copernican revolution that led to considering physical exercises as a critical means to enhance brain functions and cognitive performance. Since then, several studies have confirmed the benefits of endurance and muscular resistance training on executive functions, attention and memory (e.g., Netz, 2019). More recently, it has been reported that older individuals that have a high level of motor fitness (Voelcker-Rehage, 2008; Voelcker-Rehage et al., 2010; Ludyga et al., 2020) or who participated in complex coordination training programs demonstrated superior cognitive performance, especially in executive functions and perceptual speed (Voelcker-Rehage et al., 2011; Niemann et al., 2014). These findings suggested that repetitive practice of complex movements might be a very effective strategy to improve brain functions and cognition in older adults due to embodiement of cognition in human behavior (e.g., Raab and Araújo, 2019). It might be the case since, due to the so-called age-related cognitive-motor dedifferentiation, cognitive mechanisms and their related brain structures become more and more involved in movement control (e.g., Sleimen-Malkoun et al., 2013). However, while there is abundant literature on the effects of endurance or muscular resistance training on cognitive performance interventional studies that have investigated whether and how complex movement training may transfer to the efficiency of cognitive functions in older adults are scarce. The present experiment addressed this issue by using a rhythmic bimanual coordination paradigm.

In a laboratory context, bimanual coordination is frequently characterized by two stable and flexible patterns [in-phase (IP) and anti-phase (AP)] (Kelso, 1984). Conventionally, the in-phase (IP) pattern is achieved through the simultaneous activation of homologous forearm muscles groups thereby giving rise to mirror-symmetrical movements concerning the body midline; while the anti-phase pattern (AP) is achieved through the simultaneous activation of non-homologous muscles groups thereby one limb moves toward the body midline, while the other limb moves away from it and vice versa (e.g., Temprado et al., 2010, 2020). AP and IP coordination patterns can be captured by the value of relative phase (RP) between the two hands (180° and 0°, respectively), while their stability can be indexed by the magnitude of fluctuations of RP (i.e., the SD of RP) (Kelso, 1984; Haken et al., 1985; Temprado et al., 2010). The dynamics of bimanual coordination reflect i) the existence of these stable patterns and ii) the appearance of spontaneous transitions from AP to IP when the frequency of movements increases.

Over the last 20 years, the role of cognition in the control of bimanual coordination patterns has been the subject of numerous studies in young (Lee et al., 1996; Pellecchia and Turvey, 2001; Temprado et al., 2002, 2010; Pellecchia et al., 2005; Shockley and Turvey, 2005) and older adults (Wishart et al., 2000; Lee et al., 2002; Temprado et al., 2010, 2020). In particular, it has been shown that attention and/or inhibition mechanisms were involved in bimanual coordination (e.g., Fujiyama et al., 2009; Levin et al., 2014), in the voluntary stabilization of existing patterns (Monno et al., 2002; Temprado et al., 2010), in the inhibition of spontaneous transitions (Lee et al., 1996; Temprado et al., 2002), and in the voluntary transition between the AP and IP patterns (Temprado et al., 2020). These findings open the door to the development of training protocols, grounded on bimanual coordination tasks, to improve the efficiency of cognitive functioning in older adults, and especially, inhibition functions, which are highly affected by age-related decline. In the present study, we capitalized on this framework to investigate whether, in healthy older adults, bimanual coordination training in conditions that required strong involvement of inhibition processes transferred to non-practiced cognitive and motor tasks also involving inhibitory mechanisms.

To verify this hypothesis, we assessed the effects of bimanual coordination training on the ability to maintain the AP pattern at high oscillations frequencies that is, to inhibit spontaneous transition to the IP pattern. According to a previous study (Temprado et al., 2002), we expected to observe that training delayed the transition frequency at which the spontaneous transition occurred. Then, we assessed the consequences of bimanual coordination training on performance in a non-practiced intentional pattern switching task (AP to IP et IP to AP), similar to those previously used by Temprado et al. (2020). To fulfill this objective, we assessed transfer effects of training in post-test and retention test conditions carried out immediately and 1 week after the training session, respectively. Consistent with a previous study (Temprado et al., 2002), the retention test should allow to determine whether an overcompensation of training effects take place during the retention period.

We expected to observe a decrease in switching times, especially for the AP to IP direction, as a result of bimanual training. Finally, we tested the effects of bimanual training in two non-practiced cognitive tasks that is, the Color Word Stroop Test and the MAPIT. We expected to observe decreases in response times, in the two tasks. Such results would demonstrate the existence of transfer effects, presumably due to the training of common (inhibition) processes between the bimanual coordination task and the non-practiced cognitive tasks. To further understand the transfer effects, if existed, we used mediation analyses to determine whether performance improvement in the non-practiced tasks resulted from the mediation of inhibition mechanisms trained during bimanual coordination practice.

2. Methods

2.1. Participants

Only older adults were tested. Seventeen participants, 6 women and 11 men (mean age 72.18 ± 4.04), were included according to the following self-reported criteria: (i) age ≥ 65 ≤ 80 years, (ii) normal or corrected-to-normal vision and hearing, and (iii) agreeing to follow the entire protocol (5 participants weren't able to finish the program). The non-inclusion criteria were: (i) pain or disability affecting the hand, arm, or shoulder (e.g. arthritis), (ii) upper or lower limb surgery in the last 6 months, (iii) an Mini Mental State Ewamination (MMSE) score ≤24 (Trzepacz

et al., 2015) (mean 28.8 ± 1.2). Participants signed written informed consent.

2.2. Design

The protocol was approved by the French ethic committee CERSTAPS IRB00012476-2022-12-05-181. It consisted of two training sessions in a bimanual coordination task and three testing sessions (pre-test, post-test, and retention) in two bimanual coordination tasks and two cognitive tasks. In each testing session, both training and transfer effects were assessed. Training effects were assessed in the practiced bimanual coordination task while transfer effects were assessed in the non-practiced motor and cognitive tasks. The 5 sessions (of about 75 min each) were spread over 3 weeks. During the first week, participants completed the pre-test. During the second week, they performed two training sessions and one post-test session on three different days (i.e., with 1 day off in between). During the third week, 7 days after the second training session, they performed the retention test (see Table 1). For the evaluation session, the order of presentation of cognitive and motor tests were randomized. Exception was made for the spontantaneous transition frequency test, which served as assessment test and, accordingly, was always performed before the others.

2.3. Intervention

Participants had to perform the AP pattern, starting at the transition frequency (TF) identified in the pre-test, minus 0.25 Hz (see below). The training frequency was then increased gradually by 0.25 Hz after each block of 10 trials. They were instructed to resist to the transition to IP that is, to inhibit the switching from AP to IP (see description of patterns in Figure 1). Bimanual coordination training was divided in two separate sessions of 50 trials each (i.e., a total of 100 trials of 20 s).

2.4. Testing

Two motor and two cognitive tasks were used during the testing sessions. The effect of bimanual coordination training was assessed through the measurement of changes in the spontaneous transition frequency (TF), while transfer effects were assessed through performance measurement in (unpracticed) intentional switching motor task, Stroop task and the MAPIT, respectively.

2.4.1. Spontaneous transition frequency

The spontaneous transition frequency (TF) between the AP and IP patterns was measured in each testing session. The bimanual coordination task consisted of pronation-supination movements of the forearms in the frontal plane, in synchronization with a metronome according to the AP or IP pattern. For each of the two coordination patterns, 3 to 5 familiarization trials, consisting of oscillating at their spontaneous frequency, were provided to participants. Then, the transition frequency was determined by asking participants to perform the AP pattern, following an auditory metronome. The oscillation frequency was increased from 1 to 3 Hz by steps of 0.25 Hz, changing every 10 s. They were instructed not to resist when they felt they were losing the AP coordination for the easier IP pattern. Ten trials were performed. The effective frequency at which transition occurred to the IP pattern (which may be different from the frequency prescribed by the metronome) was recorded online by a lab-customized LabVIEW program. The effective frequency at which a transition was observed for at least 60% of the trials was considered the reference frequency for the training session. Effective oscillation frequencies were calculated based on averaged cycle periods in each metronome condition. Mean values of discrete relative phase (DRP) allowed us to determine when the transition started.

The procedure used to analyze bimanual coordination performance was similar to the one used by Temprado et al. (2020). The raw signals were processed with two customized Matlab routines (MathWorks Inc, Natick, M.A, United States). The first 5 s of each trial allowed to ensure that a stable pattern was performed. They were filtered with a Butterworth filter (cut-off frequency 10 Hz, order 2). Then, the amplitude centering procedure was used to remove frequency artifacts of the non-sinusoidal signals, when existing. According to Lamb and Stöckl (2014), the normalization was based on the function:

$$\left(y\left(ti\right)\right) = 2\left(\frac{2(y\left(ti\right) - \min\left(y\left(t\right)\right))}{\max\left(yt\right) - \min\left(y\left(t\right)\right)}\right) - 1$$

This function transformed the original values y(t) in such a way that the minimum value of g(y(t)) equals −1 and the maximum value of g(y(t)) equals 1.

Detection of spontaneous transition frequency. Effective oscillation frequencies were calculated on the basis of averaged cycle periods in each metronome conditions. Then, mean values and SD of discrete relative phase (DRP) were calculated and tracked to determine when the transition started. The transition was considered starting when the last value of DRP = 180° ± 45° was followed by five consecutive DRP values lower than 135°. The same procedure was applied to identify the end of transition to the IP pattern. The transition considered accomplished when the value of DRP post-transition was equal to 0°±45° for at least 3 consecutive cycles. Notably, a transition occurring during the first second of a given step of frequency was considered occurring in the previous step.

2.4.2. Intentional switching between bimanual coordination patterns

Performance in intentional switching tasks was assessed, in two directions (APtoIP and IPtoAP) to determine whether the effects of bimanual coordination training transferred to an unpracticed motor task presumably involving similar inhibition mechanisms. Two blocks of 10 trials from AP to IP and from IP to AP were presented in random order. The oscillation frequency was paced by a metronome set at the transition frequency (TF) identified in the pre-test, minus 0.25 Hz. Between the 15th and 18th s, the metronome was changing its signal's tone, indicating to the

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TABLE 1 Overview of the protocol.

	First week	Second week			Third week
	Pre-test	First training session	Second training session	Post-test	Retention-test
Cognitive test	MMSE Stroop test MAPIT test	50 trials of AP at increasing frequency	50 trials of AP at increasing frequency	Stroop test MAPIT test	Stroop test MAPIT test
Bimanual coordination tests	Spontaneous transition frequency detection test (10 trials) Intentional switching: 10 trials in each direction (IPtoAP and APtoIP)			Spontaneous transition frequency detection test (10 trials) Intentional switching: 10 trials in each direction (IPtoAP and APtoIP)	Spontaneous transition frequency detection test (2 x 10 trials) Intentional switching: 10 trials in each direction (IPtoAP and APtoIP)

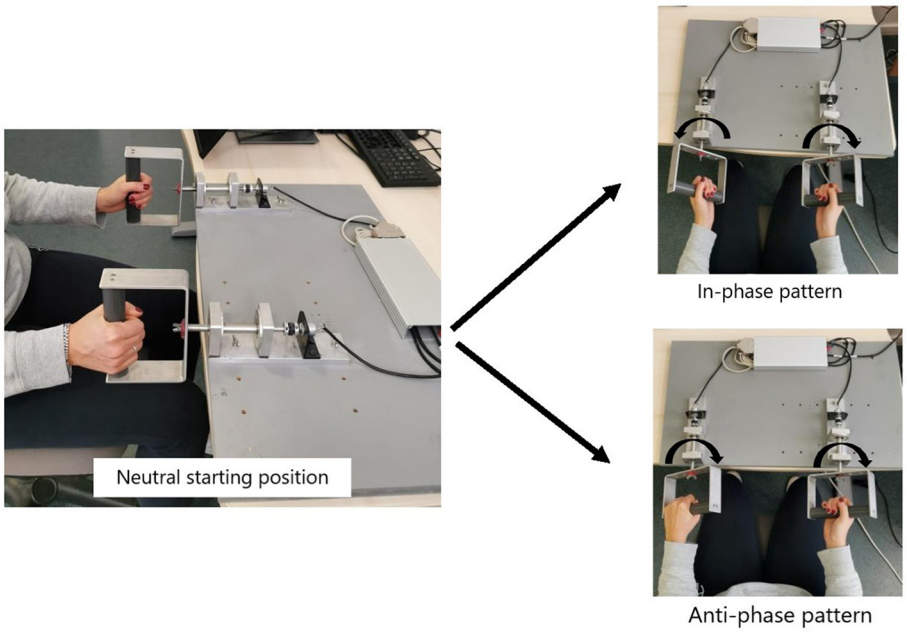

FIGURE 1
Device used for the bimanual coordination task and visual representation of IP (In-phase) and AP (Anti-Phase) patterns.

participants to change as fast as possible from the ongoing pattern to the other one. Each trial lasted 30 s.

According to our previous study (Temprado et al., 2020), to analyze intentional switching, in each condition, we calculated the continuous relative phase (CRP), after the application of the Hilbert transform sign according to the following formula:

$$CRP\ (t_i\ ) = CRP_{left}\ (t_i\ )\ CRP_{right}\ (t_i\ )$$
$$\arctan\left(\frac{H_1\ (t_1)\ x_2\ (t_1) - H_2\ (t_1)\ x_1\ (t_1)}{x_1\ (t_1)\ x_2\ (t_1) - H_{21}\ (t_1)\ H_2\ (t_1)}\right)$$

Then, we calculated the mean and SD of the CRP for each participant. After calculation, the times series of CRP were divided into pre-switching and post switching phases (Lamb and Stöckl, 2014). For the pre-switching phase, we calculated the mean and SD of CRP. CRP artifact was taken into consideration, two cycles before and one after were deleted, so we calculated the CRP two cycles before and one after our region of interest. The TST was defined as the time lapsing between the switching signal and the first mean value of CRP post-transition that preceded at least 3 s of stabilization within a range of 45° around the CRP value corresponding to the requested pattern (i.e., either IP or AP). In addition, the switching phase was decomposed into RT that is, the interval between the signal of changing given by the metronome and the first value of RP outside of +/– 45° of the value corresponding to the currently performed pattern (i.e., 180° or 0°).

Reaction times (RT) and Total Switching Times (TST) were calculated for the two switching directions. In each condition, continuous relative phase (CRP) was calculated for each participant. Then, the times series of CRP were divided into pre-switching and post-switching phases (Lamb and Stöckl, 2014). For the pre-switching phase, two measures of response times were defined (see Temprado et al., 2020, for a similar procedure). The TST was the time lapse between the switching signal and the first mean value of CRP post-transition that preceded at least

3s of stabilization within a range of 45° around the CRP value corresponding to the requested pattern (i.e., either IP or AP). The RT was the interval between the signal of change given by the metronome and the first value of RP outside of +/− 45° of the value corresponding to the currently performed pattern (i.e., 180° or 0°) (see Figure 2 for visual details).

2.4.3. Cognitive and motor inhibition

The Color Words Stroop Test (CWST) was used to test cognitive inhibition. It was carried out on a computer with lab-customized software. Participants were comfortably seated in front of a screen (Dell24 P2418HT, 23.8 inches). A colored word appeared on the screen and they were asked to indicate the color of the word by pressing the corresponding letter on the keyboard in front of them as quickly as possible. The keyboard was adapted so that only the letters required for the test were visible on the keyboard. Four different colors were used: green, blue, red, and yellow. Thus, depending on the consistency between semantics and color, the condition was considered either congruent (C) or incongruent (I). Neutral trials (N) were also presented in different words (e.g., arm, leg...) and were written in one of the different colors (green, blue, red, and yellow). After familiarization with 9 words not used for the test, 75 trials were presented randomly for testing (25 congruent, 25 incongruent, and 25 neutral; color words and answers per color were balanced). Each word remained on the screen until the answer was given. In each condition, the number of errors and the reaction time (RT) that is, the time elapsed between the appearance of the word and the pressing of the key on the keyboard, were recorded. Using a similar procedure as those used by Temprado et al. (2020), we didn't calculate inhibition costs.

The MAPIT (Nassauer and Halperin, 2003; Jennings et al., 2011) was used to assess, separately, perceptual (PI) and motor inhibition (MI). The test was carried out on a computer lab-customized software (ICE ® software, https://trello.com/b/EtNCNrZH/ice). Its general principle consisted of responding as fast as possible to the direction or location of arrows presented on the screen (Dell24 P2418HT, 23.8 inches) by pressing a corresponding key on a modified keyboard, in which only two keys ("Q" and "M"), used for the right direction and left directions, respectively, were visible (see Figure 3). Each trial started with the fixation of a black cross presented in the center of the screen, which disappeared when the arrow appeared and remained on the screen until the participant pressed the key. The test consisted of 3 different blocks of trials designed to assess either perceptual or motor inhibition (see Figure 3): (i) *a preliminary block* of 80 trials used as familiarization in which participants had to press the key corresponding to the direction an arrow or square's location on the screen (i.e., either right or left), (ii) *a perceptual inhibition block* of 80 trials in which participants had to press the button corresponding to the direction of the arrow's pointing, even if the location of the arrow was opposite (e:g. arrow pointing to the left and placed on the right of the screen), and (iii) *a Motor inhibition block* of 80 trials in which the arrows were presented in the center of the screen and participants were asked to either to press the button corresponding to the direction of the arrow's pointing, or the opposite direction (for details see supplementary material). Based on measured median reaction times (RT) (Jennings et al., 2011), perceptual (PI) and motor (MI) interference scores were calculated as follows:

PI = Median RT of the perceptual incongruent – Median RT of the perceptual congruent condition

MI = Median RT of the motor incongruent condition – Median RT of the motor congruent condition.

2.5. Statistical analyses

One-way repeated-measures ANOVAs (SPSS Inc., Chicago, IL, USA) were used to compare the performance measured during pre-test, post-test, and retention test in: (i) the trained bimanual coordination task (transition frequency, TF). A two-ways ANOVA was used to test the effects of time (test) and direction (APtoIP/IPtoAP) on switching times in the bimanual switching task, while two ways (condition x time) ANOVAs were used to compare the performance observed in the CWST (RT of neutral, congruent, and incongruent conditions) and in the MAPIT (for PI and MI interference scores). The Shapiro-Wilk Normality test was performed before all, and Newman—Keuls *post hoc* analysis was also run.

In addition, mediation analyses were carried out following the procedures from mediation and moderation in repeated measures design, using the MEMORE macro for IBM SPSS Statistics (IBM Corp., Armonk, NY, United States) (Montoya and Hayes, 2017). Mediation analysis allows to quantify the degree to which a mediator (M) acts as the "mechanism" by which an independent factor (X) affects an outcome (Y). In this variant of mediation analysis, X does not actually exist in the data and represents the effect of the intervention influencing M and Y over time. The effects of bimanual coordination training (X) on Y corresponded to the total effects "c", and the effects of the training on Y while controlling for the mediator are called the direct effects "c". The effects of the training on M corresponded to the "a" path and the effects of M on Y to the "b" paths. The amount of mediation, the indirect effect ("ab"), refers to the role of the mediator (M) in the effect of the training on Y. We tested the significance of the indirect effects using bias-corrected bootstrap confidence intervals (CIs) (based on 2000 bootstrap samples). CI that did not contain zero represents significant effects, and therefore significant mediation of X on Y through M. The centrality and normality of the residuals were verified.

Two sets of mediation analysis were carried out. The first one aimed to determine whether training-related enhancement of intentional switching variables (i.e., RT and TST) was mediated by improvements in inhibition capacities, as measured by the CSWT and the MAPIT. The second set of analyses aimed to determine whether transfer effects observed in CWST and MAPIT were mediated by enhanced performance in the intentional switching task. The threshold chosen for statistical significance is $p<0.05$ (details in Figure 4). This type of mediations analysis has been recently widely used in a variety of research domains related to interventions, and in different populations (Bell et al., 2018; Boidin et al., 2020; Sidhu and Cooke, 2021).

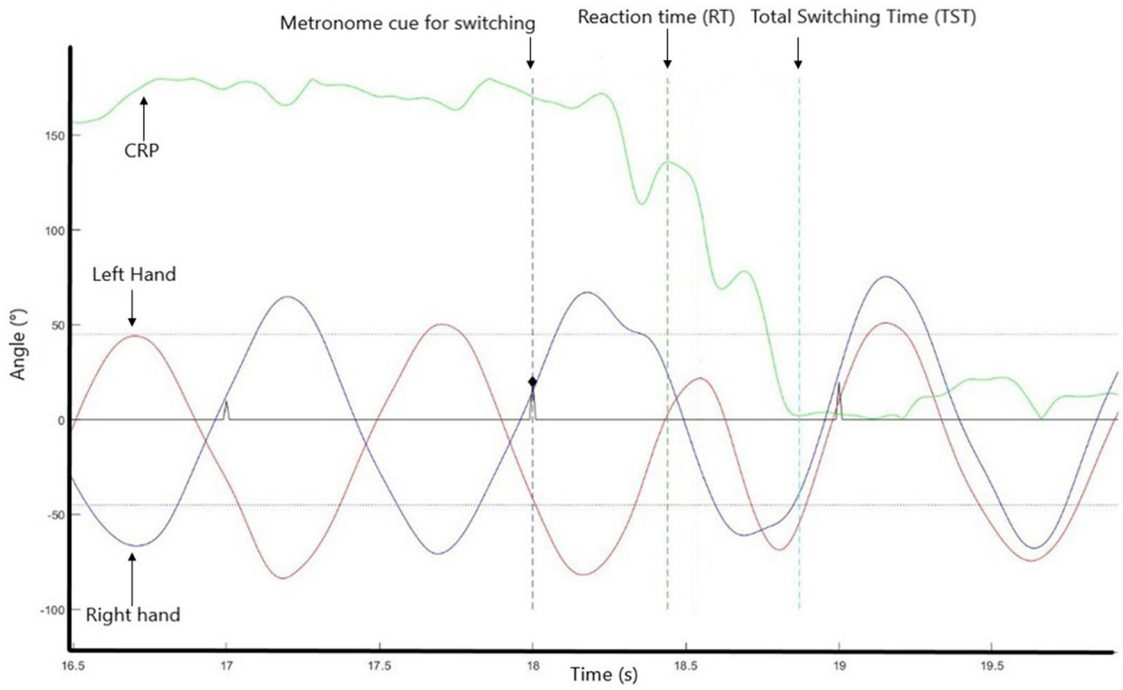

FIGURE 2
Decomposition of the switching phase into different sub-parts.

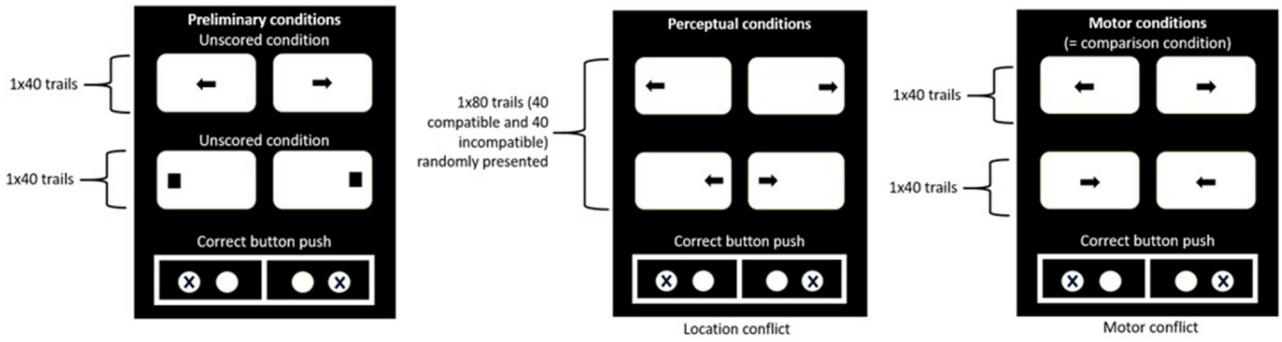

FIGURE 3
Panels of stimuli presented in the different conditions of the MAPIT.

3. Results

3.1. Training effects on the maintenance of the AP pattern

The one-way ANOVA performed on the mean effective transition frequency revealed an effect of time [$F_{(2,32)} = 69.83$, $p < 0.01$]. For testing sessions, he Newman-Keuls *post-hoc* test revealed a significant improvement between the pre-test (1.68 ± 0.28) and the post-test (2.15 ± 0.32), as well as between the pre-test and the retention test (2.16 ± 0.37), of about 0.5 Hz, on average. In other words, transition frequency was significantly delayed after bimanual coordination training.

3.2. Transfer to the untrained intentional switching task

For TST, the two-ways ANOVA revealed significant main effects of direction [$F_{(1,31)} = 49.20$, $p < 0.01$] and time [$F_{(2,62)} = 20.49$, $p < 0.01$]. Specifically, the Newman-Keuls *post-hoc* test carried out on the two directions of switching revealed that TST was longer for the IP to AP direction than for the AP to IP direction (1,668 ± 525.04 ms, and 865 ±248.2 ms, ($p < 0.00$). Moreover, the post hoc analysis carried out on testing sessions revealed that independently of the switching direction, the TST observed in the pre-test was significantly longer than in the post-test and retention [1,505 ± 664.66 ms > 1,181 ± 530.79 and 1,151 ±474.27 ms; $p <$

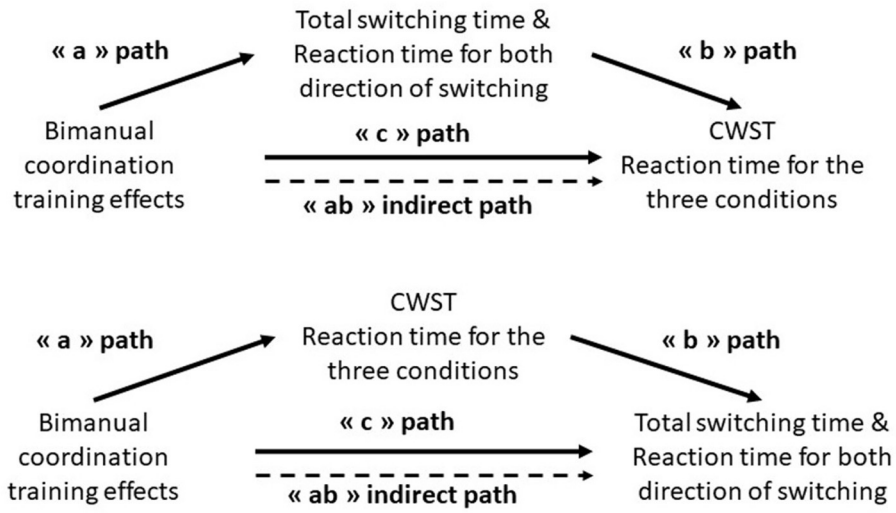

FIGURE 4
Illustration of the two mediation models.

0.001]. For RT, main effects of direction [$F_{(1,31)} = 5.59$, $p < 0.05$] and time [$F_{(2,62)} = 3.74$, $p < 0.05$] were observed. Specifically, the Newman-Keuls *post-hoc* test carried out on the two directions of switching revealed that RT was longer in the AP to IP direction than in the IP to AP direction (348 ± 83.65 ms, and 310 ± 59.92 ms; $p < 0.02$). Moreover, the *post-hoc* analysis carried out on testing sessions revealed that independent of the switching direction, RT was significantly longer during the pre-test than during the post-test and the retention test (358 ± 103.61 ms >319 ± 63.21 ms and 308 ± 67.97 ms; $p < 0.03$).

3.3. Transfer to the untrained cognitive tasks

For the CWST, the two-ways ANOVA revealed main effects of condition [$F_{(2,48)} = 3.28$, $p < 0.05$] and time [$F_{(2,96)} = 47.30$, $p < 0.01$] on response time. The incongruent condition was always slower than the congruent one, independent of the testing time (1,277 ms and 1,099 ms, respectively). Moreover, response times were shorter in the both the post-test and the retention test than in the pre-test ($p < 0.05$). Also, responses times were shorter in the retention test than in the post-test (pre-test: 1,272 ms; post-test: 1,168 ms; retention test: 1,090 ms). Interaction time x condition effect was not significant ($p > 0.63$).

For the MAPIT, the analysis revealed an effect of time on MI score [$F_{(2,30)} = 3.56$, $p < 0.05$], which improved between the pre-test and the retention test (145 ms and 86 ms, respectively). A tendency ($p = 0.07$) was observed for the difference between the pre-test and the post-test 145 and 105 ms, respectively).

3.4. Mediation analyses

The results of the first set of mediation analyses are presented in Tables 2, 3. A significant indirect effect was found for the effect of the bimanual coordination training on the reaction time of the incongruent condition of the CWST, through the TST (52.5% of the total effect) and RT (23.8% of the total effect); in the AP to IP direction. The direct effect (≪ c' ≫) was not significant after taking into account the mediators, being consistent with a full mediation hypothesis (the training no longer affects Y after controlling for M). All other mediation analyses were inconsistent (negative ≪ ab ≫) or not significant. The results of the second set of mediation analyses are presented in Table 3. A significant indirect effect was found for the effect of the bimanual coordination training on the TST in the AP to IP direction, mediated by the RT observed in the incongruent condition of the CWST (39.0 % of the total effect). The direct effect (≪ c' ≫) was not significant after taking into account the mediators, being consistent with a full mediation hypothesis. All other mediation analyses were not significant. Mediation analyses carried out with the outcome variables of the MAPIT were not significant.

4. Discussion

The present study aimed to determine if training in a bimanual coordination task involving inhibition mechanisms transferred to untrained motor and/or cognitive tasks involving similar mechanisms.

4.1. Evidence of bimanual coordination training effect on spontaneous transition frequency

As a pre-requisite, we analyzed the effects of bimanual training to resist to the transition from the AP to the IP pattern on changes in spontaneous transition frequency and the number of transitions. Results showed that repetitive bimanual coordination practice at high frequencies delayed spontaneous

TABLE 2 Training-related enhancement of intentional switching variables (i.e., RT and TST) mediation through improvements in inhibition capacities as measured by the CSWT (unstandardized reported effect).

		Coefficient	SE	t	P
Relation ≪ a ≫	RT IP to AP	29.20	25.62	1.13	0.27
	TST IP to AP*	405.05	93.43	4.33	<0.01
	RT AP to IP	47.62	30.97	1.53	0.14
	TST AP to IP*	238.75	88.57	2.69	0.01
Relation ≪ c ≫ (Total Effect)	RT Congruent*	96.00	23.28	4.12	<0.01
	RT Neutral*	80.21	35.45	2.26	0.03
	RT Incongruent*	134.24	42.54	3.15	<0.01
		Coefficient	**BootSE**	**BootLLCI**	**BootULCI**
Bootstrap analyses of the indirect ≪ ab ≫ paths	**RT IP to AP**				
	RT Congruent	27.31	21.88	−0.8070	92.86
	RT Neutral	−5.90	23.18	−48.27	29.66
	RT Incongruent	16.74	31.23	−8.22	118.28
	TST IP to AP				
	RT Congruent	−10.96	29.38	−57.16	43.83
	RT Neutral	28.68	50.77	−34.76	148.89
	RT Incongruent*	−67.43	41.52	−165.52	−6.68
	RT AP to IP				
	RT Congruent	17.91	18.29	−3.77	69.53
	RT Neutral	6.67	23.11	−25.20	68.99
	RT Incongruent*	27.31	22.06	0.1147	103.58
	TST AP to IP				
	RT Congruent	34.93	36.85	−10.55	139.59
	RT Neutral	18.13	63.51	−142.34	148.59
	RT Incongruent*	60.21	87.36	11.54	321.00

TABLE 3 Training-related enhancement of inhibition capacities as measured by the CSWT mediation through improvements in intentional switching variables (i.e., RT and TST) (unstandardized reported effect).

		Coefficient	SE	t	P
Relation ≪ a ≫	RT Congruent*	96.00	23.28	4.12	<0.01
	RT Neutral*	80.21	35.45	2.26	0.03
	RT Incongruent*	134.24	42.54	3.15	<0.01
Relation ≪ c ≫ (Total Effect)	RT IP to AP	29.20	25.62	1.13	0.2712
	TST IP to AP*	405.05	93.43	4.33	<0.01
	RT AP to IP	47.62	30.97	1.53	0.14
	TST AP to IP*	238.75	88.57	2.69	0.01
		Coefficient	**BootSE**	**BootLLCI**	**BootULCI**
Bootstrap analyses of the indirect ≪ ab ≫ paths	**TST IP to AP**				
	RT Congruent	54.31	107.31	−277.17	155.16
	RT Neutral	18.48	58.40	−100.29	138.14
	RT Incongruent	−81.35	74.19	−277.76	14.02
	TST AP to IP				
	RT Congruent	77.60	69.15	−63.00	217.42
	RT Neutral	21.04	45.16	−37.96	131.32
	RT Incongruent*	93.17	65.44	18.22	297.41

transition frequency of about 0.5 Hz. This result extend those observed by Temprado et al. (2002), in young adults, by showing that a reserve of behavioral flexibility still persisted in older adults, which allowed improving motor adaptability thanks to an appropriate training protocol.

Presumably, training to maintain the AP pattern was hypothesized to improve inhibition mechanisms. Accordingly, an important issue was whether the effects of bimanual coordination training on underlying inhibition mechanisms transferred to untrained motor task (i.e., intentional switching) and cognitive tasks (CWST and MAPIT) that involved, at least in part, similar cognitive mechanisms. The subsequent analyzes performed on the different dependent variables allowed to test this hypothesis.

4.2. Transfer of bimanual coordination training effects to the intentional switching task

The results observed for the intentional switching task (i.e., RTs and TSTs), in the post-test and the retention test, showed a transfer of bimanual coordination training to performance in the untrained intentional switching task.

First of all, for both RTs and TSTs, a significant difference was found between the two directions of switching (AP to IP and IP to AP), independent of the assessment session (pre-test, post-test and retention test). Specifically, analyses of RTs revealed that it was more difficult to dismantle the AP pattern to switch to the IP, while analyses of TSTs revealed it was more difficult to stabilize the AP pattern when switching from the IP pattern. These results are consistent with the hypothesis that, in older adults, dismantling and re-stabilizing the AP pattern more strongly involved inhibitory functions (i.e., more cognitive load) than switching from the IP pattern or stabilizing it after switching from the AP pattern.

Regarding the effects of training, as expected, both RTs and TSTs significantly decreased during post-test and retention test, in both directions of switching. Due to the required the suppression of a concurrent response (the IP pattern) to maintain the AP pattern in the training task, these results strongly suggest that inhibition processes were involved in maintaining the AP at higher frequencies during bimanual training. In this respect, they extend those reported by Temprado et al. (2002) in younger adults by showing that, in older adults, inhibitory processes were involved to resist to the spontaneous transition from AP to IP, in addition to attentional mechanisms.

Accordingly, the results observed in the pre-test and the retention test in the intentional switching task suggested training-related improvements of transition frequency presumably reflected enhanced efficiency of inhibition processes, which finally transferred to the untrained motor tasks involving (at least in part) similar cognitive mechanisms to facilitate the production of a new response by inhibiting the current one. This hypothesis was confirmed by the results observed in the CSWT and the MAPIT.

4.3. Transfer to the CWST and the MAPIT

In the CWST, RTs decreased in post-training sessions in both congruent and incongruent conditions. These results suggest that improvements in inhibitory mechanisms resulting from bimanual coordination training also transferred to an untrained cognitive task, at least in the incongruent condition, which involves similar mechanisms. Morevoer, the lack of interaction between time and conditions in the Stroop task suggests that bimanual coordination training also improved other cognitive functions (e.g., processing speed, attention…), which are presumably involved in the CWST (for a consistent interpretation, see mediation analyses). These findings are consistent with those reported by Temprado et al. (2020), which showed that, in older adults, inhibition mechanisms assessed through the CSWT, mediated performance in the intentional switching task, at least for the AP to IP direction.

The MAPIT was used to distinguish possible separate effects of training on motor and perceptual inhibition. Indeed, it has been shown that bimanual coordination not only results from the prevalence of neuromuscular constraints (i.e., simultaneous activation or homologous/non-homologous muscle groups) [e.g., (Kelso, 1984)], but also from perceptual (in particular, visual) constraints [e.g., (Zaal et al., 2000; Mechsner et al., 2001)], though to a lesser extent (Salter et al., 2004). Results showed a reduction in MI interference following training, but not on the PI interference score. These findings confirm that MAPIT is suitable to assess the involvement of inhibition mechanisms in cyclic, bimanual movement tasks, which has been a matter of debate in the literature [e.g., (Hervault et al., 2019)]. Secondly, they suggest that bimanual coordination training improved motor inhibition mechanisms instead of perceptual ones, which is consistent with the predominance of neuromuscular constraints in bimanual coordination dynamics (Kelso, 1984). In addition, this result suggests that perceptual and motor inhibition are separate mechanisms, not necessarily related in bimanual coordination performance (but see Netz et al., 2023, for different results).

Mediation analyses allowed us to further explore the role of inhibition mechanisms in the transfer effects of bimanual training. Taken together, these analyses confirmed: (i) the mediation by inhibition mechanisms assessed with the CWST in the improvement of responses times in the intentional switching task, especially in the AP to IP direction and (ii) the mediation by (inhibition) mechanisms involved in the intentional switching in the improvement of CWST performance, especially in the incongruent condition. These findings confirm that inhibition functions are strongly involved in maintaining and, therefore, dismantling and re-stabilizing the AP pattern. It could explain why intentional switching was longer from AP to IP than from IP to AP in the present study (see Temprado et al., 2020, for confirming evidence and a convergent interpretation). Notably, the PI and MI inhibition mechanisms were not involved in any mediating effects. Also, with respect to the CSWT, the lack of time x condition interaction was rather unexpected. It suggests that, at least, information processing speed has been improved, together with other processes involved to perform the task (i.e., inhibition). However, according to the fact that: (i) the to-be-trained task strongly loaded inhibition mechanisms and (ii) mediation analyzes was only significant for the incongruent RT, we contend that inhibition processes were sensitive to the transfer effect.

The question remains, however, of the different brain structures and mechanisms that could contribute to the observed effects. Identifying the neural underpinnings of training transfer effects might be an objective for future studies. With respect to the underlying mechanisms, interestingly, in the present study, learning and transfer effects were observed following a short-duration training (50 trials), compared to that used by Voelcker-Rehage et al. (2011). These results suggest that the benefits of "guidance" obtained thanks to this short-duration training could be based on other mechanisms than the "facilitation" effects resulting from the release of neurotrophic factors, during the training of longer duration.

5. Conclusion

The present study contributes, in different ways, to the existing literature on exercise and cognition in older adults. First of all, it confirmed that complex motor skills training may allow exploiting the flexibility reserve that persists in the aging neuro-cognitive system to enlarge behavioral adaptability facing higher levels of task constraints. In this respect, our results are consistent with the existing literature demonstrating the positive impact of whole-body coordination training (Voelcker-Rehage et al., 2011) or motor fitness (Voelcker-Rehage et al., 2010) on cognitive functions. They show that bimanual coordination is a suitable task to achieve this objective. Indeed, in the present study, bimanual coordination training allowed effectively and quickly improving cognitive mechanisms in non-practiced cognitive and motor tasks. Thus, it can be concluded that when common cognitive mechanisms are at work in cognitive and motor tasks, training them in motor tasks may transfer to cognitive tasks. It remains however to determine whether the present finings can be extended to other types of complex movements.

Thirdly, this study is the first to test and detect positive cognitive improvements after a bimanual coordination training, which is of high impact for the field of age-related cognitive-decline prevention. Indeed, our findings (re)open the question of what type of physical and/or motor training programs may be most effective to improve cognition and cognitive-motor behavior in older adults (see also (Raichlen and Alexander, 2017; Tait et al., 2017; Herold et al., 2018; Torre et al., 2021; Torre and Temprado, 2022a,b). Indeed, though it is commonly considered that endurance training should be preferably used in combination with cognitive stimulations (Torre et al., 2021; Torre and Temprado, 2022a,b), when referring to the program duration, our results suggest that complex motor skill training might be even more efficient than endurance training for obtaining strong and transferable effects on cognitive function. Thus, instead of combining physical (endurance) training and cognitive stimulations, a promising combination might be those associating endurance training and complex motor skills training. This hypothesis has been scarcely been addressed in the literature (Raichlen and Alexander, 2017) and should be the objective of further studies. In particular, the present results remain to be extended to different complex motor skills training programs.

6. Limitations of the study

A limitation of the present study might be the lack of a control group. Indeed, while transfer effects of the training were strong and reliable they could, at least in part, reflect a test-retest effect. Notably, few studies showed that Stroop task delivered repeteadly through smartphone application may be used as a short and valid method to screen some forms of encephalopathy, thereby suggesting that it the Stroop test presents a high test/re-test reliability and is resistant to test/re-test learning effect (see Franzen et al., 1987 for confirming evidence). In addition, the causal effect of the intervention on cognition was explored through mediation analyses, which allowed quantifying the extent to which a variable participates in the transmittance of change from a cause to its effect. Specifically, mediation analyses explored how the changes in bimanual coordination from before to after the training, participated in the improvement in cognitive abilities. While it does not replace control group, mediation analyses give a robust understanding of the relationship between cognition and bimanual coordination, and how training coordination could improve cognitive abilities. In this respect, these analyses suggested that the presence of a test-retest effect was not enough to explain the observed results. One could argue that test retests effects may be more pronounced in some participants and not others, causing the within subject association between mediators changes and outcomes changes. While this could explain some of the results, mediation were only seen in a small specific part of our outcomes (not known to be more sensitive to test retests than the others). Distinguishing fast from slow learners, if the formers, in the mediator fields are the same in the outcome field, and given the high specificity of these variables among our set of variables, this highlights a strong relationship between mediator and outcomes. Nevertheless, further studies are necessary to confirm these results and to extend them to different complex motor skills training programs.

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 CERSTAPS IRB00012476-2022-12-05-181. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by MT and LA. The first draft of the manuscript was written by MT and revised by J-JT and AL. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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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Beta cortical oscillatory activities and their relationship to postural control in a standing balance demanding test: influence of aging

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Background: Age-related changes in the cortical control of standing balance may provide a modifiable mechanism underlying falls in older adults. Thus, this study examined the cortical response to sensory and mechanical perturbations in older adults while standing and examined the relationship between cortical activation and postural control.

Methods: A cohort of community dwelling young (18–30years, *N*=10) and older adults (65–85years, *N*=11) performed the sensory organization test (SOT), motor control test (MCT), and adaptation test (ADT) while high-density electroencephalography (EEG) and center of pressure (COP) data were recorded in this cross-sectional study. Linear mixed models examined cohort differences for cortical activities, using relative beta power, and postural control performance, while Spearman correlations were used to investigate the relationship between relative beta power and COP indices in each test.

Results: Under sensory manipulation, older adults demonstrated significantly higher relative beta power at all postural control-related cortical areas ($p<0.01$), while under rapid mechanical perturbations, older adults demonstrated significantly higher relative beta power at central areas ($p<0.05$). As task difficulty increased, young adults had increased relative beta band power while older adults demonstrated decreased relative beta power ($p<0.01$). During sensory manipulation with mild mechanical perturbations, specifically in eyes open conditions, higher relative beta power at the parietal area in young adults was associated with worse postural control performance ($p<0.001$). Under rapid mechanical perturbations, specifically in novel conditions, higher relative beta power at the central area in older adults was associated with longer movement latency ($p<0.05$). However, poor reliability measures of cortical activity assessments were found during MCT and ADT, which limits the ability to interpret the reported results.

Discussion: Cortical areas are increasingly recruited to maintain upright postural control, even though cortical resources may be limited, in older adults. Considering the limitation regarding mechanical perturbation reliability, future studies should include a larger number of repeated mechanical perturbation trials.

KEYWORDS

sensory perturbations, mechanical perturbations, aging, cortical control of posture, EEG

1. Introduction

With a rapidly increasing number of individuals over 65 years of age globally, more people face functional impairment associated with the aging process, such as reductions in balance function and increases in fall risk (Lord et al., 2018). Nearly 30% of older adults report falling (Bergen et al., 2016), and falling once doubles the chances of falling again (O'loughlin et al., 1993). Falls lead to injuries, reductions in quality of life, and even death(Kannus et al., 1999; Hartholt et al., 2011; Bergen et al., 2016), with death rates in the United States having increased 30% from 2007 to 2016 for older adults (Burns and Kakara, 2018). Considering the severe consequences of falls in older adults, it is essential to further our understanding on the mechanisms underlying falls and identification of modifiable factors that can reduce the fall rate in older adults.

Standing postural control ability tends to decline with increased age, and is significantly associated with falls (Quijoux et al., 2020). Postural control is defined as the act of maintaining, achieving or restoring a state of balance that may involve either a fixed-support or a change in support response (Pollock et al., 2000). Studies investigating postural control commonly utilize posturography to quantitatively assess postural stability (Sullivan et al., 2009). Specifically, larger postural sway areas have been associated with worse postural stability and a higher risk of falling (Johansson et al., 2017). Older adults have demonstrated increases in postural sway ranges and center of pressure (COP) velocities while standing with eyes open or close (Roman-Liu, 2018). Older adults have also exhibited larger COP peak displacements after perturbations while standing in comparison to young adults (Kanekar and Aruin, 2014; Quijoux et al., 2020).

Upright postural and balance control requires a complex interplay within and between the sensory and the motor systems. Furthermore, there is strong evidence for the crucial contribution of the cerebral cortex in the control of balance (Jacobs and Horak, 2007; Maki and McIlroy, 2007; Papegaaij et al., 2014). A growing number of studies have demonstrated increasing cortical activities in more challenging balance conditions (Wittenberg et al., 2017; Malcolm et al., 2021; Barollo et al., 2022; Tsai et al., 2022). Specifically, cortical activity and high-order cognitive processes are important when static postural control is challenged by mechanical and sensory perturbations, as the responsive adjustments depend on the integration of reliable sensory feedback and planning and execution of appropriate motor responses (O'Connor and Kuo, 2009; O'Connor et al., 2012; Francis et al., 2015; Franz et al., 2015, 2017; Goodworth et al., 2015; Malcolm et al., 2021; Tsai et al., 2022).

As suggested by current electroencephalography (EEG) studies, multiple brain regions and cortical beta band (13–30 hz) electrical activities are involved in maintaining upright static balance in adults (Ibitoye et al., 2021; Malcolm et al., 2021; Barollo et al., 2022; Tsai et al., 2022). The parietal-occipital region, frontal-central region, and occipital lobe are involved in response to visual challenges while standing (Chang et al., 2016; Malcolm et al., 2021; Tsai et al., 2022). Parietal and central areas beta band power were sensitive to proprioceptive challenges while standing (Tse et al., 2013). Electrical activity at the central coronal reference curve, such as Cz (related to sensory and motor cortex), Pz (related to parietal lobe), Fz (related to frontal lobe), and nearby electrodes are associated with responses to mechanical perturbations while standing (Adkin et al., 2006; Jacobs et al., 2008; Mochizuki et al., 2009; Smith et al., 2014). Previous work also investigated the association between cortical activities and postural control abilities while standing. Specifically, in response to backward mechanical perturbation, higher cortical beta powers are associated with larger perturbations (Ghosn et al., 2020).

Recent EEG work (Ibitoye et al., 2021; Malcolm et al., 2021; Tsai et al., 2022) has started to examine age-related changes on the cortical control of upright stance, confirming prior evidence suggesting (Rubega et al., 2021) that the cortical neural activities during the balance task also changes along with aging and are associated with poor postural control and higher fall risk (St George et al., 2021). However, while modifications to stance and visual feedback have been primarily used in studies examining age-related changes, a wider examination of age-related changes due to sensory manipulation and mechanical perturbations could provide valuable information about aging's effect on cortical contributions to balance control in more complex environments, crucial for linking to changes in fall risk.

Thus, the purpose of this study was to examine (a) the effect of aging on the cortical response to sensory manipulation and mechanical perturbations while standing and (b) the relationship between cortical activation and the underlying postural control. We hypothesized that (1) compared to young adults (YA), older adults (OA) would demonstrate significantly higher relative beta power at postural control-related cortical areas, specifically at Fz, Cz, and Pz; and (2) increased relative beta band power would be found as task difficulty increased, particularly in OA. Secondarily, we examined the association between relative beta power and postural control performance.

2. Methods

This study consisted of a single session cross-sectional experimental design. Community-dwelling adults with the following inclusion criteria were recruited (1) Right-handed; (2) Young adults between 18 to 30 years of age and older adults over 65 years of age. (3) Free of chronic or acute neurological conditions, such as Parkinson's disease, Huntington's disease, stroke, epilepsy, and seizures; and (4) Free of severe heart conditions, such as heart attack, heart failure, and angina. Exclusion criteria included: (1) Cognitive impairment, as defined by a Modified Telephone Interview for Cognitive Status (TICS-M) questionnaire score lower than 18 (Cook et al., 2009); (2) Physical disability or inability to walk independently without an assistive device; and (3) Severe chronic pain that limits physical function. Once in the study, all participants read and signed a written informed consent form. The protocol and procedures have been reviewed and approved by the Institutional Review Board of the University of Illinois Urbana Champaign.

To incorporate sensory and mechanical perturbation and provide comparable results to previous studies, the Sensory Organization Test (SOT), Motor Control Test (MCT), and Adaptation Test (ADT) were used in this study. Participants were asked to stand as still as possible in all three tests, while high-density electroencephalography (EEG), and center of pressure (COP) data was recorded. SOT, MCT, and ADT are clinically used standardized instrumented balance tests performed using the SMART EquiTest-Clinical Research System (SECRS, Neurocom, a division of Natus). The SOT is designed to assess a patient's use of sensory systems that contribute to balance and identify any abnormalities

in the systems (Mcguirk, 2005). The six conditions of the SOT manipulate or eliminate information normally delivered to the patient's eye, head, feet, and joints. Specifically, there are three trials per condition and 20 s per trial in the SOT. The SOT measures an individual's ability to suppress the misleading information from the conflicting senses and use the remaining sensory input to maintain an upright stance (Honaker and Criter, 2013). Thus, in this study, the SOT introduces visual and somatosensory perturbations using sway-referenced mechanical ankle rotations, as part of the different sensory and minor mechanical perturbations presented to participants. To provide higher levels and two different types of mechanical perturbation, the MCT and ADT were conducted after the SOT. The MCT contains six conditions, including three forward and three backward translations graded in magnitude [small (2.8 degrees/s), medium (6.0 degrees/s), and large (8.0 degrees/s)], which were scaled to subject's height, with three trials of each condition and 2.5 s per trial (Jacobs and Horak, 2007; NeuroCom International, 2008). The ADT consists of two different conditions (toes-up, toes-down with an 8-degree platform rotation at a rate of 20 degrees/s) with five trials of each condition and 2.5 s per trial. In each trial, a sudden and randomly timed movement (8 degree over 400 ms) of the platform about the ankle in the toes-up (dorsiflexion) and toes-down (plantar flexion) planes elicit an automatic balance response (NeuroCom International, 2008) to participants. The MCT contains six conditions, including three forward and three backward translations graded in magnitude [small (2.8 degrees/s), medium (6.0 degrees/s), and large (8.0 degrees/s)], which were scaled to each subject's height, with three trials of each condition and 2.5 s per trial (Jacobs and Horak, 2007; NeuroCom International, 2008). Furthermore, baseline functional balance, cognitive, and psychological function was evaluated to help control for potential covariates in cortical activation and postural control. Functional balance was evaluated by the MiniBESTest battery. The repeatable battery for the assessment of neuropsychological status (RBANS) was also used to identify and characterizing abnormal cognitive decline (Randolph et al., 1998) of the participants. Lastly, the fall risk of the participants was assessed by the Falls Efficacy Scale-International (FES-I; Delbaere et al., 2010).

2.1. Cortical activation assessment

High-density EEG data from a 64-channel active system (ActiCHamp system, Brain Vision LLC, Morrisville, NC USA) were recorded at 1 kHz, using the average of the left and right mastoids as reference. EEG sensor placement was based on the international 10–10 system. All three tests were recorded as one continuous EEG recording. Raw EEG data were imported into EEGLAB (version 2020.0) using MATLAB (The MathWorks, Natick, MA, USA) for pre-processing. Pre-processed data were then labeled based on the start and end markers of each trial under each condition in each test, and epoch to eliminate preparation and resting time in between each trial. Thus, 20s epochs from SOT paradigms and 2.5 s epochs from MCT and ADT paradigms were used for followed EEG analysis. As supported by previous literature regarding the aging effect on cortical control of postural, the main outcome measurement of the EEG data was relative beta (13–30 Hz) power (% Power) at Fz, Cz, and Pz (Adkin et al., 2006; Jacobs et al., 2008; Mochizuki et al., 2009; Tse et al., 2013; Smith et al., 2014; Chang et al., 2016; Ghosn et al., 2020). Equation 1 was used to calculate relative beta power for each participant in each unique condition. In which, power was computed by 'bandpower' function in MATLAB. This function computes the average power in the input signal vector based on the selected frequency range. The total power was calculated to ½ sampling rate to provide reliable results. Thus, the total power was calculated with a range of 0 to 500 Hz, while band of interest is 13-30 Hz for the beta wave. Relative beta power was calculated at the electrode level; thus, the results were specific to electrodes and bands of interest.

$$Relative\ power\ of\ band\ of\ interest = \frac{absolute\ power\ of\ the\ band\ of\ interest}{total\ power\ of\ the\ condition} \quad (1)$$

Before calculating Relative beta power, a grand average calculation was performed on each unique condition, thus eliminating the trial effect. Additionally, an interclass correlation coefficient (ICC) analysis were used to determine the trial effect use the epoch data before grand average. Each condition's clean EEG data was re-referenced to a subject level baseline average voltage; therefore, the results describe the changes relevant to a baseline condition (eyes open standing).

2.2. Postural control assessment

COP data were collected through the SERCS. The primary outcome measure from the COP data in SOT is Equilibrium Score. Equilibrium score reflecting the overall coordination under each SOT condition and calculated by comparing the angular differences between the patient's estimated maximum and minimum sagittal plane body sway to a theoretical maximum displacement (12.5 degree) and provided a score between 100 (no body sway) to 0 (fall; Honaker and Criter, 2013). The major outcome measure in MCT is the time elapsed (Latency) which SECRS directly reports. Latency is defined as the time in milliseconds between the onset of a translation and the onset of the patient's active force response to the induced sway. Specifically, latency detection is based on differentiation of force plate data from each foot. The resulting velocities are analyzed with four separate algorithms, each of which produces a latency estimate. Latency estimates that differ by 10 milliseconds or less are taken as identical. The longest latency estimate is then considered the latency. The number of algorithms that find the same latency is the "quality factor," or degree of consistency. A quality factor of 4 indicates all four algorithms agree. When no two algorithms agree, a quality factor of 1 is assigned, and the longest latency estimate is used. If none of the algorithms detect a onset of response, no latency can be identified, and a quality of 0 appears on the display/printout. Essentially, this determines how long it takes to go from the onset of the perturbation to the onset of the center of gravity balance correction response to maintain upright stance, with shorter latency corresponding to a faster reaction to the perturbation (NeuroCom International, 2008; Shepard and Janky, 2008). The primary outcome measure from the COP data in ADT is the sway energy score (range 0 to 300) directly reported by SECRS. This score was calculated based on COP position in the anterior–posterior direction during each perturbation condition (Vanicek et al., 2013) using the following formula:

$$Sway\ Energy = C1 * PY'(RMS) + C2 * PY''\ (RMS).$$

Where PY′ denote velocity and PY″ denote acceleration, C1 and C2 are weighting constants used to give dimensionless energy values:

$$C1 = \frac{1}{in/\sec} \text{ and } C2 = \frac{0.025}{\sec^2}$$

A higher sway energy score corresponds to a higher force required to overcome the postural instability (Trueblood et al., 2018).

2.3. Statistical analysis

All the statistical analyses were performed using R (R 4.0.3, Rstudio 1.2.1335). There were four sets of statistical analyses that were performed to answer the research questions. The independent t-test was used to test for cohort demographic differences. The ICC analysis was used to assess the trial effect in each test paradigm. For primary outcome measurements, linear mixed effect models (LMMs) were used to identify the cohort differences for cortical activities and postural control performance. Specifically, LMMs of relative power of beta band at Fz, Cz, and Pz were used to test the hypotheses of aging effect and age-task interaction effects on relative power during SOT, MCT, and ADT. LMMs were also constructed on COP equilibrium score, COP average latency score, and COP sway energy to identify the aging effect on postural control from the biomechanical aspect. When significant interaction effects were found, Least Square Means (LSM) posthoc comparisons were performed, and a $p < 0.05$ was considered statistically significant. Moreover, Spearman correlations were used to investigate the relationship between relative beta power and COP indices in each test, and between relative beta power in each test and miniBest score. The correlation strength was evaluated based on Evans's method (Evans, 1996). Thus, the relative beta power was averaged on test conditions level and on subject level accordingly. Additional details of LMMs are described in Supplementary materials Section 1.2.

3. Results

3.1. Descriptive characteristics

Overall, the two participant groups were not significantly different in cognitive function, gender, and self-reported fall risks (Table 1). In comparison to the young adult (YA) group, the older adult (OA) group was significantly older and had lower functional balance, as demonstrated by lower miniBest scores.

TABLE 1 Participants demographics.

	Young adults (n=10) mean (standard deviation)	Older adults (n=11) mean (standard deviation)
Age	21.90 (1.91)	72.64 (5.63)*
Sex (F/M)	4/6	5/6
RBANS	97.00 (10.53)	104.64 (9.89)
Visuospatial/ Constructional	87.80 (15.54)	80.09 (7.11)
Attention	107.70 (15.56)	118.36 (15.76)
FES-I	18.20 (1.75)	19.00 (2.49)
MiniBEST	26.89 (0.93)	24.36 (2.25)*

RBANS, repeatable battery for the assessment of neuropsychological status; FES-I, falls efficacy scale-international; *, statistically difference between groups, $p < 0.05$.

3.2. Postural control performance

3.2.1. SOT equilibrium score

To achieve residual normality in LMMs, the SOT equilibrium score (Eq) went through outlier removal and log transformation of the data. As the raw data was negatively skewed, the transformed data negatively correlates with the original score. A significant condition effect ($p < 0.01$) was found. Specifically, in comparison to the eyes open condition (estimate: 1.48, standard error: 0.16), eyes closed condition ($b = 0.53$, $p < 0.01$), eyes open sway surrounding condition ($b = 0.77$, $p < 0.01$), eyes open sway platform condition ($b = 1.44$, $p < 0.01$), eyes closed sway platform condition ($b = 2.02$, $p < 0.01$), eyes open sway surrounding and platform condition ($b = 2.03$, $p < 0.01$) all demonstrated higher log transformed equilibrium score, corresponding to higher postural sway. There were no statistically significant age or age condition interaction effects on equilibrium score.

3.2.2. MCT average latency

To achieve model residual normality, average latency went through outlier removal and square-root data transformation. As the raw data was positively skewed, transformed data is in a positive relationship with original data. Significant condition ($p < 0.01$) and age effects ($p < 0.01$) were found for the average latency, but no age × condition interaction effect was found. For age effects, compared to YA (estimate: 11.85, standard error: 0.15), OA demonstrated significantly higher average latencies ($b = 0.73$, $p < 0.01$). For the condition effect, compared to small forward perturbations (estimate: 12.59, standard error: 0.15), forward large perturbations ($b = -0.42$, $p < 0.05$), backward median perturbations ($b = -0.50$, $p < 0.01$), and backward large perturbations ($b = -0.94$, $p < 0.01$) demonstrated statistically significant shorter average latencies.

3.2.3. ADT sway energy

Sway energy score went through outlier removal and achieved model residual normality. Linear mixed effect models indicated significant condition ($p < 0.01$) and age effects ($p < 0.01$) on sway energy scores. For age effects, compared to young adults (estimate: 56.52, standard error: 4.04), older adults demonstrated higher sway energy scores ($b = 17.34$, $p < 0.01$). For condition effect, compared to toe down condition (estimate: 56.36, standard error: 4.04), toe up condition demonstrated higher sway energy score ($b = 17.50$, $p < 0.01$). There were no statistically significant age × condition interaction effects found in any of the measures.

3.3. Cortical activities in response to perturbations

In data pre-processing, an average of 0.20 channels (range 0–1) were visually rejected in the YA group and an average of 0.55 channels

(range 0–1) were visually rejected in the OA group. For SOT, an average of 0.10 trials (range 0–6) were rejected in the YA group and an average of 0.18 trials (range 0–6) were rejected in the OA group. For MCT, an average of 0.10 trials (range 0–6) were rejected in the YA group, and an average of 0.09 trials (range 0–6) were rejected in the OA group. For ADT, 0 trials were rejected in the YA group and an average of 0.20 trials (range 0–2) were rejected in the OA group.

3.3.1. Cortical activation distribution pattern and ICC results

Figure 1 demonstrates EEG topographic maps for beta-band absolute power separated based on age groups, tests, and conditions. Differences between OA and YA groups can be found in all tests and conditions. Specifically, higher activations in beta-band are observed in the areas around central and right parietal-occipital regions. To access the intertrial reliability of EEG findings, the intraclass correlation value on EEG data before grand averages were performed in SOT, MCT, and ADT tests was calculated. Specifically, the SOT demonstrated a good reliability in all conditions (ICC: 0.875, 95% CI: 0.851–0.895). However, there was a poor reliability in the ADT (ICC: 0.423, 95% CI: 0.338–0.514) and MCT (ICC: 0.416, 95% CI: 0.35–0.481).

3.3.2. SOT relative beta power

Linear mixed effect models suggested significant condition ($p < 0.01$), age ($p < 0.05$), electrode ($p < 0.01$), and age condition interaction effects (Figures 2A, $P < 0.01$) on relative beta power. For age effect, compared to YA, OA demonstrated higher relative beta power ($b = 0.09$, $p < 0.01$). For electrode effect, compared to Cz, relative beta power was significantly lower at Pz ($b = -0.02$, $p < 0.01$). For condition effect, compared to the eyes open condition, eye closed condition ($b = -0.09$, $p < 0.01$), eye open sway platform condition ($b = -0.03$, $p < 0.01$), eye close sway platform condition ($b = -0.10$, $p < 0.01$), and eye open sway surrounding and platform condition ($b = -0.04$, $p < 0.01$) demonstrated statistically significant lower relative beta power.

Figure 2A illustrates the age condition interaction effect on relative beta power. Young adults increased relative beta power from the first condition to the last condition, while older adults decreased relative beta power. Moreover, compared to eye open condition, young adults ($b = 0.048$, $p < 0.01$) and older adults ($b = 0.089$, $p < 0.01$) demonstrated lower relative beta power in eye close condition. Similarly, compared to eye open sway platform condition, young adults (b = 0.043, $p < 0.05$) and older adults ($b = 0.061$, $p < 0.01$) demonstrated lower relative beta power in eye close sway platform condition.

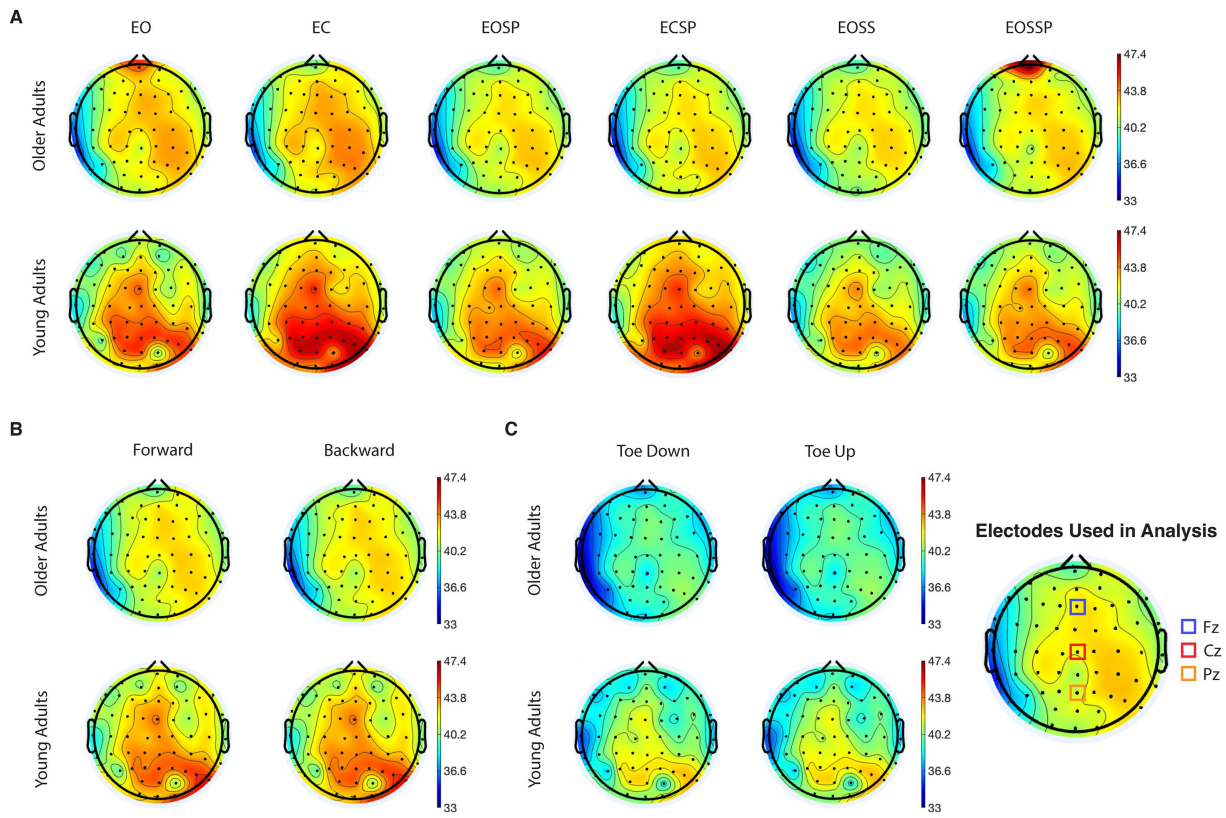

FIGURE 1
Grand average topographical maps of electroencephalography (EEG) absolute power for beta frequency band during **(A)** sensory organization test, time duration 20s, **(B)** motor control test, time duration 2.5 s, and **(C)** adaptation test, time duration 2.5 s. The red regions correspond to high concentration of maximal (58.5 dB) and blue areas correspond to high concentration of minimal (33 dB). EO, eyes open condition; EC, eyes closed condition; EOSS, eyes open sway surrounding condition; EOSP eyes open sway platform condition; ECSP, eyes closed sway platform condition; EOSSP, eyes open sway surrounding and platform condition.

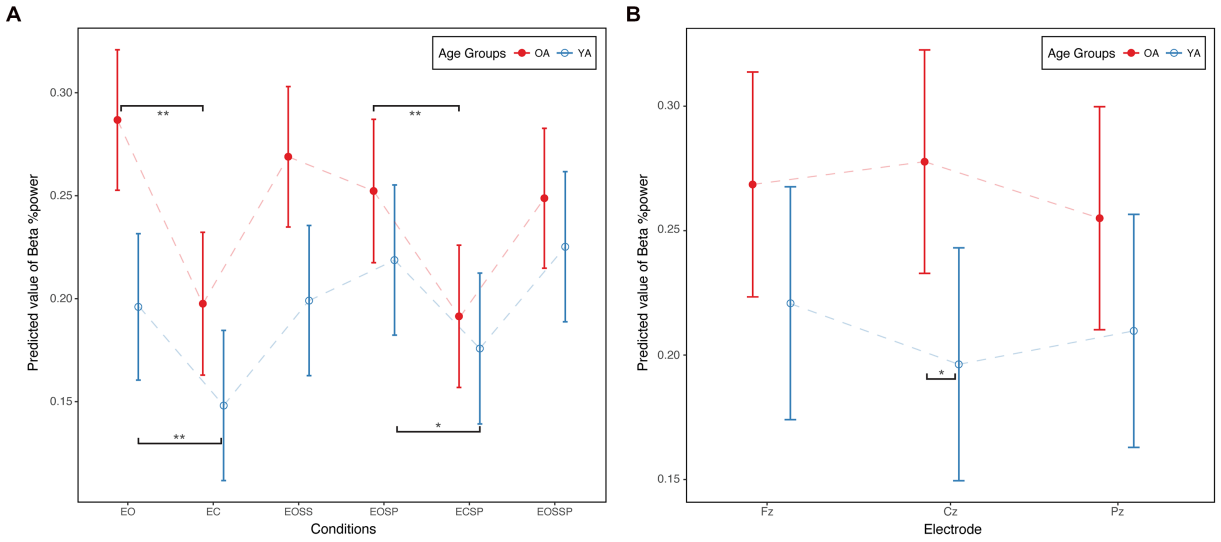

FIGURE 2
(A) Age×condition interaction in SOT. **(B)** Age×electrode interaction in MCT. Beta %Power, beta band relative power; EO, eyes open condition; EC, eyes closed condition; EOSS, eyes open sway surrounding condition; EOSP eyes open sway platform condition; ECSP, eyes closed sway platform condition; EOSSP, eyes open sway surrounding and platform condition. OA, older adults; YA, young adults. *p<0.05.**p<0.01.

3.3.3. MCT relative beta power

Linear mixed effect models suggested significant condition ($p<0.01$) and age electrode interaction effects (Figures 2B, $P<0.05$) on relative beta power. Specifically, compared to the forward median amplitude condition, the backward median amplitude condition demonstrated significantly lower relative beta power ($b=-0.040$, $p<0.01$). For the age electrode interaction, older adults demonstrated statistically significantly higher relative beta power at Cz compared to young adults ($b=0.081$, $p<0.05$, Figure 2B).

3.3.4. ADT relative beta power

Linear mixed effect models suggested a significant condition effect ($p<0.01$) on relative beta power. Specifically, compared to the toe up condition, the toe down condition demonstrated significantly higher relative beta power ($b=0.03$, $p<0.01$).

3.4. Correlation between cortical activation and postural control

For relative beta power, only a very weak negative correlation was found in overall level at Pz ($\rho=-0.160$, $p<0.10$). The age subgroup analysis revealed no correlation in OA, but a significant moderate negative correlation in YA at Pz ($\rho=-0.436$, $p<0.001$). Moreover, the age and condition subgroup analysis at Pz suggested that in the eyes open and eyes open sway surrounding conditions, higher relative beta power was strongly correlated with lower equilibrium scores in YA (EO: $\rho=-0.81$, $p<0.01$; EOSS: $\rho=-0.69$, $p<0.05$). No other statistically significant correlation was identified in subgroup analysis.

Significant correlations were found between relative beta power and average latency score at Fz ($\rho=0.214$, $p<0.05$) and Cz ($\rho=0.300$, $p<0.01$) during MCT paradigms. Moreover, subgroup analysis found positive correlations between relative beta power and average latency score in OA at Fz ($\rho=0.299$, $p<0.05$) and Cz ($\rho=0.315$, $p<0.05$), but not in YA. Moreover, the age and condition subgroup analysis at Cz suggested that in the forward small perturbation (FS) condition, higher relative beta power was strongly correlated with higher average latency in OA ($\rho=0.7$, $p<0.05$). No statistically significant relationship was detected between relative beta power and sway energy during ADT paradigms.

4. Discussion

This study investigated the effects of aging on cortical activities in response to sensory manipulation and different types of mechanical perturbation while standing and their relationships with condition-specific postural control performance and function balance ability. Our main findings were that: (1) under sensory manipulation, OA demonstrate significantly higher beta power at all postural control-related cortical areas; (2) under rapid mechanical perturbation, OA demonstrate significantly higher relative beta power at central areas; (3) As task difficulty increased, YA increased relative beta power while OA demonstrated decreased relative beta power; (4) during sensory manipulation with mild mechanical perturbations, specifically in the easier eyes open conditions, higher relative beta power at the parietal area in YA was associated with worse postural control performance; and (5) under rapid mechanical perturbation, specifically in novel conditions, higher relative beta power at the central area in OA are associated with longer movement latency. However, poor reliability measures of cortical activity assessments were found during MCT and ADT, which limits the ability to interpret the reported results.

Confirming our first hypothesis, older adults displayed significantly higher relative beta power at postural control-related cortical areas, relative to younger adults. These observations were consistent with the literature, where higher cortical engagement has been found in older adults under challenging postural conditions (Seidler et al., 2010). Moreover, our results suggest that the

compensatory cortical activity seen in older adults is task specific, meaning that aging influences cortical oscillatory activity differently depending on the type of postural perturbation. Our results further support the compensation theory in aging functional brain recruitment patterns (Seidler et al., 2010). Compensation theory suggests that older adults require additional brain activity to perform the task at the same level as young adults, as was observed in the SOT paradigms.

Confirming our second hypothesis, there were significant age by condition interaction effects in relative beta power in the sensory organization test. As task difficulty increased, greater beta band relative power was found in young adults, consistent with prior work (Ghosn et al., 2020). However, decreased beta band relative power was found in older adults as task difficulty increased. This finding is consistent with recent work in older adults, which found increased beta desynchronization as balance demands increase (Malcolm et al., 2021). Combined with the significantly higher general relative beta power in older adults, it is very likely that older adults already had reached a limit in cortical activity with eyes open and may have been unable to further increase beta activity as balance demands increased. Alternatively, the decrease in beta activity in older adults may be associated with beta desynchronization and use of voluntary-controlled movement strategies (Seeber et al., 2014) to overcome the postural control challenge brought about increased task difficulties, rather than the use of automatic postural responses to the sensory perturbations in young adults.

Consistent with prior work (Ghosn et al., 2020), higher relative beta power was correlated with worse postural control performance under sensory manipulation and rapid mechanical perturbations. Further, postural control-EEG connectivity has been found to result in positive beta oscillatory networks in older adults, such that increased beta network connectivity has been found with increased sway (Ibitoye et al., 2021). As beta power is sensitive to both sensory and mechanical perturbations and aging, cortical beta activity may be a good electrophysiological marker to assess and predict the postural control ability of an individual in the context of aging.

The present study has several limitations. First, the primary outcome measurement was focused on power spectral density, which was calculated on the time windows of each trial of each test condition. Due to this limitation, in mechanical perturbation tests, which include a clear perturbation onset, we cannot investigate the corresponding changes before and after the perturbation onset. Analysis focus on before and after perturbation is needed to investigate whether the changes of beta power is related to anxiety, fear and lack of confidence about the balance task. Second, this project was focused on using well-established clinical instrumented balance tests MCT and ADT to introduce mechanical perturbations, which has limited repeated trials and demonstrated poor reliability in EEG results. Future studies investigating cortical control of balance specific to mechanical perturbation should include larger repeated trials to improve intra-trial reliability. Third, in EEG preprocessing, we implemented a grand average to minimize the trial effect, resulting in limited data points in correlation analysis, which led to a lower correlation coefficient and non-significant relationship in subgroup analysis. Thus, future work should examine a larger sample size to make more generalizable conclusions regarding the relationship between cortical activities and postural control and balance performance. The current study focused on cortical activities and postural control performance, which indicates the shift from an automatic postural response towards a more cortically engaged strategy due to aging. However, evidence from the peripheral motor system, such as muscle activation patterns, is needed to further explain and confirm these observations. Thus, future work should incorporate electromyography and cortical-muscular coherence to connect cortical activities and movement executions.

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 University of Illinois Urbana Champaign. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YH, SP, and MH contributed to study design, revised the manuscript. YH and MH carried out participant recruitment, YH carried out the data collection, drafted the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2023.1126002/full#supplementary-material

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Unleashing the potential of dance: a neuroplasticity-based approach bridging from older adults to Parkinson's disease patients

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Parkinson's disease (PD) is a neurodegenerative disorder that affects >1% of individuals worldwide and is manifested by motor symptoms such as tremor, rigidity, and bradykinesia, as well as non-motor symptoms such as cognitive impairment and depression. Non-pharmacological interventions such as dance therapy are becoming increasingly popular as complementary therapies for PD, in addition to pharmacological treatments that are currently widely available. Dance as a sensorimotor activity stimulates multiple layers of the neural system, including those involved in motor planning and execution, sensory integration, and cognitive processing. Dance interventions in healthy older people have been associated with increased activation of the prefrontal cortex, as well as enhanced functional connectivity between the basal ganglia, cerebellum, and prefrontal cortex. Overall, the evidence suggests that dance interventions can induce neuroplastic changes in healthy older participants, leading to improvements in both motor and cognitive functions. Dance interventions involving patients with PD show better quality of life and improved mobility, whereas the literature on dance-induced neuroplasticity in PD is sparse. Nevertheless, this review argues that similar neuroplastic mechanisms may be at work in patients with PD, provides insight into the potential mechanisms underlying dance efficacy, and highlights the potential of dance therapy as a non-pharmacological intervention in PD. Further research is warranted to determine the optimal dance style, intensity, and duration for maximum therapeutic benefit and to determine the long-term effects of dance intervention on PD progression.

KEYWORDS

dance, neurodegeneration, tremor, rhythm, sensorimotor integration

Highlights

- Dance interventions are a multi-task practice.
- In healthy older adults dancing induces both neuroplasticity and motor changes.
- Patients with Parkinson's disease would experience multiple benefits with regular dance-instructed interventions.
- Optimal dance style, intensity, and duration for maximum therapeutic effect depend on the participants.
- It is suggested to involve certified dance instructors during interventions with patients.

Introduction

Parkinson's disease (PD) is a neurological disorder caused by programmed cell death of dopamine-producing neurons in the basal ganglia, leading to progressive deterioration of motor symptoms. PD affects 1% of people over 60 years of age and 3% of people over 80 years of age (Balestrino and Schapira, 2020). Tremor, bradykinesia, rigidity, postural instability, impaired balance and coordination disorders are the most common motor symptoms (Moustafa et al., 2016; Müller et al., 2019; Balestrino and Schapira, 2020). In addition, cognitive impairment, psychological problems, fatigue, and pain are the representatives of non-motor symptoms. These PD symptoms affect quality of life, especially when the disease progresses over time and symptoms accumulate, making even activities of daily living increasingly difficult, leading to reduced independence and withdrawal from social life (Soh et al., 2013).

Although the main cause of PD is the decrease of 60–70% of dopaminergic cells in the substantia nigra, this neurodegeneration is associated with multiple brain changes, such as atrophy of cortical gray matter in frontal, temporal, occipital, and limbal regions (Pagonabarraga et al., 2013; Rektorova et al., 2014; Chen et al., 2016), as well as changes in functional connectivity in cortical-striatal pathways (Tessitore et al., 2019). The most frequent finding in PD showed reduced connectivity in the posterior putamen (Tessitore et al., 2019), and reduced connectivity within the basal ganglia network (Szewczyk-Krolikowski et al., 2014; Rolinski et al., 2015). At the cortical level, decreased resting-state functional connectivity has been found in the supplementary motor area (SMA) (Wu et al., 2011; Esposito et al., 2013; Agosta et al., 2014), while increased functional connectivity in the premotor cortex (PMC) has been described as a compensatory mechanism (Wu et al., 2011) to preserve global motor functions. Furthermore, significantly reduced expression of neurotrophic factors such as Glia-Derived-Neurotrophic Factor (GDNF) and Brain-Derived-Neurotrophic-Factor (BDNF) in substantia nigra has been reported (Chauhan et al., 2001), leading to loss of dopamine transporter binding (Fisher et al., 2013).

Activity-dependent neuroplasticity could possibly modify disease progression in neurodegenerative disorders, for example by restoring basal ganglia homeostasis and synaptic integrity in PD (McMahon and Chazot, 2020). Previous studies have shown positive short-term effects of traditional physical therapy on both motor and non-motor symptoms of patients with PD (Sharp and Hewitt, 2014; Tomlinson et al., 2014). Short-term aerobic training was found to elevate the binding potential of striatal dopamine D2 receptors in individuals with early-stage PD (Fisher et al., 2013). After 10 days of intensive training a significant increase in serum levels of BDNF has been observed, and this change was maintained throughout 4 weeks of training (Frazzitta et al., 2014). Four weeks of multidisciplinary intensive rehabilitation treatment decreased symptom progression, with the decrease attributed to enhanced BDNF tyrosine receptor kinase B signaling in lymphocytes (Fontanesi et al., 2016). Six weeks of dynamic balance training resulted in performance improvements in patients with PD and healthy controls. Healthy controls exhibited gray matter changes in the left hippocampus, while in PD patients, performance improvements were correlated with gray matter changes in the right anterior precuneus, left inferior parietal cortex, left ventral premotor cortex, bilateral anterior cingulate cortex, and left middle temporal gyrus. A 3-month aerobic training program resulted in increases in functional activity in the hippocampus, striatum and cerebellum in PD patients, as well as in the striatum in healthy controls (Duchesne et al., 2016).

However, there is no evidence of long-term benefit or preference for any specific physical therapy intervention (Tomlinson et al., 2013; Sharp and Hewitt, 2014). Recent research and studies have led to physical therapy guidelines recommending various non-pharmacological physical interventions (e.g., Domingos et al., 2018; Grimes et al., 2019; Osborne et al., 2022). These physical therapy guidelines for patients with PD recommend improving muscle strength, aerobic capacity, balance, gait, and functional mobility through the utilization of cueing techniques and cognitive movement strategies (Mak et al., 2017).

Dancing is consistent with these guidelines and may provide similar or even better overall health benefits compared with traditional exercise for patients with PD. Recently, dancing has gained interest as an intervention for older adults because of its combination of motor learning and non-motor engagement (Westheimer, 2008; Kattenstroth et al., 2010; Karpodini et al., 2022; Wu et al., 2022). Studies have shown that dancing can produce positive motor and non-motor outcomes, as well as improve quality of life in both healthy older adults and patients with PD with mild to moderate symptoms (e.g., McNeely et al., 2015,a,b; Shanahan et al., 2015, and for more recent reviews see Karpodini et al., 2022; Wu et al., 2022). In a meta-analysis conducted by Zhang et al. (2023) comparing 109 studies and 14 types of exercise (e.g., dancing, Nordic walking, strength training, tai chi) to assess long-term changes in motor function in patients with PD, dancing was found to be the most effective exercise. Dancing showed the strongest overall improvement in motor function, which can be attributed to the additional motor learning involved.

However, dance-induced neuroplasticity has been described to a limited extent in patients with PD. To our knowledge, only one single case study has been published showing significantly increased network connectivity between the basal ganglia and premotor cortices following dance intervention (Batson et al., 2014). Therefore, the aim of this review is to gather information on

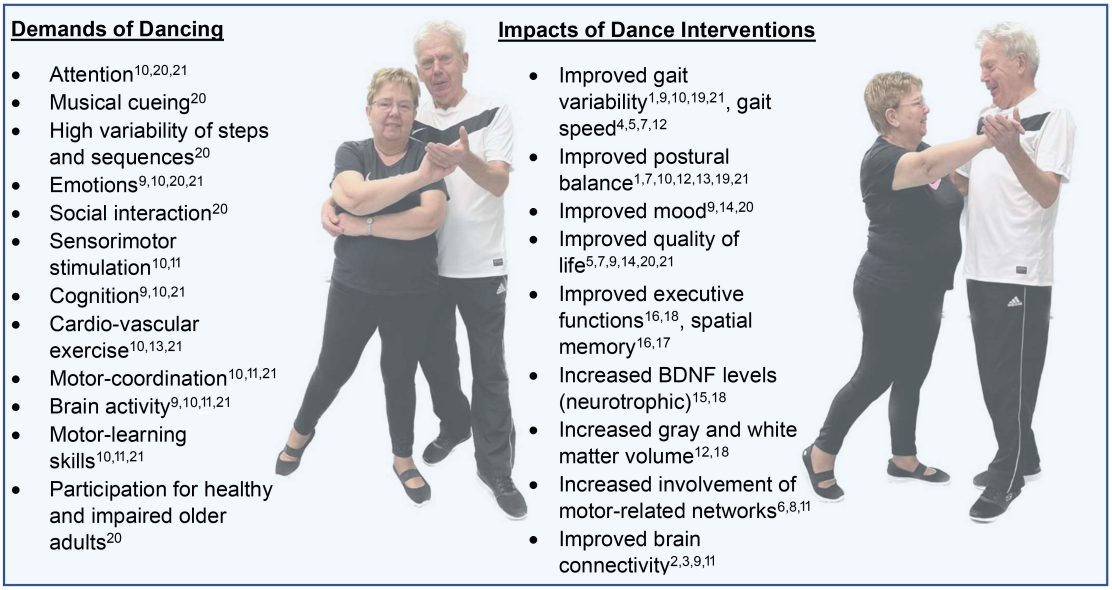

FIGURE 1
Demands of dancing and impacts of dance-interventions. Indicated are studies that demonstrate the demands or impacts, of which the full citation can be found in the references. Note that the citations do not exhaustively cover the impacts and demands, and are predominantly covered by the cited (systematic) reviews, while in the main body of the text detailed claims from specific studies can be found. [1] Allen et al. (2017); [2] Batson et al. (2014); [3] Burzynska et al. (2017); [4] Duncan and Earhart (2012); [5] Duncan and Earhart (2014); [6] Esposito et al. (2013); [7] Hackney and Earhart (2009c); [8] Ji et al. (2018); [9] Karpodini et al. (2022); [10] Kattenstroth et al. (2010); [11] Li et al. (2015); [12] McKay et al. (2016); [13] McNeely et al. (2015a); [14] McNeely et al. (2015b); [15] Müller et al. (2017); [16] Niemann et al. (2016); [17] Porat et al. (2016); [18] Rehfeld et al. (2018); [19] Shanahan et al. (2015); [20] Westheimer (2008); [21] Wu et al. (2022).

the possible mechanism of how dancing can induce neuroplastic and motor changes in patients with PD and to provide valuable evidence for prospective studies of dance-intervention.

Effects of dancing on motor and non-motor symptoms in patients with PD

Dancing is a promising rehabilitation strategy because its multisensory nature addresses multiple sensorimotor systems through whole-body movements in complex environments (Batson et al., 2014). Dancing is a typical multitasking practice that engages aerobic capacity, balance and postural control, gait, and cognitive skills with music and rhythmic cueing (e.g., Earhart, 2009; Kalyani et al., 2019; Pereira et al., 2019; **Figure 1**), and fulfills the requirements of clinical guidelines for physical therapy for patients with PD.

The parameters of dance vary across different dance styles, and several systematic reviews have shown that a variety of dance styles applied separately as an intervention improve functional fitness in older adults (Hwang and Braun, 2015; Fong Yan et al., 2018; Liu et al., 2021). Hence dancing interventions might influence PD symptoms differently. Tango, for instance, is characterized by firm walking steps and involves quick stops and starts that could counteract freezing episodes, so participation in tango interventions could strengthen the brain network for initiating movements. Ballet offers especially flowing, rhythmic movements and waltz works on backward walking, sidesteps and turns, whereas step-dance get the hips to swing which might specifically impact tremor and non-motor symptoms.

There are already several certified dance programs for PD (e.g., *NeuroTango®*, *Dance for PD®*, *Dance Movement Therapy®*) that have been shown to positively impact motor and cognitive abilities and quality of life in patients with PD (Hackney and Earhart, 2009a,b,c; Duncan and Earhart, 2012, 2014; Allen et al., 2017; Beerenbrock et al., 2020; Krotinger and Loui, 2021). These programs for PD use different music speeds and have different overall lesson structure. A short description of these certified dance programs for PD and the various outcomes, including significant observations from RCT studies using these certified dance programs for patients with PD are summarized in **Table 1**.

Ten RCTs were identified for Hackney/Eckhart *Adapted Tango*. In general, participation in dance interventions with *Adapted Tango* improved the quality of life of PD patients, as evidenced by lower Parkinson's disease questionnaire (PDQ-39) scores (e.g., Hackney and Earhart, 2009a,b) and improved movement disorder society-unified Parkinson's disease rating scale I (MDS-UPDRS-I) scores (Duncan and Earhart, 2014). Motor changes in neuromuscular control of gait (Allen et al., 2017) and improved balance were observed after only a few weeks of intervention (Hackney and Earhart, 2009c; McKay et al., 2016; Allen et al., 2017). Trends of overall improvement were particularly evident around week 12–13 of the intervention (Hackney and Earhart, 2009a,b; McKee and Hackney, 2013; Holmes and Hackney, 2017), while a substantial extension of the intervention to 48 weeks and beyond resulted in further improvement in scores at both DMS-UPDRS-II and III

TABLE 1 Structured dance models for patients with PD.

Dance model General structure of individual lesson	Intervention weeks/lessons per week/minutes per lesson/presence of dance instructor/partnered dance/study reference	Outcomes
Adapted Tango according to Hackney/Earhart 60–70 min: 5 min greeting and practice 10 min warm-up 10 min new steps 15 min music/rhythm training 17 min amalgamation and encapsulation 3 min closure	3/5/90/Y/Y Allen et al., 2017*	Changes in neuromuscular control of gait and balance
	48/2/60/Y/Y Duncan and Earhart, 2012**	MDS-UPDRS-III ↑ MDS-UPDRS-II ≈ MDS-UPDRS-I ≈ MiniBESTest ↑ FOG-Q ≈ 6MWT ↑
	96/2/60/Y/Y Duncan and Earhart, 2014**	MDS-UPDRS-III ↑ MDS-UPDRS-II ↑ MDS-UPDRS-I ↑ MiniBESTest ↑ 6MWT ↑ TUG ≈ Walking velocity ≈ FOG-Q ≈
	48/2/60/Y/Y Foster et al., 2013**	Participation ↑ Activity retention ↑ New social activities ↑
	13/2/60/Y/Y Hackney and Earhart, 2009a,b**	Mobility ↑ Social support ↑ PDQ-39 ↓
	2/5/90/Y/Y Hackney and Earhart, 2009c**	MDS-UPDRS-III ↑ BBS ↑ Walking dual task ↑ TUG ≈ 6MWT ≈
	12/4/90/Y/Y Holmes and Hackney, 2017*	Improved skills for participation in daily activities and increased QOL
	5/5/90/Y/Y McKay et al., 2016*	MDS-UPDRS-III ↑ BBS ↑ FAB ↑ DGI ↑ 6MWT ≈ TUG ≈ FOG-Q ≈ EMG ≈
	12/2/90/Y/Y McKee and Hackney, 2013**	MDS-UPDRS-III ≈↑ FAB ↑ TUG ↑ PDQ-39 ↑ FOG-Q ↑
Dance for PD® 60–70 min: Seated exercises 20–40 min: Warm-up, Rhythmic warm-up; Storytelling through movement; Geographic sequence. Barre 10–20 min: Plie and relevé; Rhythmic exercise; Tendu and alagio. Center 15–30 min: Rhythmic walking; Partnered dance; Other dances; Mirroring improvisation; Pass the pulse.	12/2/60/Y/Y Carapellotti et al., 2022*	PDQ-39 ↓ TUG ↑ PHQ-9 ↑
	12/2/60/Y/Y Kalyani et al., 2019**	PDQ-39 ↓ Cognitive skills ↑ Psychological symptoms ↓
	16/2/75/Y/Y Krotinger and Loui, 2021**	BAT ↑ Sensorimotor coupling ↑ UPDRS ↑

(Continued)

TABLE 1 (Continued)

Dance model General structure of individual lesson	Intervention weeks/lessons per week/minutes per lesson/presence of dance instructor/partnered dance/study reference	Outcomes
NeuroTango® 60 min: Welcome; Personal wellbeing assessment; Motivation Preparatory brain warm-up sitting exercises; Preparatory balance and coordination standing exercises Partnered tango dances (10–35 min) Personal wellbeing assessment; Chill-out	10/1/60/Y/Y Poier et al., 2019** 10/1/60/Y/Y Beerenbrock et al., 2020*	PDQ-39 ≈ ↓ BMLSS ↑ body awareness ↑ motor symptoms and movement ↑ general feelings ↑ body sensations and disease-related feelings ↑
Dance Movement Therapy 15 min check-in 20 min warm-up: sitting/standing 5 min break 30 min process work: activities of physical, social and emotion conditions; prop work; partner and group work. 5 min break 10 min relaxation 5 min closure	8/2/90/Y/Y Lihala et al., 2021*	MoCA ↑ PDQ-39 ↓ Better overall cognition and QOL

BAT, beat alignment test; BBS, berg balance scale; BMLSS, brief multidimensional life satisfaction scale; DGI, dynamic gait index; DT-TUG, dual-task timed up and go; EMG, electromyography; FAB, Fullerton advanced balance scale; FES-I, falls efficacy scale international; FOG-Q, freezing of gait questionnaire; MiniBESTest, mini-balance evaluation systems test; MoCA, Montreal cognitive assessment; 6MWT, 6-Min walk test; PDQ-39, Parkinson's disease questionnaire-39; PHQ, patient health questionnaire-9; QOL, quality of life; TUG, timed up and go; UPDRS, Unified Parkinson's disease rating scale; Y = yes; ↑ = significant increase; ↓ = significant decrease; ≈ unchanged. Note that for the studies indicated by * the outcomes are reported as a difference between pre and post test results, while for the studies indicated by ** the outcomes are a comparison of test results between intervention and control group.

(Duncan and Earhart, 2014), with walking endurance in particular improving significantly (6-min walk test, 6MWT, Duncan and Earhart, 2012, 2014).

Limitations in comparing RCTs for the same dance intervention model include, first, that individual lessons may not have been delivered structurally according to **Table 1**, as instructions were monitored by different research groups. Second, the duration of the tabulated interventions varied widely (mainly for Hackney/Eckhart Adapted Tango), whereas different timing of interventions was lacking for the other models. Thus, a wide variety of intervention parameters from insufficiently consecutive RCT studies prevents the reporting of very detailed efficacy outcomes for the four types of PD dance intervention models. In addition, it remains to be determined what style of dance applied at which intensity and duration, or whether a combination of dance styles as an intervention would yield the greatest long-term therapeutic benefit for patients with PD. Nevertheless, dance therapy improves mobility and quality of life in patients with PD.

Neuronal mechanism of music

Parkinson's disease is associated with a loss of internal cueing systems that impairs rhythmic motor tasks and musical rhythm perception, based on decreased dopaminergic activity in corticostriatal circuits in patients with PD (Grahn, 2009; Rose et al., 2020). Furthermore, patients with PD exhibit impaired beat perception and sensitivity caused by impaired basal ganglia and motor activity and connectivity (Grahn and Rowe, 2009).

While the music itself plays an important role by itself, dancing requires matching movement patterns to the timed beat of the music. More specifically, dancing requires matching the musical rhythm, and rhythmic auditory cues must be combined with visual cues to coordinate movement (e.g., Earhart, 2009; Pereira et al., 2019). Overall, music and dance provide external auditory and visual cues that lead to deficits in timing and cues due to basal ganglia impairments in patients with PD (Krotinger and Loui, 2021). Music contributes to the activation of areas such as the putamen and releases biochemical mediators such as endorphins (Lihala et al., 2021), as well as dopamine (Stegemöller, 2014). One characteristic of music is the groove, which conveys the way auditory rhythms excite the motor system and drives sensorimotor coupling (Krotinger and Loui, 2021). Applied to PD, this suggests that groove may be a factor that can influence responsiveness to dance interventions due to its effect on spontaneous motor excitability (Krotinger and Loui, 2021). Taken together, this modulates the reward and motivation systems contributing positively to various tasks and behaviors. Hence, experiencing music (both passively and actively performing) and music as therapy leads to neuroplastic changes (e.g., Stegemöller, 2014; Chatterjee et al., 2021; Olszewska et al., 2021). Evidence from healthy adults indicates that musical training impacts gray matter structure in premotor and supplementary motor areas (Gaser and Schlaug, 2003; Chaddock-Heyman et al., 2021). People with musical training also showed superior beat perception (Grahn and Rowe, 2009). Auditory cues appear to be most effective in improving gait compared to visual and proprioceptive cues (Hackney et al., 2015), but it depends on the person's beat perception and ability to synchronize movement with music. Thus, for rehabilitative purposes salience of a beat and familiarity with music should be considered, because when these are considered, interventions show promising results in gait, with less variable

strides, faster stride velocity, and better synchronization (Hackney et al., 2015). A possible mechanism is given by Zhang et al. (2023) who mention that rhythmic stimulations during dance interventions for patients with PD are an external cue that increases activity in the putamen, which then facilitates movement, and compensates for the lack of dopaminergic stimulation.

Dancing induced-neuroplasticity

Cortico-basal ganglia loops are essential in dancing because they control posture, movement, and action selection (Nambu, 2004; Li et al., 2015). Entrainment of dance steps to music is supported by the activation of the anterior cerebellar vermis (Brown et al., 2006). In addition, the right putamen is involved in voluntary control of metric movements. Spatial navigation is one of the most notable features in dancing and is associated with activation of the medial superior parietal lobe in the control of muscle contraction during spatial navigation of leg movements in dancing (Brown et al., 2006). This reflects proprioceptive and somatosensory contributions to spatial cognition/awareness during dancing.

One of the best investigated dance styles in patients with PD is the Argentine Tango, a partnered dance with leading and following roles: distinctions in internally-guided (IG = leading) and externally-guided (EG = following) movements have been postulated by several authors (Hackney et al., 2015; Drucker et al., 2019; Kashyap et al., 2021), suggesting that EG movements rely more heavily on the cerebello-thalamo-cortical circuit (CTC), whereas IG movements rely more on the striato-pallido-thalamo-cortical circuit, which is known to be impaired in patients with PD. IG training focuses on critical aspects of movement such as longer steps, quicker movements and is thought to achieve normal speed and amplitude in patients with PD (Hackney et al., 2015). Improved movement initiation, faster reaction times were stated for EG, as well as facilitating effects for alleviating freezing of gait. In partnered Argentine Tango, the leader (IG) self-initiates direction, timing and amplitude of movements, whereas the follower (EG) receives proprioceptive, visual, auditory and tactile cues from the leader (IG) explaining the use of circuits patterns for both, leader and follower. Behavioral data revealed improved balance and endurance performances for IG groups (Kashyap et al., 2021). Patients with PD, who were the follower (EG), showed improvements in freezing of gait, endurance, spatial memory and working memory as well as a reduction in depressive symptoms. Ongoing fMRI analysis showed initial evidence that neural pathways are affected differently after IG and EG training. Only the EG group had significant increase in recruitment of CTC pathway and increased activation in the motor cortex (Kashyap et al., 2021).

Several intervention studies have attempted to shed light on the neuroplasticity of dance compared to other sports in healthy older adults (Ehlers et al., 2017; Müller et al., 2017; Baniqued et al., 2018; Rehfeld et al., 2018).

Six months of dancing for instance showed an increase in anterior and medial cingulate cortex (which is associated with working memory, cognitive control and attention regulation), in the left supplementary motor area and left precentral gyrus (preprocessing and executive function within the motor system), left medial frontal gyrus, left superior temporal gyrus, left insula, and left postcentral gyrus (which transmits information from proprioceptive organs such as neuromuscular spindles, joint and tendon receptors). The most remarkable increase in white matter was observed in the corpus callosum, which connects almost all parts of both hemispheres and enables coordinated movements (Rehfeld et al., 2018). An aged-matched fitness group exercising strength-endurance, endurance and flexibility for 6 months revealed smaller and less pronounced volume increases, mainly in the cerebellum (unconscious planning and execution of movements) and visual areas (Rehfeld et al., 2018). In this study the level of BDNF increased significantly only in the dance group.

Müller et al. (2017) showed a significant increase in gray matter volume in the left precentral gyrus (control of voluntary motor functions) and a significant increase in BDNF levels after six months of dancing, whereas the fitness group showed no significant change. A total of 18 months of dancing increased volume in the parahippocampal region (associated with working memory and episodic memory retrieval), although the BDNF levels returned almost to baseline. In the fitness group, however, brain volume and BDNF levels remained stable during the 18-month training period.

Summary and conclusion

Dance interventions have been shown to be beneficial in improving quality of life, balance, and mobility in older patients, including those with PD. These interventions, which involve multisensory, cognitive-motor demands, have demonstrated multifaceted effects on older participants, whether healthy or with neurological disorders. Specific dance styles that focus on movement initiation, postural control, walking, flexibility, social interaction, and fun may be necessary to address the predominant motor symptoms of PD. Dancing for PD is gaining popularity as a community-based intervention (e.g., Westheimer, 2008), but the only structured and studied dance intervention is the *Dance for PD*® model (Hackney et al., 2007; Heiberger et al., 2011; McNeely et al., 2015; Westheimer et al., 2015), and more recently *NeuroTango*® (Schlafhorst, 2020a,b). While these certified dance programs have provided evidence for motor and cognitive skills in patients with PD (Hackney and Earhart, 2009a,b,c; Duncan and Earhart, 2012, 2014; Allen et al., 2017; Beerenbrock et al., 2020; Krotinger and Loui, 2021), the underlying neural mechanisms remain poorly understood.

Dancing places various demands on the sensorimotor system, and studies in healthy older adults and young adults have revealed neuroplastic changes associated with dancing (see **Figure 1**). Brain areas and circuits involved in movement initiation, planning, sequencing, and control, such as the premotor cortex, supplementary motor area, and cortico-striatal circuits including the basal ganglia (putamen and striatum), have been shown to benefit from dancing. However, these regions and functions often exhibit decreased activity and lower connectivity in patients with PD. Further imaging studies, including prospective investigations, are needed to elucidate the neural mechanisms of dancing in PD patients. An imaging study of tango step performance has highlighted the involvement of the putamen, a region that suffers from the presence of PD (Brown et al., 2006). However, this is only one of many avenues that can be pursued to understand the neural mechanisms of dancing in PD.

Collaboration between patient groups, care centers, and certified dance instructors is recommended to develop tailored dance interventions that can induce neuroplastic changes that lead to improved quality of life. Structured dance models developed specifically for this purpose are presented in **Table 1**. While dance interventions have demonstrated positive outcomes in cognitive-motor skills and quality of life in older adults (Hwang and Braun, 2015; Fong Yan et al., 2018; Liu et al., 2021; Wang et al., 2022), further research is needed to determine the optimal parameters, including dance style, duration, and intensity, for maximum therapeutic benefit. In addition, further studies are needed to understand the neuroplastic changes induced by dance interventions in PD patients (Batson et al., 2014; Mak et al., 2017). As an emerging field, the neuroscience of dance utilizing Mobile Brain/Body Imaging, can provide valuable insights into brain plasticity, dynamics, and behavior in more ecologically valid research settings (Barnstaple et al., 2021).

Overall, dance interventions hold promise for positively impacting motor skills, quality of life, mood, and neuroplasticity. However, much remains to be discovered regarding their specific effects in PD patients, and determining the optimal parameters will be critical to their therapeutic potential. However, the existing literature on dance interventions for older adults shows clear short- and long-term benefits attributable to changes in the brain. Given the aging population in our society, dance interventions could be a valuable and socially accepted tool to counteract cognitive, motor, and social impairments. Further research in this area, including prospective imaging studies, will contribute to a better understanding of the effects of dance and its potential as a therapeutic intervention.

Ethics statement

Written informed consent was obtained from the individuals for the publication of any identifiable images or data included in this article.

Author contributions

UM provided the conceptual idea, which was further developed with the help of CM, SJ, and KR. CM wrote the first version of the manuscript. CM and SJ extracted the parameters of the structured dance models. KR and UM wrote the text on neuroplasticity. All authors were responsible for editing the manuscript, critical evaluation, and approval of the final version of the 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.

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Online physical exercise program with music improves working memory

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Objective: The spread of coronavirus disease (COVID-19) has limited the implementation of face-to-face non-pharmacological treatment for the prevention of dementia. As a result, online non-pharmacological treatment has become increasingly important. In this study, we used an online conferencing system to implement an online version of a physical exercise program with music, and examined its effect on cognitive function.

Methods: The participants were 114 healthy older adults [63 men and 51 women; mean age of 70.7 years (standard deviation = 4.6)]. Seventy-five participants were allocated to the physical exercise with music group (60 min, once a week, total 20 sessions), while the remaining 39 participants were assigned to the control group, and only underwent the examinations. In the physical exercise with music group, we performed neuropsychological examinations and brain tests both before and after the exercise program. Neuropsychological tests included the Mini-Mental State Examination, Raven's Colored Progressive Matrices (RCPM), the Rivermead Behavioral Memory Test, graphic imitation, word fluency (WF) (animal names and initial sounds), and the Trail Making Test-A/B. As an assessment of brain function, we developed an online examination of subtle cognitive decline, including tests of number and word memory, spatial grasp, the N-back task, and change inference.

Results: In the N-back task, the physical exercise with music group improved significantly relative to the control group (p = 0.008).

Discussion: The present findings suggest that the online version of the physical exercise with music program improved working memory, which mainly involves the frontal lobe.

KEYWORDS

physical exercise, music, COVID-19, dementia, neuropsychological test, working memory

Abbreviations: ExM, physical exercise with music; COVID-19, coronavirus disease; Cont, control; LM, Logical Memory; WF, word fluency; BA, brain assessment; CS, cognitive scores.

1. Introduction

Dementia affects over 55 million individuals worldwide (Gauthier et al., 2021), and this prevalence is increasing such that 78 million may be diagnosed with dementia by 2030 (Gauthier et al., 2021). Although there are two broad categories of dementia treatments, i.e., pharmacological and non-pharmacological therapy, there are currently no successful pharmacological interventions that can cure dementia or halt its progression (Mecocci and Boccardi, 2021). Therefore, non-pharmacologic therapies that are believed to be safe with minimal side effects are actively implemented to treat dementia. These therapies include cognitive interventions, music therapy, reminiscence, and physical exercise (Yorozuya et al., 2019; Ito et al., 2022; Sharew, 2022). Non-pharmacological interventions can be delivered separately or as part of a multimodal approach. Multimodal non-pharmacological interventions combine two or more types of non-pharmacological interventions (Han et al., 2017), and are typically recommended as the "gold standard" for treating dementia (Schneider and Yvon, 2013; Livingston et al., 2020; Sharew, 2022).

In our previous studies, we examined the effects of a non-pharmacological intervention that combined physical exercise with music therapy (ExM). We found that both neuropsychological testing and brain imaging indicated that ExM was effective in the primary prevention of dementia (Satoh et al., 2014, 2020; Tabei et al., 2017). The goal in these previous studies was to use a non-pharmacological ExM intervention to maintain and improve cognitive function in healthy older people living in the community. The physical exercise regimen was identical for the ExM and exercise-only groups. However, music was played during the exercise routine in the ExM group, while the exercise-only group only heard a percussive sound that counted the beat. Both groups performed the exercises for 1 h per week for 1 year. As a control, a brain test group who did not complete any special activities was also included. The results showed that visuospatial cognition and cognitive status were significantly improved in the ExM group compared with those in the other two groups (Satoh et al., 2014). Furthermore, brain magnetic resonance imaging analysis of changes in brain volume revealed that the brain test group showed progressive age-related atrophy over the 1-year period, whereas the volume of the frontal lobes in the ExM and exercise groups was maintained or increased, with a greater increase in the ExM group (Tabei et al., 2017). We also examined the effects of a 5-year ExM intervention on cognitive function in healthy older adults (Satoh et al., 2020). The results showed that the long-term ExM intervention enhanced multidimensional cognitive function in the study sample, and that it was particularly beneficial for improving psychomotor speed.

The lockdown measures put in place to contain the spread of coronavirus disease (COVID-19) during 2020 led to severe limitations in access to healthcare services for individuals with dementia (Gauthier et al., 2021). These measures also led to a general reduction in the number of non-pharmacological therapies implemented during the pandemic. A previous study showed that low-cost, scalable in-home programs were effective in supporting the physical health of previously inactive adults during the COVID-19 pandemic (Beauchamp et al., 2021). To expand upon this, we developed an online version of an ExM program and tested its effectiveness in the primary prevention of dementia among healthy older adults. We conducted neuropsychological examinations and online cognitive tests to evaluate the effectiveness of the intervention. We hypothesized that the effects of the online version of the ExM program would be similar to those of face-to-face ExM.

2. Materials and methods

2.1. Study participants

We used the internet to recruit participants for our experiment. The goal of the experiment was to investigate the effect of an online version of the ExM on cognitive function. We sent a direct email describing the study goals to approximately 1 million older persons (≥65 years old) who were members of SAISON Credit Card, which is the parent company of the Research Institute of Brain Activation in Japan. The research ethics committee of the Advanced Institute of Industrial Technology in Japan approved the experimental protocol, and all participants provided written informed consent prior to participation. The study was performed according to the guidelines of the Declaration of Helsinki. The inclusion criteria were as follows: (a) 65 years of age or older; (b) physically and mentally healthy; (c) normal vision or vision corrected with glasses, contact lenses, etc.; (d) ability to hear instructions clearly; (e) living independently; (f) have access to a personal computer, tablet, or smartphone with the ability to use the Zoom app[1]; (g) have Wi-Fi access at the location where they will be participating; (h) have an email address and willing to be contacted via email. Participants were excluded if they met any of the following exclusion criteria: (a) apparent history of cerebrovascular attack; (b) presence of chronic disease such as malignancy or infection; (c) severe cardiac, respiratory, or orthopedic problems that would prevent participants from exercising; (d) use of medication that could adversely affect cognition (antidepressants or antipsychotics); (e) a previous diagnosis of dementia; or (f) attendance rate less than 75%. The inclusion and exclusion criteria for the control (Cont) group were identical to the aforementioned requirements. Participants in the control group were simply required to undergo neuropsychological and physiological assessments at baseline and 6 months after the start of the study.

Between February 9 and 5 May 2021, 228 respondents expressed interest in participating in the ExM group, and 136 were interested in participating in the Cont group. In the ExM group, 88 participants dropped out (did not complete neuropsychological testing). In the Cont group, 60 participants dropped out (did not complete neuropsychological testing). During the second assessment, 7 participants dropped out of the ExM group, while 37 dropped out of the Cont group (did not complete neuropsychological testing). We analyzed participants whose overall attendance rate was above 75%. Consequently, data from a total of 114 participants were included (**Figure 1**).

1 https://zoom.us/

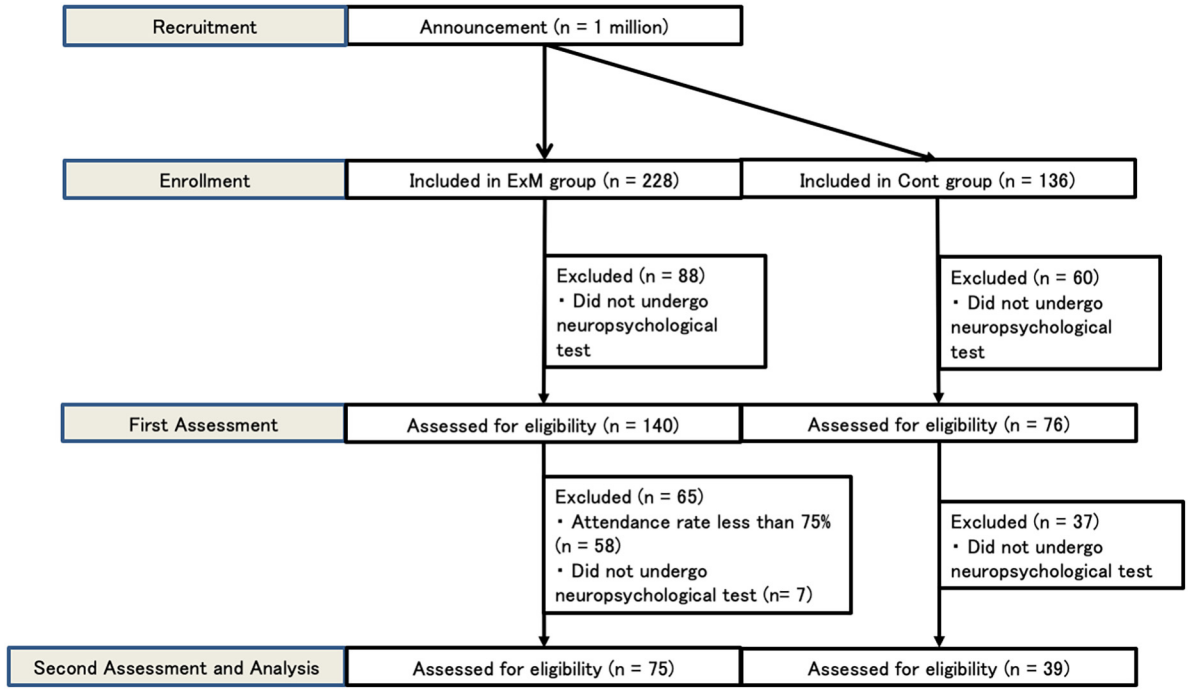

FIGURE 1
Flow chart of ExM and Cont group recruitment. Cont, control group; ExM, physical exercise with music group.

2.2. Exercise intervention

The ExM program was described in detail in our previous papers (Satoh et al., 2014, 2020; Tabei et al., 2017). The intervention period spanned over a period of 6 months, and participants were involved in a total of 20 exercise sessions. The exercise intensity gradually increased with each session. The exercise program and musical accompaniment were developed by the Yamaha Music Foundation approximately 20 years prior via a collaboration between the Japan Fitness Association and sport medicine experts. The musical accompaniment is classified as "synthesizer-heavy, dance-pop music." The ExM program consists of nine stages and was implemented by professional trainers. Exercises from the face-to-face program were implemented directly online. Individuals participated in the online version of the ExM (60 min, once a week, 20 times in total). The ExM was delivered to participants in real-time via Zoom, which is an application developed to hold seminars and conferences online using devices such as computers, smartphones, and tablets. Individuals participated in the ExM program by launching the Zoom software on a computer, smartphone, or tablet. Using the camera, the instructor provided appropriate instructions for the exercise. The participants' microphones were muted during the exercise program to limit sound disturbances and other problems.

2.3. Neuropsychological assessment

The neuropsychological assessment procedures were as described previously (Satoh et al., 2014, 2020; Tabei et al., 2017). The Mini-Mental State Examination (Folstein et al., 1975) and Raven's Colored Progressive Matrices (Raven and Court, 1993) were used to screen cognitive ability and quantify intellectual function, respectively. Memory was evaluated using the Logical Memory (LM)-I/-II subtests of the Rivermead Behavioral Memory Test (Wilson et al., 1985), which includes immediate and delayed recall of four short stories with different levels of difficulty and numbers of words. We used different stories for the pre- and post-testing periods to avoid familiarity with the story content. Visuospatial constructional ability was evaluated using the method described by Strub and Black (2000). Five types of figures (vertical diamond, two-dimensional cross, three-dimensional block, three-dimensional pipe, and triangle within a triangle) were shown to the participants, who were asked to draw them one by one. Each drawing was scored on a scale from 1 to 4 (0: poor, 1: fair, 2: good, and 3: excellent), with a maximum score of 15. Frontal lobe function was assessed using two tasks: the word fluency (WF) task and the Trail-Making Test-A/B task (Partington and Leiter, 1949). The WF task had category and letter domains. For the categorical WF task, participants were asked to name as many animals as possible in 1 min. For the letter WF task, participants were asked to say the name of objects that begin with each of the four phonemes, *ka, sa, ta*, and *te* (Dohi et al., 1992). We used the average scores for the four phonemes for statistical analyses. The neuropsychological tests described above can be conducted either in person or online using Zoom (Satoh et al., 2021a). Our group developed an online brain assessment tool (BA) for evaluating subtle cognitive decline (Satoh et al., 2021b). In the previous study, 5,000 participants completed the online BA, which consisted of five subtests: number memory, word memory, mental rotation, N-back, and judgment tests. Based on the results of our preceding research (Satoh et al., 2021a), cognitive scores (CS) were calculated

using the following formula: CS = ([raw score] − [mean of raw scores])/(standard deviation of raw scores) × 10 + 50. Additional details are available in our previous paper (Satoh et al., 2021b). The BA can be completed on the internet within 30 min. These neuropsychological assessments were administered before and after the 6-month intervention period among the ExM group. Cont group participants performed these assessments twice with an interval of 6 months.

2.4. Statistical analyses

We searched for group differences in the demographic variables, and assessed post-intervention changes in the neuropsychological assessment results between the ExM and Cont groups. The data regarding gender were evaluated using the chi-square test for dichotomous variables. The data regarding age, educational history, and cognitive function test scores were analyzed using the Shapiro–Wilk test. Based on the results, we performed t-tests for continuous variables and the Mann–Whitney U test for non-parametric data. Statistical analyses were conducted using IBM SPSS Statistics software version 27 (IBM Corp., Armonk, NY, United States).

3. Results

The participants were 114 healthy older adults (75 in the ExM and 39 in the Cont group; 63 men and 51 women; mean age 70.4 years). The age and educational history did not significantly differ between the two groups (**Table 1**). Although previous studies have suggested that a longer educational history may reduce the risk of developing dementia by either increasing the ease of clinical detection of dementia or imparting prior knowledge that delays the onset of the clinical symptoms (Stern et al., 1994), we found no significant differences in the present data. In the N-back task, the ExM group showed significantly greater improvement compared with the control group ($p = 0.008$). The groups did not significantly differ in terms of the other test measures (**Table 2**).

4. Discussion

The results indicated that the ExM group showed significantly higher improvements than the control group in the BA N-back task. The results suggested that the online version of ExM improved working memory. In contrast, there was no improvement in frontal lobe function as measured by the WF task or the Trail-Making Test-A/B task. Previously, it was assumed that there was one overarching frontal lobe syndrome, but it is now clear that several different cognitive and behavioral processes are mediated by the frontal lobes (Henri-Bhargava et al., 2018). For example, the dorsolateral prefrontal cortex is responsible for working memory, goal-directed attention, task switching, planning, problem solving, and novelty seeking (Jones and Graff-Radford, 2021). The ventral lateral prefrontal cortex is responsible for inhibition, response selection, and monitoring, whereas the medial prefrontal cortex is responsible for self-awareness, motivation, emotion regulation, and updating goal-directed behavior (Jones and Graff-Radford, 2021). The orbitofrontal cortex is involved in personality, inhibition, and emotional and social reasoning (Jones and Graff-Radford, 2021). The above-mentioned evidence suggests that the BA N-back task, the WF task, and the Trail-Making Test-A/B task measure different cognitive and behavioral processes, and that this was reflected in the improvement we observed in the N-back task but not in the Trail-Making Test-A/B and WF tasks. In a previous study (Tabei et al., 2017) in which the ExM was conducted face-to-face, significantly higher improvements were found for visuospatial processing. Visuospatial processing has been shown to consistently activate frontal regions such as the superior and inferior parietal regions responsible for spatial attention and the dorsolateral prefrontal cortex and anterior cingulate gyrus involved in working memory (Cohen et al., 1996; Silk et al., 2006). In a previous study that used face-to-face ExM (Tabei et al., 2017), the most important of the multiple brain regions involved in visuospatial processing could not be identified because the BA N-back task was not performed. Taken together, the results of this study and the previous study of face-to-face ExM (Tabei et al., 2017) suggest that physical exercise while listening to music has a positive effect on working memory.

With regard to memory, a previous study (Tabei et al., 2017) reported that within-group comparisons showed significant post-intervention improvements in the LM-I and -II subtests of the Rivermead Behavioral Memory Test in the ExM group. However, we only found a significant trend in the LM-II subtest when using the online version of the ExM. This could be related to the difference in the intervention period between the studies (1 year versus 6 months) or the difference between face-to-face and online interactions. Further research is needed to assess these possibilities.

While the online version of the ExM appears to be an effective alternative to face-to-face exercise programs in situations like the COVID-19 pandemic because it can be conducted at home, it may also be disadvantageous in that individuals do not have to physically go to the exercise center, resulting in a lack of commitment regarding participation and higher dropout rates. Individuals may be more likely to withdraw from the online ExM program because they have fewer chances for interaction and camaraderie among participants. Since the effects of ExM are expected to be sustained over a long period of time (Satoh et al., 2020), interactions and camaraderie among the participants could increase the sense of continuity and decrease the dropout rate.

This study had several limitations. First, the intervention period was 6 months. A previous study with healthy older participants applied an intervention period of 1 year. Therefore, future studies with a 1-year intervention using the online ExM are needed. Second, we did not compare our program with other interventions. Previous studies have assessed the effects of exercise without music and included these participants as a comparison group. Therefore, in the future, the online ExM program should be compared with other interventions to determine the source of changes in frontal lobe function. Third, it would be helpful to examine the extent to which participants in each group had active lifestyles. Last, access to online interventions is limited for older adults. It is often difficult for older people to operate a computer or tablet and thus to participate in neuropsychological testing and ExM. Although a national study (Sōmushō, 2021) showed that the use of digital technology is increasing among Japanese older adults, future studies and programs must implement methods to mitigate this "digital divide" to facilitate the ease of participation amongst older individuals.

TABLE 1 Characteristics of study participants.

			ExM	Cont	*P*-value
Age (SD), years			70.4 (4.3)	71.3 (4.9)	0.291
N (male: Female)			75 (36.39)	39 (27.12)	0.157
Education (SD)			14.91 (2.3)	15.41 (2.4)	0.370
Cognitive status	MMSE	Score	28.85 (1.4)	28.80 (1.3)	0.745
	RCPM	Score	31.88 (3.2)	33.60 (2.0)	0.147
		Time	251.00 (46.2)	267.90 (92.8)	0.972
Memory	LM-I		11.52 (3.3)	10.30 (4.4)	0.327
	LM-II		10.18 (3.0)	9.85 (4.5)	0.778
Visuospatial	Necker cube		2.88 (0.3)	3.00 (0.0)	0.250
	Copy		14.61 (0.7)	14.40 (0.7)	0.246
Frontal	WF	Category	17.22 (4.3)	16.40 (2.8)	0.572
		Letters	10.21 (2.5)	9.98 (3.3)	0.806
	TMT	-A	111.72 (33.1)	114.50 (33.7)	0.816
		-B	134.97 (40.2)	137.40 (81.2)	0.356
BA	Number memory		48.99 (12.8)	49.69 (12.3)	0.778
	Word memory		48.44 (12.1)	46.90 (9.6)	0.491
	Mental rotation		49.12 (16.1)	49.59 (12.5)	0.874
	N-back		51.37 (14.5)	55.56 (14.2)	0.142
	Judgment		51.16 (12.5)	47.59 (11.7)	0.143
	CS		49.85 (10.4)	49.75 (8.1)	0.959

ExM, physical exercise with music group; Cont, control group; SD, standard deviation; CS, cognitive score; MMSE, Mini-Mental State Examination; RCPM, Raven's Colored Progressive Matrices; LM, logical memory; WF, word fluency; TMT, Trail-Making Test; BA, brain assessment. Values in parentheses indicate standard deviation.

TABLE 2 Neuropsychological assessment result before and after intervention.

Test		Pre- and post-intervention differences, mean (± SD)			
			ExM	Cont	*P*-value
Cognitive status	MMSE	Score	0.46 (1.7)	0.30 (0.8)	0.370
	RCPM	Score	0.90 (2.2)	−0.80 (2.5)	0.070
		Time	−14.37 (45.1)	−27.00 (27.5)	0.403
Memory	LM-I		1.44 (2.6)	0.75 (3.1)	0.471
	LM-II		1.95 (2.8)	−0.05 (4.6)	0.080
Visuospatial	Necker cube		0.07 (0.4)	−0.10 (0.3)	0.216
	Copy		−0.07 (0.7)	−0.10 (1.1)	0.860
Frontal	WF	Category	−2.10 (3.2)	−2.10 (3.8)	0.998
		Letters	0.40 (2.3)	−1.08 (2.0)	0.065
	TMT	-A	1.94 (22.4)	−7.8 (24.7)	0.248
		-B	1.91 (40.6)	−10.4 (56.5)	0.695
BA	Number memory		7.23 (11.1)	7.67 (9.84)	0.835
	Word memory		3.24 (10.9)	2.74 (8.4)	0.979
	Mental rotation		−1.32 (15.8)	−1.51 (12.6)	0.947
	N-back		7.57 (12.5)	1.21 (10.6)	0.008*
	Judgment		5.59 (11.2)	6.08 (12.9)	0.652
	CS		4.25 (6.7)	3.15 (5.2)	0.375

Cont, control group; ExM, physical exercise with music group; LM, logical memory of the Rivermead Behavioral Memory Test; MMSE, Mini Mental State Examination; RCPM, Japanese Raven's Colored Progressive Matrices; SD, standard deviation; TMT, Trail-Making Test; WF, word fluency; BA, brain assessment; CS, cognitive scores; *$p < 0.05$.

5. Conclusion

In conclusion, the significant observed improvement in the N-back task suggests that the online version of the ExM improves working memory.

Data availability statement

The datasets presented in this article are not readily available because. Consent has not been obtained from the participant, so no one other than those involved in the study will have access to the dataset. Requests to access the datasets should be directed to tabei-kenichi@aiit.ac.jp.

Ethics statement

The studies involving human participants were reviewed and approved by The Research Ethics Committee of the Advanced Institute of Industrial Technology in Japan. The patients/participants provided their written informed consent to participate in this study.

Author contributions

KT and MS conceptualized and designed the experiments and wrote the manuscript. JO, CK, and MA conducted the experiments. KT analyzed the data. JO and YO contributed materials. All authors read and approved the final version of the manuscript.

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Conflict of interest

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Publisher's note

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Environmental enrichment through virtual reality as multisensory stimulation to mitigate the negative effects of prolonged bed rest

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Prolonged bed rest causes a multitude of deleterious physiological changes in the human body that require interventions even during immobilization to prevent or minimize these negative effects. In addition to other interventions such as physical and nutritional therapy, non-physical interventions such as cognitive training, motor imagery, and action observation have demonstrated efficacy in mitigating or improving not only cognitive but also motor outcomes in bedridden patients. Recent technological advances have opened new opportunities to implement such non-physical interventions in semi- or fully-immersive environments to enable the development of bed rest countermeasures. Extended Reality (XR), which covers augmented reality (AR), mixed reality (MR), and virtual reality (VR), can enhance the training process by further engaging the kinesthetic, visual, and auditory senses. XR-based enriched environments offer a promising research avenue to investigate the effects of multisensory stimulation on motor rehabilitation and to counteract dysfunctional brain mechanisms that occur during prolonged bed rest. This review discussed the use of enriched environment applications in bedridden patients as a promising tool to improve patient rehabilitation outcomes and suggested their integration into existing treatment protocols to improve patient care. Finally, the neurobiological mechanisms associated with the positive cognitive and motor effects of an enriched environment are highlighted.

KEYWORDS

physical inactivity, bed rest, disuse, mechanical unloading, non-physical interventions, virtual reality

Introduction

Prolonged bed rest has been identified as a risk factor for physiological deconditioning since 1947. A seminal study entitled "The Dangers of Going to Bed," (Asher, 1947) called attention to the risks it posed to older adults and the general population. Recent research conducted on hospitalized older adults has revealed that these patients spend up to 86% of their hospital days inactive, even though only a small percentage of cases, 5%, had a medical indication for bed rest (Jasper et al., 2020). This type of behavior is detrimental to both the physical and mental health of patients and poses a significant risk for functional

independence and chronic disability, collectively referred to as hospital-associated disability (Loyd et al., 2020).

Recent advances in the field of aerospace science and the development of experimental models of forced bed rest in healthy subjects provided a better physiological understanding of immobilization and strategies to counteract immobilization-induced functional deterioration. Prolonged immobilization can lead to adverse consequences not only in older adults, but also in younger individuals, affecting cardiovascular (Hoffmann et al., 2022), endocrine (Belavy et al., 2012), immune (Hoff et al., 2015), gastrointestinal (Iovino et al., 2013), vestibular (Dyckman et al., 2012), and cognitive (Lipnicki et al., 2009) systems. An interesting phenomena of non-uniform loss of muscle mass and strength was recently systematically reviewed on 318 subjects exposed to experimental bed rest (Marusic et al., 2021). After longer periods of bed rest, such as 35 days, the decline in strength was found to be two times higher compared to muscle atrophy. In the early days of bed rest, such as 5 days, even higher ratios were reported (Marusic et al., 2021). These findings raise new questions about the underlying mechanisms responsible for the disproportionate decline in strength compared with muscle atrophy. They also highlight the importance of early interventions to prevent or minimize the adverse effects of prolonged bed rest.

Body posture and prolonged bed rest also directly affect the brain, which was mainly studied with electroencephalography (EEG) and functional magnetic resonance imaging (fMRI). One of the first reviews to examine EEG dynamics under bed rest conditions reported changes in the theta and alpha bands suggestive of cortical inhibition, and highlighted the need for further evidence in this area (Marušič et al., 2014). More specifically, the 6° head-down tilt position (HDTP) during the bed rest reduced the resting-state spectral power within the delta, theta, alpha, and beta frequency bands (Brauns et al., 2021b). Lower activity in alpha and beta frequency bands was also observed in several sources within the centroparietal and occipital regions. These effects occurred shortly after posture establishment, remained stable during 60 days of bed rest, and returned to baseline upon the end of the bed rest (Brauns et al., 2021b). In addition to posture-specific changes in brain activity, functional brain changes, such as decreased amplitudes of P300 and late positive potential (LPP) of the event-related potentials (ERPs) indicated that 30-day bed rest adversely affected affective picture processing suggesting that physical inactivity might play a role in emotion regulation. These effects were localized in the insula, precuneus, and cingulate gyrus (Brauns et al., 2019). Furthermore, the investigation into electrocortical correlates of selective attention showed that a 60-day bed rest negatively affected task performance and ERP potentials in fronto-central and parietal brain regions. Importantly, these data did not return to their baseline values after an eight-day recovery period (Brauns et al., 2021a). A preliminary data on eight bedridden healthy older adults showed increased P100 and P200 amplitudes and decreased P100 latencies after being exposed to 14 days of horizontal bed rest (Marušiè et al., 2021). Finally, Friedl-Werner et al. (2020) used fMRI to show impaired memory formation and associated dysfunctional mechanisms in the hippocampus and parahippocampus after 60 days of continuous bed rest. Taken together, these studies suggest that immobilization and inactivity resulting from prolonged bed rest induce functional brain changes and cognitive impairments, the recovery of which may be longer than the cessation of bed rest. To counteract the formation of dysfunctional brain mechanisms and cognitive impairment, appropriate intervention strategies must be implemented during bed rest as part of a comprehensive recovery strategy. The recovery process following prolonged bed rest deconditioning is a complex and multifactorial process influenced by several factors, including the duration of bed rest, age, overall health status, and the degree of deconditioning. In older adults, the detrimental effects of skeletal muscle deconditioning are particularly pronounced and may even lead to catabolic changes in muscle tissue that favor the development of sarcopenia, as shown in a recent meta-analysis (Di Girolamo et al., 2021). In addition to various countermeasures developed to alleviate the deleterious effects of prolonged immobilization, such as centrifugation (Kramer et al., 2020), nutritional support (Gao and Chilibeck, 2020), and aerobic interventions (Holt et al., 2016), non-physical rehabilitation interventions (Marusic and Grosprêtre, 2018) administered during immobilization resulted in significant improvements in cognitive (Marusic et al., 2018, 2019) as well as physical function (Marusic et al., 2015; Paravlic et al., 2018). Non-physical rehabilitation encompasses interventions that focus on cognitive and/or sensory stimulation to improve cognitive and physical function rather than physical exercise or movement. Interventions aimed at enhancing sensory stimulation include multiple modalities, including visual, auditory, and tactile stimulation, with the goal of promoting an engaging and interactive experience for the individual. Virtual reality (VR) as a form of enriched environment holds the potential of a breakthrough technology for non-physical rehabilitation by providing multisensory information and more realistic simulations to improve patient rehabilitation outcomes. This paper reviewed current non-physical rehabilitation practices, assessed the potential impact of integrating VR systems in enhancing the recovery process, and finally highlighted the implicated neurobiological mechanisms associated with beneficial cognitive, and motor effects of enriched environment exposure. The report provided a synthesis of existing empirical evidence and suggested future avenues for investigation in this field.

Non-physical rehabilitation techniques

The frailty commonly experienced by bedridden patients poses a challenge to the implementation of conventional physical rehabilitation therapies in the early stages of hospitalization. The resulting deprivation of sensory input, including somatosensory and proprioceptive information, along with bed confinement, leads to rapid alterations in the organization of the sensorimotor system (Langer et al., 2012). These alterations revealed to have detrimental effects on postural balance and mobility (Koppelmans et al., 2017), movement duration and accuracy (Bassolino et al., 2012), tactile acuity (Lissek et al., 2009), and muscle properties (Clark et al., 2006). The decline in motor performance is attributed to the lack of feedback and feedforward mechanisms of motor control, which affects postural predictions and real-time movement

adjustments (Scotto et al., 2020). To counteract immobilization-induced functional decline, non-physical rehabilitation methods such as cognitive interventions (CI), motor imagery (MI), action observation (AO), and their combination, provide a valuable compensatory strategy (Marusic and Grosprêtre, 2018). These types of interventions can create an enriched environment in which certain cognitive functions can be trained (Marusic and Grosprêtre, 2018) or even a neural resemblance to actual voluntary movement can be established (Fox et al., 2016; Grosprêtre et al., 2016).

The field of CI encompasses various approaches, such as cognitive stimulation, cognitive rehabilitation, and cognitive training, as described by Marusic and Grosprêtre (2018). Briefly, cognitive stimulation involves social and group cognitive activities, including discussions and therapeutic conversations, with the goal of improving social and cognitive functioning. Cognitive rehabilitation uses personalized programs to improve activities of daily living, with healthcare providers, patients, and families working together to achieve goals primarily by improving cognitive function. Cognitive training consists of personalized, guided exercises tailored to individual abilities to improve cognitive function and can be delivered in paper-pencil or computerized versions (Marusic and Grosprêtre, 2018). As for the effects of bed rest on cognitive function, the results are still controversial; some studies indicated a positive (facilitating) effect, while others showed the opposite (Lipnicki and Gunga, 2009). Although there is limited literature on cognitive interventions during bed rest (Marusic et al., 2019), it is reasonable to assume that cognition (such as working memory, selective attention, inhibition, and cognitive flexibility) forms the basis of any non-physical intervention.

MI in which movements are mentally rehearsed through a kinesthetic experience or a visual representation with an internal or external perspective (Decety, 1996) elicits intracortical and corticospinal modulations that attenuate the deleterious effects of immobilization (Rannaud Monany et al., 2022). The kinesthetic experience, i.e., imagining the sensation experienced during the action, showed to be more efficient in motor learning (Fontani et al., 2014), in gaining (Yao et al., 2013), and in maintaining muscle strength (Paravlic et al., 2018), thus being generally more successful in activating sensorimotor representations (Meugnot et al., 2015; Oldrati et al., 2021). At the neurological level, the use of kinesthetic imagery resulted in greater similarity of activated brain networks to actual motor execution compared to visual methods (Yang et al., 2021). The results may be attributed to the insufficient sensory information in visual MI, which negatively affects the individual's ability to form a vivid and detailed representation of the movement. Studies employing a combination of AO and MI showed increased effectiveness in motor learning and rehabilitation outcomes, supporting to our hypothesis and demonstrating superiority over the use of each method individually (Eaves et al., 2016; Marusic and Grosprêtre, 2018). In this combined approach, the internally generated kinesthetic representations of an action are synchronized with the concurrent perception of the movement, augmenting the sensory experience of individuals through the integration of visual and auditory inputs, thereby enhancing the vividness of the MI task and leading to an increased sense of embodiment (Meers et al., 2020). With this in mind, the integration of enriched environments such as VR, which create the illusion of physical movement, has the potential to enhance the activation of motor-related brain regions. As a result, specific neural circuits are further activated, facilitating the desired neuroplastic adaptations (Slater, 2017).

Enriched environments: a multisensory approach for enhanced rehabilitation

In everyday life, people are typically exposed to variety of multimodal experiences, from the sounds of nature to the sights of the surrounding environment. However, in a hospital setting, these experiences are often limited, leading to a more restricted sensory experience. In addition, patients' attention may be disproportionately focused on their struggles, which may impair their ability to participate effectively in the rehabilitation process.

Despite the effectiveness of MI and AO in mitigating the loss of various physiological factors and facilitating motor recovery in bedridden patients, the implementation of these practices is generally limited to highly controlled and structured rehabilitation environments with limited variability and complexity compared with the unpredictable and dynamic nature of daily living. Failure to consider the impact of broader contextual factors, such as emotional and environmental influences, on real-world performance will limit the rehabilitation experience and may compromise the overall effectiveness of rehabilitation outcomes. XR-based environmental enrichment systems, in contrast, allow for the implementation of realistic scenarios engaging the patient's sensorimotor system (Brugada-Ramentol et al., 2022) due to the enhanced simulation of the kinesthetic, visual, and auditory senses. Moreover, the three-dimensionality (3D) of VR showed to elicit stronger fronto-parietal activations compared to AO and its two-dimensional (2D) representations (Jastorff et al., 2016).

Recent systematic reviews and meta-analyses have demonstrated the efficacy of VR in the rehabilitation of various conditions, including stroke (Leong et al., 2022), Parkinson's disease (Kashif et al., 2022), and cerebral palsy (Ziab et al., 2022), with demonstrated functional improvements (Howard, 2017) and structural changes in the brain (Feitosa et al., 2022). However, according to Šlosar et al. (2022), a clearer terminology for the variety of digital environments (see **Figure 1** for an overview) should be used to study the effects of interventions. Following this terminology, we proposed to use such non-physical interventions in conjunction with technological advances (**Figure 1**) in bedridden patients to mitigate the deterioration caused by bed rest.

Personal computers and consoles with displays and controlling gadgets (PC)

In a 14-day bed rest study (Marusic et al., 2015), a computer-assisted spatial navigation intervention consisting of moving through virtual environments using a joystick controller was used to counteract the adverse effects of immobilization on gait performance in healthy older adults. Compared with the control group (passive watching of TV), the intervention group showed significant improvement in dual-task effects for

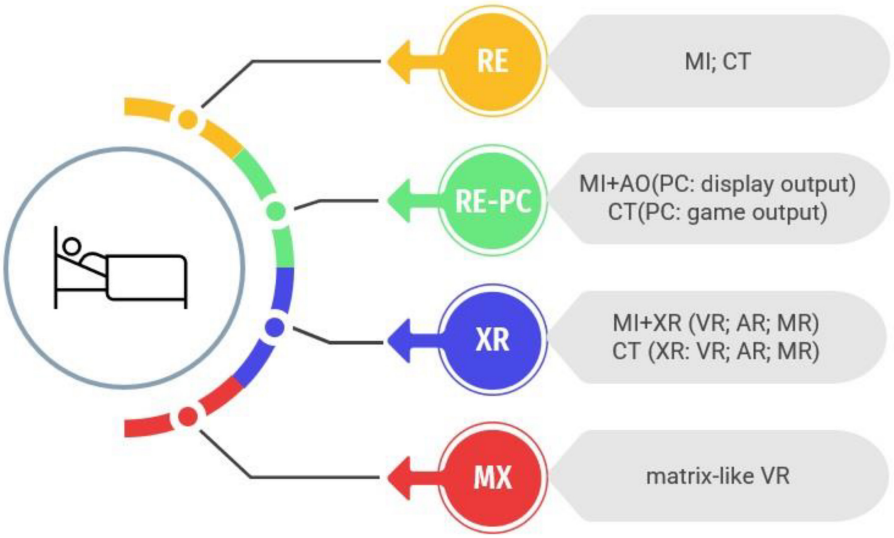

FIGURE 1
Evolution of intervention systems for bedridden patients: from real environment to fully immersive technologies. Intervention systems for bedridden patients have evolved over time, beginning with motor imagery (MI) and cognitive training (CT) in real environments (RE). These interventions have been enhanced with the use of personal computers and consoles (PC), incorporating action observation (AO) and displaying images through various screens. Advancements in technology have now made it possible to employ extended reality (XR) applications, such as virtual reality (VR), augmented reality (AR), and mixed reality (MR), in combination with MI or CT. Future developments aim to create fully immersive technologies that stimulate both the interoceptive and exteroceptive senses, a concept referred to as "Matrix-like" VR (MX).

self-selected and fast paced gait speed after bed rest. In the same study, control subjects were found to have increased gait variability under dual-task conditions (Marusic et al., 2015). The effects of such an intervention are explained in more detail in Marusic et al. (2019). In a usability study, Knols et al. (2017) demonstrated high acceptance and adherence to a gaming console adapted to be easily positioned at the patient bedside. Despite lacking clinical validation, the COPHYCON prototype showed significant short-term effects on measures of prefrontal cortex function in healthy elderly participants. In a study with patients with spinal cord injury (Villiger et al., 2013), an interactive game was integrated into an AO plus execution protocol. Wheelchair-bound participants were asked to observe an avatar performing movements with the lower limbs, and then mimic these movements by ankle flexion, hip extension, knee flexion, and leg adduction/abduction to control the avatar and complete gaming tasks. After a 4-week intervention period, assessments of gait capacity, postural stability, and muscle strength showed significant gains in lower extremity functionality. In addition, 50% of participants experienced reductions in both the intensity and unpleasantness of neuropathic pain symptoms. A study by Roosink et al. (2016) explored the use of a virtual feedback mechanism in a MI intervention for patients with the same pathology. The rehabilitation protocol consisted of performing MI of walking while seated in a wheelchair in front of a screen displaying an avatar walking through a forest. Participants were asked to concentrate on the sensory experiences produced by the interactive feedback, which was triggered by swinging their arms equipped with inertial sensors to match the pace of the imagined walking. The feasibility study reported improved vividness of MI with minimal adverse effects, indicating promising results for the response to MI interventions utilizing interactive feedback. Im et al. (2016) investigated the effects of combining MI (kinaestheic imagination of movements) with an interactive feedback mechanism on corticomotor excitability in both healthy older adults and stroke patients. They found that the combination resulted in increased amplitudes of motor evoked potentials compared to MI alone. This has significant implications for rehabilitation and recovery during periods of immobilization, as the combined approach can be utilized to target specific motor functions and improve motor performance, aiding in the recovery of lost motor abilities.

Virtual reality (VR)

In contrast to PC-assisted interventions, VR systems allow users to experience a fully synthetic, computer-generated digital environment that replaces the physical world (Šlosar et al., 2022). The increased sense of embodiment that is perceived positively influences the user's perception of their own body movements (Kong et al., 2017), leading to more accurate and effective outcomes in physical therapy. At the neurophysiological level, a study by Choi et al. (2020) demonstrated that event-related desynchronizations exhibited greater amplitudes with more distinct spatial features of the brain when MI is performed using a VR headset, compared to the display of the same images on a monitor. This modulation of neural activity by the degree of immersion provides important evidence for the use of VR technology in rehabilitation practice for bedridden patients (Xie et al., 2022). A recent study by Köyağasıoğlu et al. (2022) found that a 4-week intervention combining VR and MI significantly improved balance skills in healthy adults. While no significant differences were found in the center of pressure variable using a

TABLE 1 Comparative overview of intervention approaches for enriched environment.

Intervention approach	Potential benefits	Distinctive features
Personal computers and consoles (PC)	Provides interactive and engaging activities to stimulate cognitive functions.	Familiar and widely accessible technology.
	Provides a diverse array of games and applications, fostering a stimulating environment.	Suitable for patients with varying levels of computer experience.
Virtual reality (VR)	Creates a fully immersive and interactive digital environment, enhancing sensory experiences.	Greater sense of immersion, leading to more effective outcomes in rehabilitation.
	Provides a more realistic and vivid experience, promoting a stronger sense of presence.	Potentially better neuro-physiological modulation during tasks due to the immersive nature.
	Allows for realistic simulations and scenarios for therapeutic purposes.	May facilitate improved body movement perception during virtual exercises.
	Offers a more stimulating and engaging atmosphere compared to traditional therapies.	Provides personalized and tailored programs with authentic scenarios for effective MI and AO practices.

stabilometry device compared to a group combining PC and MI, the VR group demonstrated superior results on the Star Excursion Balance Test, particularly in posteromedial and posterolateral reach distances. In a similar experimental design, Bedir and Erhan (2021) compared the effects of 2D vs. 3D MI intervention on shot performances of archery, bowling, and curling athletes. Their findings showed the advantages of VR mental training in terms of shot performance after the 4-week training period. Yoshimura et al. (2020) investigated the effects of a VR contribution to the MI practice on the acquisition of prosthetic control using a prosthetic simulator in healthy individuals. Although the study was conducted with non-amputee participants, it yielded positive results in terms of supporting the daily activities of amputees, as evidenced by the enhancement in short-term prosthetic control acquisition following the acute practice of VR plus MI. In addition, self-assessed VR-based AO immersion level was found to have a negative correlation with the execution time of the bilateral manual dexterity task, supporting the idea that immersion is a crucial modulator of experience (Cummings and Bailenson, 2016) and thus has a positive influence on motor learning performance. See **Table 1** for an overview of the potential benefits and distinctive features of different enriched environment approaches in long-term immobilization.

In cases of functional decline due to immobilization, XR holds the potential to mitigate the early stages of muscle disuse-related declines in strength, which are attributed to loss of neuromuscular function (Campbell et al., 2019). The central and peripheral neural changes that occur can be effectively counteracted by corticospinal excitability elicited by MI in combination with VR. To illustrate the potential benefits of this approach, we adapted the figure from Marusic et al. (2021) showing the effects of bed rest on muscle atrophy and strength by adding a curve depicting the hypothetical decline in muscle strength if a XR intervention were implemented in conjunction with non-physical training interventions (**Figure 2**).

Despite the physical limitations imposed by illness or postoperative conditions that prevent patients from participating in conventional physical therapy, the psychosocial aspect of recovery is often overlooked. Previous research has found an association between the presence of anxiety and depressive symptoms and prolonged bed rest after discharge from critical care (Peris et al., 2011) and in experimental studies of bed rest (Ishizaki et al., 1994; Dimec Èasar, 2015). Enriched environments have been shown to be a critical tool in motivating patients to participate in rehabilitation practices (Boiko et al., 2022). They provide a stimulating and engaging atmosphere that promotes mental and emotional well-being, thus addressing patients' often neglected psychosocial needs, resulting in better overall outcomes.

Neurobiological mechanisms supporting beneficial effects of enriched environments

Several enriched environments related neurobiological mechanisms have thus far been recognized as neuroprotective and their effectiveness was also demonstrated in neurodegenerative disorders, such as in delaying the onset of Alzheimer's disease (AD) (Liew et al., 2022) and the progression of Parkinson's Disease (PD) (Alarcón et al., 2023). The following paragraphs highlight the most commonly known mechanisms, however, are not meant to provide an extensive overview (for this, see Liew et al., 2022; Alarcón et al., 2023).

Several animal studies have demonstrated that exposure to enriched environments led to beneficial effects on hippocampal structures, such as promoting hippocampal neurogenesis (Garthe et al., 2016), as well as increasing proliferation of progenitor cells and hippocampal cell survival (Olson et al., 2006; Ramírez-Rodríguez et al., 2014; Grońska-Pęski et al., 2021). Furthermore, the enriched environments exposure also restored the impaired neurogenesis in adult transgenic rodent models of AD after the deposition of Aβ plaques (Rodriguez et al., 2011; Valero et al., 2011; Llorens-Martín et al., 2013). The structural changes increasing the volume of the hippocampus may result in improved cognitive function (Hüttenrauch et al., 2016), while the hippocampal activity of the excitatory neurons could promote learning and memory formation (Stuchlik, 2014). Furthermore, enriched environments revealed to promote the expression of neurotrophins, such as the brain-derived neurotrophic factor (BDNF) (Kazlauckas et al., 2011; Kondo et al., 2012; Xu et al., 2015; Dandi et al., 2018), and nerve growth factors (NGF) (Torasdotter et al., 1998; Gelfo et al., 2011), which induce the differentiation and survival of neurons (Miranda et al., 2019), and regulate the excitatory and inhibitory transmission in the adult brain.

The dopaminergic system plays a central role in the pathology of PD and its dysfunction was implicated in movement and coordination difficulties (Glenthøj and Fibiger, 2019). Rodent models of PD mimic the neurodegeneration of the nigral

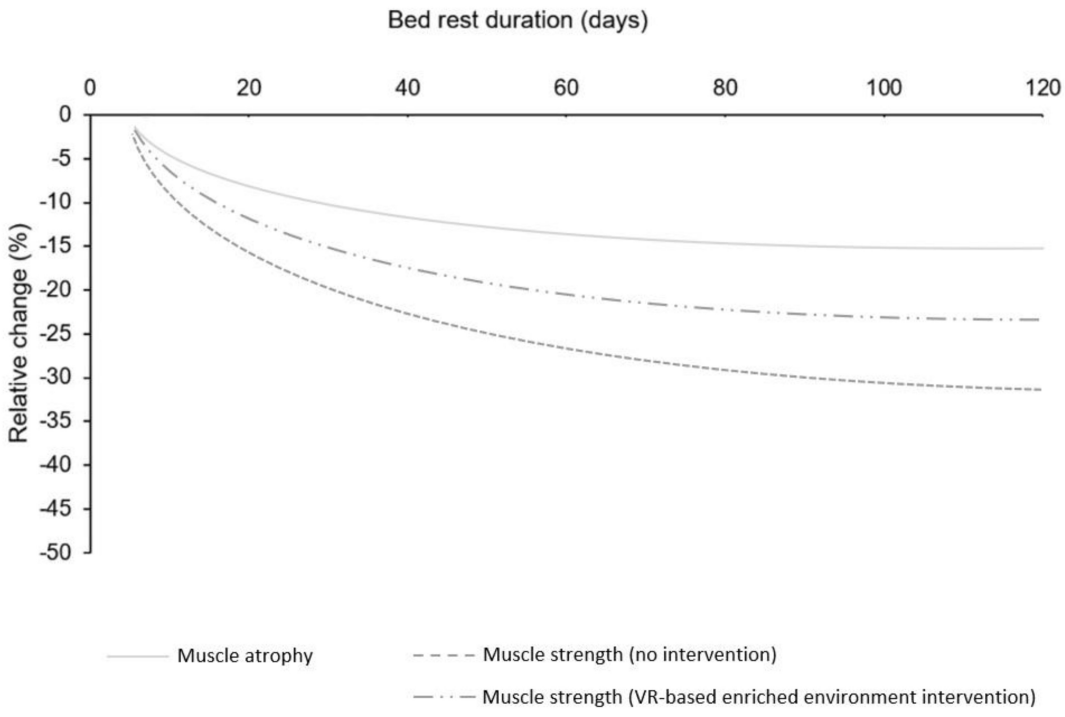

FIGURE 2
Speculative decline in muscle strength following XR intervention in conjunction with non-physical intervention: Adapted from Marusic et al. (2021).

dopaminergic system by inducing lesions and these studies have demonstrated that exposure to enriched environments beneficially affected the dopaminergic system including dopamine metabolism, the enzymes implicated in both dopamine synthesis and degradation, dopamine receptors, and its storage into vesicles (Jungling et al., 2017). The beneficial effects of enriched environments were also demonstrated in other neurotransmitter systems affected by PD, namely cholinergic, glutamatergic, and GABAergic (Alarcón et al., 2023).

Taken together, the neurobiological mechanisms supporting enriched environments, indicate that interventions combining sensory, cognitive, and physical stimulation at a heightened level could be used as a strategy for preventing cognitive/motor decline, but also as an approach or supporting treatment in managing aspects of complex neurodegenerative disorders.

Conclusions and future perspectives

From a neurophysiological standpoint, observing movements promotes the development of motor skills (Ferrari, 1996). Among cutting-edge technologies, XR presents a viable way to activate the sensorimotor system and consequently boosting cognitive abilities and adaptability. XR in combination with MI can serve as a tool for enhanced sensorimotor feedback that promotes procedural learning. The use of 3D visualization systems that provide real-time 360-degree visual scanning can enhance the effectiveness of MI by allowing participants to rely on relevant stimuli and cues in a way that mimics real-world scenarios, thus overcoming the limitations of conventional 2D display methods used in AO. The enhanced proprioception, i.e., the sense of the position and movement of the body and its parts, and the vestibular system that arise from the user's head movements while using a VR device (Michalski et al., 2019) provide a more interactive experience.

VR systems allow precise control of rehabilitation treatment, including manipulation of stimuli and distractors, so therapy sessions can be tailored to each individual's needs. In this regard, the sensory information delivered through head-mounted displays goes beyond visual data, incorporating synchronized auditory information to further immerse the participant in the desired virtual environment. Current research focuses on incorporating haptic stimuli into VR-assisted MI to enhance the illusion of body ownership and the overall experience (Du et al., 2021). In addition, studies showed that the use of synchronized visual-haptic neurofeedback during MI can lead to improved outcomes in traditional neurofeedback training with brain-computer interfaces, particularly with respect to sensorimotor cortical activation (Wang et al., 2019).

Emerging evidence suggests that XR-based enriched environments may offer superior multisensory stimulation than traditional approaches, such as AO techniques combined with MI. However, the use of XR in bedridden patients is an area that requires further investigation, as most studies were limited to feasibility and usability assessments in symptomatic patients. In the absence of randomized controlled trials of the efficacy of XR in bedridden patients, it is difficult to draw definitive conclusions about its effectiveness. Future research is needed to fully understand the potential benefits and limitations of using XR-based enriched environments for bedridden patients and to explore how this technology can be integrated into existing treatment protocols to improve patient outcomes.

Author contributions

UM, LŠ, and RP contributed to the initial idea and structure of the review. LŠ, UM, and MP contributed to the writing of the first draft of the manuscript. All authors contributed to the subsequent revisions and approved the final manuscript.

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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Virtual reality as a tool to explore multisensory processing before and after engagement in physical activity

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Introduction: This pilot study employed a non-randomized control trial design to explore the impact of physical activity within a virtual reality (VR) environment on multisensory processing among community-dwelling older adults.

Methods: The investigation compared both chronic (over 6 weeks) and acute effects of VR-based physical activity to a reading control group. The evaluation metrics for multisensory processing included audiovisual response time (RT), simultaneity judgments (SJ), sound-induced flash illusion (SIFI), and temporal order judgments (TOJ). A total of 13 older adults were provided with VR headsets featuring custom-designed games, while another 14 older adults were assigned to a reading-based control group.

Results: Results indicated that acute engagement in physical activity led to higher accuracy in the SIFI task (experimental group: 85.6%; control group: 78.2%; p = 0.037). Additionally, both chronic and acute physical activity resulted in quicker response times (chronic: experimental group = 336.92; control group = 381.31; p = 0.012; acute: experimental group = 333.38; control group = 383.09; p = 0.006). Although the reading group showed a non-significant trend for greater improvement in mean RT, covariate analyses revealed that this discrepancy was due to the older age of the reading group.

Discussion: The findings suggest that immersive VR has potential utility for enhancing multisensory processing in older adults. However, future studies must rigorously control for participant variables like age and sex to ensure more accurate comparisons between experimental and control conditions.

KEYWORDS

aging, audiovisual integration, physical activity, multisensory, virtual reality

Introduction

Physical activity has been consistently shown to play a crucial role in maintaining and improving cognitive and perceptual processes. This is particularly relevant for older adults, as illustrated in foundational studies by Colcombe and Kramer (2003). Perceptual processes like multisensory integration—the ability to combine and interpret sensory information from various sources such as vision, hearing, and touch—are enhanced by regular physical exercise. This leads to better cognitive function, motor learning, and overall well-being (Colcombe and Kramer, 2003; Hillman et al., 2008).

The majority of research on the effects of physical activity on cognition involves traditional exercise forms like biking and treadmill running. Studies often span several months and focus on older adults, with or without cognitive impairment. For instance, in a landmark study by Colcombe et al. (2006), they found significant increases in brain gray and white matter among aerobic exercise participants, particularly in regions tied to cognitive functions like attention and memory. A follow-up study (Erickson et al., 2011) established a direct link between aerobic exercise and memory improvements.

However, most research has focused on the chronic effects of exercise. Yet, single bouts of aerobic exercise also hold promise for improving cognitive and perceptual function (Davranche and Audiffren, 2004; Davranche and Pichon, 2005; Lambourne et al., 2010; Chang et al., 2012; Pontifex et al., 2019). Specifically, limited studies have investigated how aerobic exercise influences multisensory processing in older adults. One seminal study by O'Brien et al. (2017) found that after 60–80 min of aerobic exercise, sensitivity to the Sound Induced Flash Illusion (SIFI) increased, particularly when the aerobic activity was unpredictable.

The underlying mechanisms for these effects are thought to be multifaceted. Changes in arousal levels, indicated by metrics like heart rate and skin conductance, are often cited (Lambourne et al., 2010; Chang et al., 2012; Pontifex et al., 2019). Other physiological factors such as the production of neurotrophic factors like BDNF, IGF-1, and VEGF also play roles in cognitive and perceptual function enhancement (Cotman et al., 2007; Chang et al., 2012; Pontifex et al., 2019).

The COVID-19 pandemic highlighted the need for alternative physical activity options. This is particularly crucial for older adults, who faced disruptions to their exercise routines due to closures of fitness facilities. Exergames, or interactive games that combine physical activity and gaming, have thus emerged as a viable alternative. Virtual reality (VR) exergaming (Šlosar et al., 2022) can offer an especially immersive experience and has shown promise in enhancing physical activity, motor learning, cognitive function, and emotional well-being in older adults (Miller et al., 2014; Molina et al., 2014; Amorim et al., 2019; Campo-Prieto et al., 2021; Yen and Chiu, 2021).

Yet, there is limited research on the effects of VR-based physical activity on sensory integration processes in older adults. Merriman et al. (2015) studied balance training using a VR display that was placed approximately 2 M away from the participant (i.e., non-immersive environment) and found a correlation between improved balance and susceptibility to the SIFI. Given the potential risks associated with aging, such as falling and poor decision-making due to perceptual processing changes (Setti et al., 2011a; Donoghue et al., 2014; Merriman et al., 2015), VR interventions may offer unique benefits.

In light of these gaps, our project aims to extend the evidence related to the effects of acute and long-term physical activity in a VR setting on perceptual processes. Specifically, we hypothesize that a 6-week VR the intervention will positively impact multisensory integration processes. These hypotheses are based on previous research suggesting both acute and chronic exercise can influence these processes (O'Brien et al., 2017; Basharat and Barnett-Cowan, 2023).

To this end, we developed an immersive VR physical activity intervention called Seas the Day, specifically tailored to the needs and preferences of older adults. This pilot study assesses the impact of this intervention on multisensory integration, aiming to contribute to our understanding of how alternative forms of exercise can benefit cognitive and perceptual function in older adults.

Methods

This study is based on data from a larger pilot, non-randomized controlled trial that assessed the effects of a VR physical activity game on cognition, perception, mental well-being, changes in physical activity behaviour outside of the game, and game experience in community-dwelling older adults. Primary outcomes reflect the feasibility of a VR intervention that engaged upper extremity movement and assessments to evaluate its effects on cognition and perception. Effectiveness analyses presented below are exploratory. Assessments were conducted both before and after the 6-week intervention period (chronic effects) and before and after game plan on several days within the intervention period (acute effects).

Intervention: VR hardware and software

Seas the Day[1] is a custom-made VR intervention co-created to promote exercise among older adults. The game is publicly available and has been designed to foster an enjoyable physical activity session using a Tai-Chi routine, boat rowing task, and fishing. Seas the Day requires the use of the standalone VR headset, Oculus Quest 2 and the entire experience lasts 15–20 min. Generally and for the purpose of this study, the headset was an all-in-one solution for participants to engage with the VR games, through the use of two controllers. Seas the Day was designed to be played in a seated position to prevent falls as shown in Figure 1.

Intervention: reading

Participants read from a physical book for 15–20 min in the comfort of their homes. Each participant read what they felt was interesting and engaging. When inquired about the content of the materials participants read, none revealed it to be content that increased their heart rate or their level of anxiety. Informally, participants reported the activity to be relaxing and engaging.

Participants

The study included a convenience sample of 13 participants in the experimental (physical activity intervention) group and 14 participants in the control (reading) group, all of whom were community-dwelling older adults with or without cognitive impairment. Participants were recruited through various sources, including the Waterloo Research in Aging Pool (WRAP), the Centre for Community, Clinical and Applied Research Excellence (CCCARE) mailing list, professional networks, and personal social media accounts.

1 https://www.oculus.com/experiences/quest/4164068860279573

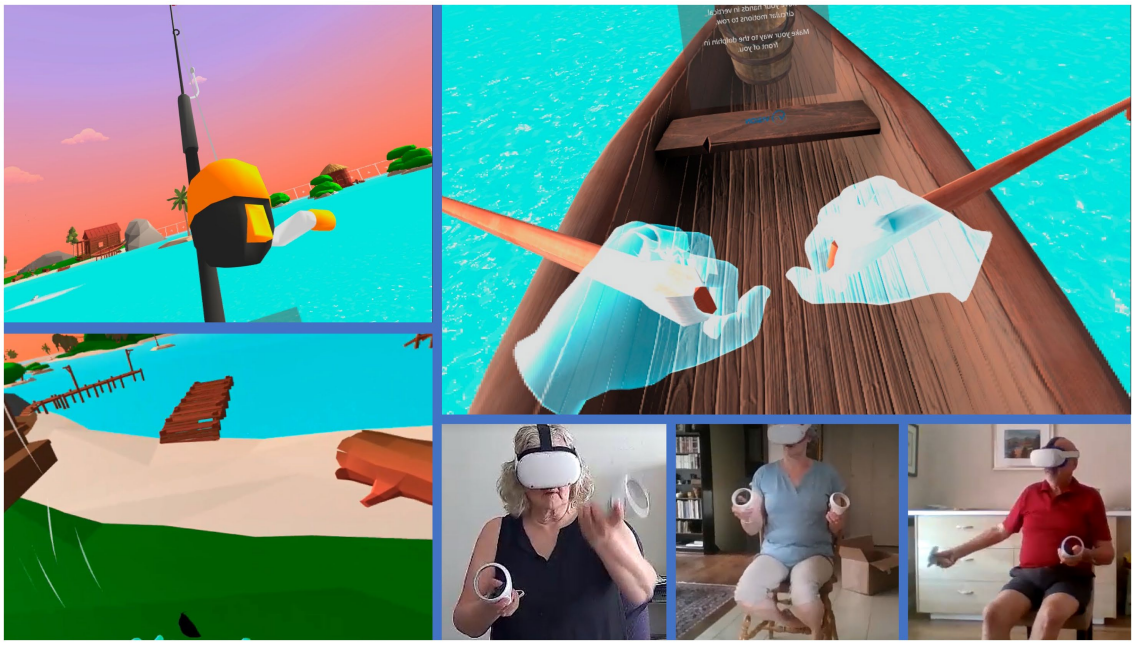

FIGURE 1
Screenshots of Seas the Day, a VR intervention to promote exercise among older adults.

The inclusion criteria were as follows: aged 60 years or older, able to provide consent, able to complete the Montreal Cognitive Assessment (MoCA) with a score of 18 or higher, able to communicate verbally in English, able to participate in light-to-moderate unsupervised activity without requiring medical approval, ability to access a laptop or desktop PC, and access to internet at their residence. Participants were excluded based on criteria related to dementia, hearing impairment, ear infection, middle ear diseases, uncorrected visual impairment, motion sickness, pre-existing conditions that preclude exercise, or having a heart pacemaker. Demographic information was collected for both the physical activity (mean age = 68.46, n = 6 females) and reading (mean age = 74.83, n = 12 females) intervention groups. See Tables 1, 2 below for further information regarding the participants included in the study as part of the experimental and control group, respectively.

Procedure

Participants were asked to play Seas The Day three times a week for 6 weeks. Seas The Day was the only game that participants had access to in the provided VR headset. Participants were encouraged to maintain consistency in engaging with the VR intervention by playing in the mornings and preferably on the same days every week. They were notified that each intervention session would take approximately 15–20 min to complete. Participants were introduced to the OMNI rate of perceived exertion scale and were encouraged to achieve a light to moderate intensity (as indicated by the scale; ≤6 out of 10) when playing the game. Set-up of the VR intervention and ongoing participation in the intervention were supported in a number of ways. First, participants were provided with step-by-step software and hardware manuals (see Mehrabi et al., 2022). Second, each participant met with study staff or trainees for a remote introductory session *via* a video conference platform. The team member showed participants how to use the system while sharing their screen, so participants could see and become familiar with the visual information and the overall interaction with the system. The team member also demonstrated how to calibrate the system and played the game, stage by stage, while answering any questions as they arose. Participants were then encouraged to interact with the system during a familiarization session where they tried engaging with the intervention in the presence of a team member. During the familiarization session, participants were encouraged to speak aloud about what they were seeing and experiencing so they could be guided by the team member if they faced any difficulties. In addition to the familiarization session, participants were able to contact study staff and trainees to troubleshoot the system *via* email, phone, text or video calls at any time, as most appropriate for the situation and the participant's comfort. During the troubleshooting video calls and to facilitate the explanation, participants were offered screen-sharing options as well as the option to see the view from the frontal camera of the study staff or trainee's computer to see how the team member was located and moving in the physical space. Finally, study staff and/or trainees interacted with participants on a bi-weekly basis to ensure that participants were playing the game and engaging with the cognitive and perceptual tasks appropriately.

This study specifically used data from four perceptual tasks (audiovisual RT task, SIFI, SJ task, and TOJ task) to investigate the effects of engagement in physical activity in a virtual environment in community-dwelling older adults to determine how chronic (6 weeks) and acute bouts of physical activity within virtual environments, as compared to reading, impact multisensory integration processes. Participants completed various assessments, questionnaires, and cognitive tasks at baseline, before, and after selected intervention

TABLE 1 Demographic details regarding sex (males = 7), age (mean = 68.46, s.e. = 1.34), education (1 individual with a high school degree or equivalent; 8 with at least some post-secondary education including post-secondary certificate, diploma, or degree; 4 with postgraduate degrees), and ethnicity (all Caucasian, but one).

ID	Sex	Age	Education	Ethnicity	MoCA	PASE - B	PASE - PI
1	M	61	Post-Secondary	Caucasian	27	153.27	133.75
2	F	71	Post-Secondary	Caucasian	27	50	113.6
3	F	64	Post-graduate degree	Mixed	22	153.64	142.4
5	M	77	Post-graduate degree	Caucasian	29	97.74	60.61
6	F	60	Post-secondary	Caucasian	28	124.85	166.56
7	M	67	Post-secondary	Caucasian	29	176	143.2
8	F	67	Some post-secondary	Caucasian	28	52.31	83.2
9	M	70	Post-graduate degree	Caucasian	25	164.4	233.42
10	F	70	High school diploma	Caucasian	28	172.86	174.82
11	M	69	Post-secondary	Caucasian	30	219.67	176.3
12	M	75	Post-graduate degree	Caucasian	21	85.25	39.5
14	F	69	Post secondary	Caucasian	28	60.61	67.31
15	M	70	Some post-secondary	Caucasian	25	58.6	32.53

Cognitive function of each participant was assessed using the Montreal Cognitive Assessment (MoCA) and the scores of each participant have been reported above (mean = 26.69, s.e = 0.75). Participants also reported on their habitual exercise habits using the Physical Activity Scale for the Elderly (PASE) both at baseline (B; mean = 120.71, s.e. = 15.72) and at post-intervention (PI; mean = 120.55, s.e. = 16.84); the values self-reported by each participant are presented in the table. A higher PASE score indicates higher level of physical activity.

TABLE 2 Demographic details regarding sex (males = 2), age (mean = 74.83, s.e. = 1.48), education (4 individuals with high school degrees or equivalent; 7 with at least some post-secondary certificate, diploma, or degree; 3 with postgraduate degrees), and ethnicity (all Caucasian).

ID	Sex	Age	Education	Ethnicity	MoCA	PASE - B	PASE - PI
17	F	69	Post-Secondary	Caucasian	29	131.8	111.8
18	F	76	High school diploma	Caucasian	27	131.8	106.57
19	F	80	Post-secondary	Caucasian	23	165.86	143.71
21	M	74	Post-secondary	Caucasian	24	255.81	163.7
22	F	89	Post-secondary	Caucasian	26	76.4	51.4
23	F	86	Post-graduate degree	Caucasian	28	93.6	116.89
24	F	77	High school diploma	Caucasian	24	89.91	78.11
26	F	75	High school diploma	Caucasian	29	123.2	142.23
28	F	79	Post-secondary	Caucasian	28	99.54	91.53
29	F	71	Post-graduate degree	Caucasian	30	95	130
30	M	71	Post-graduate degree	Caucasian	27	133.53	182.71
31	F	74	Post-secondary	Caucasian	20	-	148.37
33	F	77	High school diploma	Caucasian	23	163.58	140.88
34	F	75	Post-secondary	Caucasian	25	124.6	162.8

Cognitive function of each participant was assessed using the Montreal Cognitive Assessment (MoCA) and the scores of each participant have been reported above (mean = 25.93, s.e = 0.77). Participants also reported on their habitual exercise habits using the Physical Activity Scale for the Elderly (PASE) both at baseline (B; mean = 129.59, s.e. = 12.98) and at post-intervention (PI; mean = 126.59, s.e. = 9.67); the values self-reported by each participant are presented in the table. A higher PASE score indicates higher level of physical activity.

sessions. The pre-assessments took between 1 h and 40 min to 2 h and 10 min to complete. In addition, the researchers maintained bi-weekly meetings with the participants to monitor their progress and address any concerns. The post-assessments took approximately 1 h and 20 min to 1 h and 50 min to complete. Due to the fact that the materials presented in this manuscript stem from a larger pilot-study, time for testing the effects of engagement with a VR game on multisensory processes was limited and therefore not all tasks could be performed every week. Thus, the tasks with the most evidence for changes post-engagement in physical activity were selected to be performed more regularly as compared to tasks with limited evidence (see Merriman et al., 2015; O'Brien et al., 2017 for effects of physical activity on the SIFI task and see Mahoney et al., 2015; Basharat and Barnett-Cowan, 2023 for effects of physical activity on RT).

Once all the assessments and tasks were completed in week 1, participants began either the VR or reading intervention remotely from their homes. Each participant in the VR intervention group received an Oculus Quest 2 VR headset with Seas the Day installed, VR controllers, an instruction booklet, a weekly checklist for progress tracking, a VR system care guide, various questionnaires (see Table 3;

TABLE 3 Summary of data collected for the larger pilot non-randomized controlled trial (adapted from Mehrabi et al., 2022).

	Time Points														
		Baseline	Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		Post-intervention
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
Background and demographic	Demographic questionnaire	x													
	MoCA	x													
	GDS-15	x													
	GAQ	x													
Executive function	OTMT	x	x	x			x	x			x	x			x
	VF	x	x	x			x	x			x	x			x
	Modified flanker task	x	x	x			x	x			x	x			x
Multisensory integration	SIFI task	x			x	x			x	x			x	x	x
	SJ task	x													x
	TOJ task	x													x
	RT task	x	x	x			x	x			x	x			x
Physical activity, mood, and exercise self-efficacy	PAAS	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	PASE	x													x
	Exercise self-efficacy	x				x				x				x	
	PRE			x		x		x		x		x		x	
	Perceived enjoyment			x		x		x		x		x		x	
	Usability and game user experience questionnaire														x

Alongside demographic information, only the Response Time (RT), Sound Induced Flash Illusion (SIFI), Simultaneity Judgment (SJ), and Temporal Order Judgment (TOJ) tasks were analyzed for this manuscript and presented below to assess the effects of engaging in physical activity in VR and reading on multisensory processing. RPE (OMNI Rate of Perceived Exertion), perceived enjoyment, and the usability and game user experience questionnaire were completed only by those in the VR intervention group, as they pertain to their experience with Seas the Day. MoCA, Montreal Cognitive Assessment; GDS-15, Geriatric Depression Scale; GAQ, Get Active Questionnaire; OTMT, Oral Trail Making Test Part A and B; VF, Verbal Fluency test; PAAS, Physical Activity Affect Scale; PASE, Physical Activity Scale for the Elderly.

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Mehrabi et al., 2022 for further information) and blank sheets of paper for noting comments and concerns. The headset, sanitizing protocol, instruction booklet, and questionnaires were all delivered to participants' homes *via* mail or by a research team member, adhering to public health guidelines for social and physical distancing during the pandemic. Participants in the reading group received the same items as the VR group, except for the Oculus Quest 2 VR headset, VR controllers, and the VR-related questionnaires (RPE, perceived enjoyment, and game user questionnaires [Self-reported physical (e.g., motion sickness, vertigo, nausea, etc.) or emotional (e.g., fear, anxiety, etc.) discomfort]). Those in the reading group read a physical book of their choice. Chronic effects of intervention were investigated *via* comparison of performance between the two groups on baseline and post-intervention sessions, while exploratory analyses were conducted to assess acute performance by comparing the weeks between baseline and post-intervention.

Experimental setup

Participants were divided into an intervention group (physical activity in VR) and a control group (reading), recruited consecutively using the same inclusion and exclusion criteria (see Participants section). The intervention was 6-weeks long, with pre- and post-assessments as well as semi-structured interviews post-intervention. Note that in this paper we present the quantitative results related to sensory processing and the qualitative results will be discussed elsewhere in a separate publication.

The perceptual tasks presented in this manuscript were created with PsychoPy builder, exported into PsychoJS (Javascript), and hosted on Pavlovia, allowing the experiments to run in a browser with a precision of under 3.5 ms (Bridges et al., 2020). Participants completed the perceptual tasks on their computing device of choice (laptop or desktop computer) using Firefox as their browser. They were provided with instructions embedded in each task and were asked to sit in a quiet room, adjust the brightness and sound on their device, and not use headphones to ensure that the auditory stimuli appeared to stem from the same location as the visual stimuli.

During the perceptual tasks, participants were asked to directly face their personal computing device and place it at an approximate distance of 57 cm. The visual stimuli were presented as white circles subtending 2° of visual angle, appearing approximately 8° below the fixation cross (visual angle = 1.5°) for approximately 16 ms. Auditory stimuli were presented as a beep (approximately 3,500 Hz, 16 ms, 68 dBA) through the device's speakers or through external speakers placed beside the screen. Each trial began with a stimulus presented after a delay of 1,000–3,000 ms to reduce temporal predictability. Participants used a computer keyboard to input their responses for each trial. They completed the SIFI, SJ, TOJ, and RT tasks in a randomized order during the baseline and post-intervention sessions. Practice trials were conducted before each experimental task.

Detailed procedure of the perceptual tasks

Auditory stimuli were presented at a suprathreshold level (3,500 Hz, 16 ms, 68 dBA). The visual stimuli were presented as a 0.4° white circle (49.3 cd/m^2) against a black background (0.3 cd/m^2), appearing 2° below the fixation cross for 17 ms. The fixation cross, designed to minimize involuntary eye movements, resembled a combination of a bullseye and crosshair (visual angle = approximately 1.5°). Participants were instructed to fixate on this cross throughout the experimental procedure, as in previous in-lab studies. The stimulus onset asynchronies (SOAs) used in this study were chosen to ensure that participants could complete each task in a short period of time without losing interest or abandoning the task. To maintain consistency across the four perceptual tasks, the same stimuli and stimulus duration were used.

Sound induced flash illusion

The SIFI task consisted of three conditions (vision-only, auditory-only, and audiovisual). In the vision-only block, participants were shown two flashes and asked to indicate the number of flashes they saw. In the auditory-only block, participants were presented with two beeps and asked to indicate the number of beeps they heard. The following SOAs were used in these conditions: 70 ms, 150 ms, and 230 ms for both 2 beep and 2 flash conditions. There were 30 trials in each of the unimodal conditions, with each SOA presented 10 times. Participants were explicitly told to respond as accurately as possible instead of quickly. The unimodal visual condition trials were randomly interleaved with the multimodal audiovisual trials, and the auditory block was completed separately, as instructions and modality of interest differed between auditory and audiovisual conditions.

The audiovisual trials included two control conditions (1 beep/1 flash and 2 beeps/2 flashes) and an illusory condition (2 beeps/1 flash). In the audiovisual control conditions, the auditory and visual stimuli were presented simultaneously. In the 2 beeps/1 flash illusory condition, auditory-lead trials presented the auditory stimulus first, followed by simultaneous auditory and visual stimuli at variable SOAs. In vision-lead trials, the first auditory stimulus was accompanied by a visual stimulus, and the second auditory beep was presented after a variable SOA. The multimodal condition used the following SOAs: 0 ms, ±70 ms, ±150 ms, and ± 230 ms, with '+' indicating vision-lead trials and '-' indicating auditory lead trials. The three audiovisual conditions were randomly presented within the testing block to prevent response bias (see Figure 2 as well as Supplementary Figure S1; Supplementary Table S1 for further information).

Participants were asked to fixate on the fixation bullseye throughout the task and reported the number of flashes seen while ignoring the auditory stimuli. All conditions were repeated 10 times, totaling 100 trials (including 10 repetitions for 0 SOA with simultaneous presentation of a single beep and flash). In total, 166 trials were presented for all three conditions (vision-only, auditory-only, and audiovisual), including 6 practice trials to familiarize participants with the task. The task took approximately 10 min to complete. Previous literature indicates that participants may report perceiving three or more stimuli; thus, responses were not limited to '1' or '2', as participants could have perceived more than the presented number of stimuli (audio or visual). Participants were explicitly instructed to prioritize accuracy over speed.

Participants completed this task not only at the beginning and end of the intervention, but also six times during the intervention (pre- and post-gameplay or reading engagement during weeks 2, 4, and 6), for a total of 8 times.

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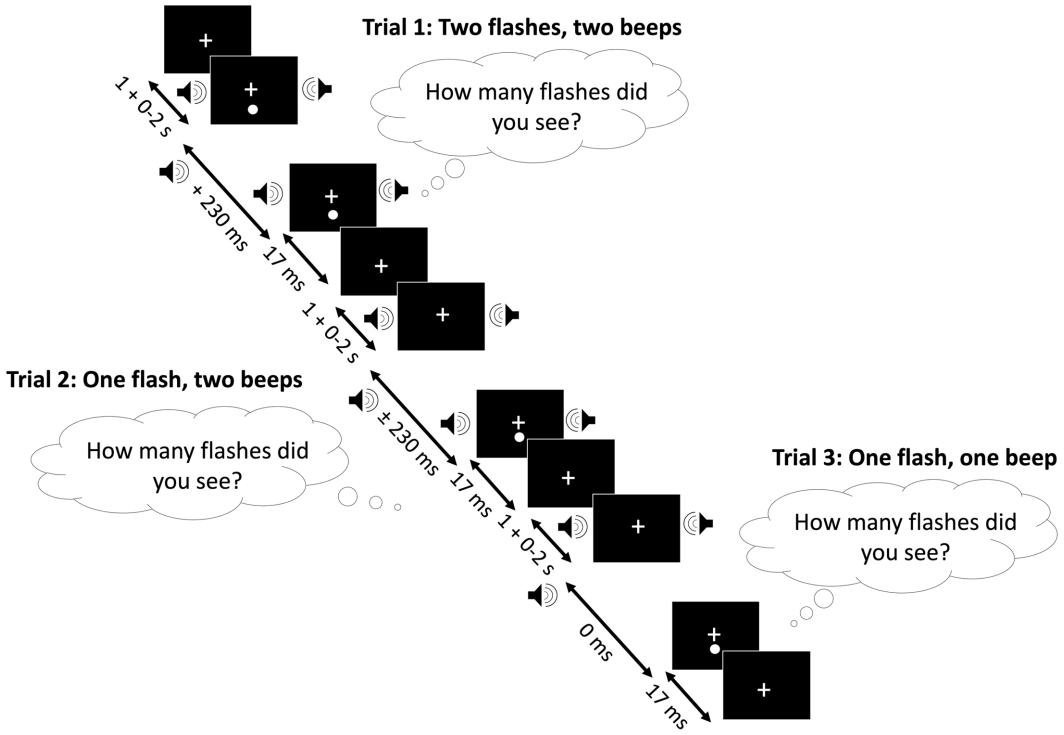

FIGURE 2
Sound induced flash illusion. The control conditions consited of the presentation of 2 flashes/2 beeps (trial 1) and 1 flash/1 beep (trial 3), while the illusory condition consisted of the presentation of 1 flash/2 beeps (trial 2). In the 1 flash/1 beep control condition, the auditory and visual stimuli were presented simultaneously. In the 2 flashes/2 beeps condition, the following SOAs were used: 70, 150, and 230 ms. In the illusory condition, the auditory stimulus was either presented prior to the presentation of the auditory and visual stimuli (auditory-lead) following a variable SOA of 70, 150, or 230 ms, or a visual stimulus was presented alongside the auditory stimulus followed by the second auditory stimulus (vision-lead) at a variable SOA of 70, 150, or 230 ms. For all the conditions, the first stimulus could appear 1–3 s after the fixation cross, and the second stimulus appeared between 0 and 230 ms after the first stimulus.

Literature reveals that In this task, when a single flash is accompanied by two beeps in close temporal proximity, it can lead to the perception of two flashes (Shams et al., 2000, 2002). It has been found that healthy younger adults generally perceive the illusion when the SOA between the beeps and flash is less than or equal to 70–150 ms, whereas older adults are susceptible over a wider range of temporal SOAs. Here, susceptibility to the SIFI at longer SOAs (e.g., 230 ms) would indicate poorer temporal multisensory processing, as it would suggest that the central nervous system is unable to differentiate which cues belong together and which do not (Setti et al., 2011a,b, 2014).

Simultaneity judgment

In the Simultaneity Judgment (SJ) task, participants were instructed to report whether they perceived the auditory and visual stimuli as occurring simultaneously (using the number '1' key) or not (using the number '2' key; see Figure 3). Participants were explicitly instructed to respond as accurately as possible, rather than responding quickly. The following SOAs were utilized: 0 ms, ±70 ms, ±150 ms, and ± 230 ms; here '+' indicates vision-lead trials while '-' indicates auditory lead trials. Ten trials were presented in a randomized order for each SOA, along with six practice trials, totaling 76 trials. This task took approximately 5–10 min to complete. Participants completed this task twice: before and after engagement in either intervention (physical activity or reading).

Temporal order judgment

The Temporal Order Judgment (TOJ) task's experimental design was identical to the SJ task, except for the task instructions. In this task, participants were asked to report whether they perceived the visual (using the number '1' key) or auditory (using the number '2' key) stimulus as appearing first. 'Synchronous' or 'I do not know' options were not provided for this task (see Figure 3). Participants were explicitly instructed to respond as accurately as possible, rather than responding quickly. This task took approximately 5–10 min to complete. Participants completed this task twice: before and after engagement in either intervention (physical activity or reading).

In both the SJ and TOJ tasks, participants were provided with the same pairs of audiovisual stimuli and they were either asked to determine if the stimuli occurred at the same or different times (SJ) or which stimulus appeared first (TOJ). These tasks have been found to be sensitive to both the temporal binding window (TBW), a window of time within which stimuli from different modalities are integrated and perceived as simultaneous, as well as the point of subjective simultaneity (PSS), the point at which

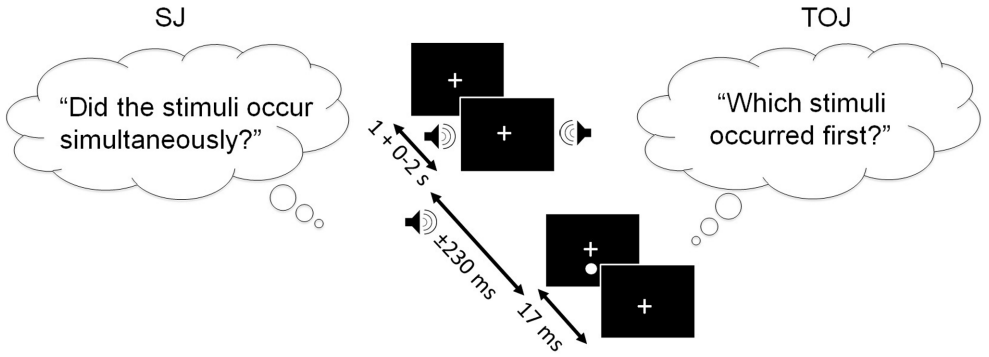

FIGURE 3
SJ task (left) and the TOJ task (right), presented with the SOAs of 0, ±70, ±150, ±230 ms (−ve = sound appeared before light). In both tasks, the first stimulus of the audiovisual pair appeared 1–3 s following the fixation cross, and the second stimulus appeared between 0 and 230 ms after the first stimulus. The figure depicts the auditory stimulus (i.e., beep) as appearing before the visual stimulus (i.e., flash). Note that the experimental design for the SJ and TOJ tasks is identical, but the instructions vary by task.

participants are most likely to perceive stimuli as occurring simultaneously for the SJ task, and the point of maximal uncertainty for the TOJ task. Literature from the SJ and TOJ tasks indicates that there is an impairment in older adult's ability to perceive the temporal order of events from multiple modalities due to a widening of the TBW (i.e., less precision) and a larger shift from true simultaneity (i.e., less accuracy; Poliakoff et al., 2006; Setti et al., 2011a,b; Chan et al., 2014a,b; Bedard and Barnett-Cowan, 2016; Basharat et al., 2018, 2019). A wider TBW has been associated with decreased speech comprehension (Maguinness et al., 2011; Setti et al., 2013), an inability to dissociate from distracting or inaccurate information (Wu et al., 2012), and an increase in susceptibility to falls (Setti et al., 2011a; Mahoney et al., 2014). Thus, a PSS closer to 0 and a narrower TBW would indicate optimal multisensory processing.

Response time task

For the Response Time (RT) task, participants were informed that they would either see a flash of light, hear a beep, or experience a combination of the two. Participants were instructed to press the response button (spacebar key) as soon as they detected any of the three experimental conditions: unisensory Visual (V), unisensory Auditory (A), or multisensory Audiovisual (AV) (audio and visual stimuli were presented simultaneously for each trial; see Figure 4). In this task, each stimulus was presented 50 times in random order, along with 6 practice trials. However, if a participant responded too quickly (<100 ms) or took longer than 3 s to respond to a trial where stimuli were presented, that trial was repeated. This task took approximately 5–10 min to complete. Participants completed this task not only at the beginning and end of the intervention period but also six times during the intervention (pre- and post-gameplay or reading during weeks 1, 3, and 5, for a total of 8 times).

Research indicates that multisensory stimuli are detected faster than unimodal stimuli and therefore may confer enhancement in activities of daily living (Laurienti et al., 2006; Peiffer et al., 2007; Diederich et al., 2008; Mahoney et al., 2011; Couth et al., 2018). Thus, a faster response time would indicate optimal integration.

Statistical analysis

Physical activity in VR and reading group comparison

Independent *t*-tests were used to compare the intervention and control group to assess differences between age, MoCA scores, and PASE scores at baseline and post-intervention.

Sound induced flash illusion

Repeated measures ANOVAs were conducted to determine whether there were sensory differences between participants in the physical activity intervention and those in the reading control. Analyses were conducted separately on the proportion correct for unimodal and multimodal conditions (Merriman et al., 2015; O'Brien et al., 2017; Chan et al., 2018), as well as on acute and long-term data. To investigate the effects of long-term exposure to unimodal and multisensory perception between community-dwelling older adults who participated in the physical activity intervention and those in the reading control, a 2 (group: experimental or control) × 2 (time: baseline and post-intervention) mixed-design ANOVA was conducted for both auditory and visual cues. In order to assess whether participation in the physical activity intervention, compared to a reading control, would reduce susceptibility to the SIFI (hypothesis 1), a 2 (group) × 2 (time) × 4 (accuracy per condition: overall, 1-flash/1-beep, 2-flash/2-beep, or 1-flash/2-beeps) mixed-design ANOVA was conducted for the multisensory cues. Exploratory analyses were further conducted to examine potential acute changes in unimodal and multisensory perception, with a 2 (group) × 6 (time: pre- and post-week 2, pre- and post-week 4, pre- and post-week 6) mixed-design ANOVA conducted for both auditory and visual cues, and a 2 (group) × 6 (time) × 4 (accuracy per condition: overall, 1-flash/1-beep, 2-flash/2-beep, or 1-flash/2-beeps) mixed-design ANOVA conducted for the multisensory cues. Mauchly's test of sphericity was conducted, and Greenhouse–Geisser adjustments were used to correct for lack of homogeneity of variance for all analyses if needed. Pairwise comparisons were also made to further assess the differences between group, condition, and time.

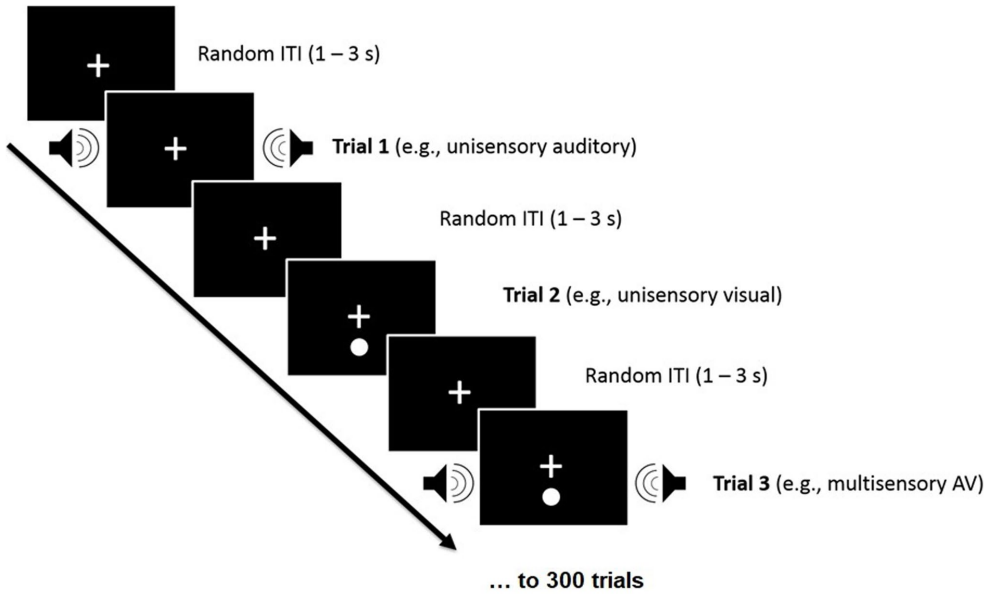

FIGURE 4
Participants were presented with unimodal [auditory (A) or visual (V)] or bimodal [audiovisual (AV)] stimuli and were asked to make speeded responses to all stimuli, regardless of sensory modality, by pressing the spacebar, which triggered the next trial. A, V, and AV stimuli were randomly presented with random inter-trial-intervals (ITIs) of 1–3 s.

To further investigate the data, difference scores were calculated by subtracting baseline accuracy from post-intervention accuracy to assess long-term changes and by subtracting pre-session accuracy from post-session accuracy for sessions 1, 2, and 3 to assess acute changes. The data were analyzed using mixed-design ANOVAs. A 2 (group) × 1 (time: baseline - post-intervention) × 4 (condition) mixed-design ANOVA was conducted to investigate the effects of chronic effects of engaging in physical activity versus reading, and a 2 (group) × 3 (time: post-session 1 - pre-session 1, post-session 2 - pre-session 2, post-session 3 - pre-session 3) × 4 (condition) mixed-design ANOVA was conducted to investigate acute changes on the multisensory trials. A 2 (group) × 3 (time) mixed-design ANOVA was conducted for the unisensory conditions to investigate acute changes. Mauchly's test of sphericity was performed, and Greenhouse–Geisser adjustments were used to correct for lack of homogeneity of variance for all analyses, if necessary. Pairwise comparisons were also conducted to further assess the differences between group, condition, and time. Additionally, independent t-tests were computed to investigate long-term changes for the unisensory conditions.

Simultaneity and temporal order judgment tasks

To estimate the accuracy (PSS values) and precision (TBW) with which participants made their judgments for SJ and TOJ tasks, psychometric functions were fitted to each participant's responses as a function of SOA using SigmaPlot version 12.5. Each task was analyzed individually for each participant, with participant data fit to both Gaussian (for the SJ task; Eq. 1) and logistic (for the TOJ task; Eq. 2) functions:

$$y = a \cdot e\left(-0.5\left(\frac{x - x0}{b}\right)^2\right) \quad (1)$$

Where a is the amplitude, $x0$ is the PSS and b is the standard deviation.

$$y = 100\left(1 + e\left(-\frac{x - x0}{b}\right)\right) \quad (2)$$

Where a is fixed to 1, $x0$ is the PSS and b is the standard deviation.

The best-fit parameters corresponding to the PSS and TBW were identified for each participant separately, and participants whose data were poorly estimated were excluded from further statistical analyses ($r^2 < 0.2$; $n = 1$ in the physical activity group, $n = 3$ in the reading group).

As we were interested in the relationships between TBWs obtained from the two tasks and not their absolute size, we chose to analyze the b values (i.e., standard deviation) of these psychometric functions as a proxy for the size of the TBW to avoid discrepancies in the literature that differ when defining the absolute size of the TBW.

To assess whether participation in the physical activity intervention, as compared to the reading control, would reduce the width of the TBW (hypothesis 2), a 2 (group: engaging in physical activity or reading) × 2 (task: SJ or TOJ) × 2 (time: baseline and post-intervention) mixed-design ANOVA was conducted for the TBW to determine the impact of task, time, and participation in the intervention (or lack thereof). The same analysis was conducted with PSS values. For both the SJ and TOJ tasks, difference scores were also calculated by subtracting baseline values from post-intervention values for the TBW and PSS, and exploratory 2 (group) × 2 (task) mixed-design ANOVAs were conducted with said difference scores

to further investigate and understand the data. Additionally, difference scores were computed for the 'a' values and an exploratory independent t-test was conducted with said values. Mauchly's test of sphericity was conducted, and if the dependent variables were not proportional to the identity matrix, the Greenhouse–Geisser adjustment was used for the mixed-design ANOVA. The Shapiro–Wilk test was used to determine normality for the independent *t*-tests. Pairwise comparisons were also made to assess differences between the tasks, intervention, and group for the mixed-design ANOVA.

Response time task

Error analysis and outlier removal

As previously mentioned, participants responded to 150 trials in total (50 per condition). Data trimming procedures were not applied (see Gondan, 2010; Gondan and Minakata, 2016; Mahoney and Verghese, 2018, 2019; Basharat et al., 2019; Mahoney et al., 2019); however, responses faster than 100 ms and slower than 1,500 ms were set to infinity rather than excluded (see Mahoney and Verghese, 2019 for a race model inequality (RMI) tutorial and (Basharat et al., 2019) where this method of data trimming was recently used). Here, we found that <1% of trials for both engagement in physical activity (average accuracy = 99.78%) and reading (average accuracy = 99.4%) groups were outliers that were set to infinity.

Mean response time analysis

In order to assess whether participation in the physical activity intervention would reduce response time more than participation in the reading control (hypothesis 3), a 2 (group) × 2 (time: baseline and post-intervention) × 3 (modality: auditory, visual, or audiovisual) mixed-design ANOVA was conducted to determine the long-term impact of time, modality, and participation in the physical activity versus reading interventions. Additionally, an exploratory mixed-design 2 (group) × 6 (time: pre-, post-week 1; pre-, post-week 3; pre-, post-week 5) × 3 (modality) ANOVA was conducted to determine the acute impact of time, modality, and participation in the physical activity versus reading interventions. To further investigate the data, difference scores were calculated by subtracting baseline response time from post-intervention response time to assess long-term changes, and by subtracting pre-session response time from post-session response time for sessions 1, 2, and 3 to assess acute changes, which were compared using exploratory mixed-design ANOVAs. A 2 (group) × 1 (time: baseline - post-intervention) × 3 (modality) mixed-design ANOVA was conducted to assess long-term effects of intervention on multisensory processing. A 2 (group) × 3 (time: post-session 1 - pre-session 1, post-session 2 - pre-session 2, post-session 3 - pre-session 3) × 3 (modality) mixed-design ANOVA was conducted to assess acute effects of intervention on multisensory processing. Mauchly's test of sphericity was conducted, and Greenhouse–Geisser corrections were applied if necessary. Pairwise comparisons were utilized to further assess the differences between time, modality, and experimental group. The same analyses as those conducted with mean RT data were conducted for the median RT data; these results can be found in the Supplementary material.

Test of the race model

The race model asserts that the response to redundant signals is produced by the modality that processes its respective signal the fastest and thus is the "winner" of the race (Raab, 1962). Race model violations are typically tested using cumulative distribution function (CDF) models, which compare the observed CDF distribution to the predicted CDF distribution (Miller, 1982).

To compute CDFs, each participant's data was sorted in ascending order for all three conditions (A, V, AV). Each participant's RTs were then quantized into 5th percentile bins until the 100th percentile was reached, yielding a total of 21 bins.

Observed CDF distributions were formed using the following equation (Eq. 3):

$$CDF_{observed} = P\,(RT_{AV} \leq t) \quad (3)$$

Where RT_{AV} represents the RT observed for the multisensory condition for any latency, *t* (Colonius and Diederich, 2006; Mahoney et al., 2011).

Predicted CDF models were formed using the following equation (Eq. 4):

$$CDF_{predicted} = \text{Min}\,[P\,(RT_A \leq t) + P\,(RT_V \leq t), 1] \quad (4)$$

Where RT_A and RT_V represent the RTs observed for unisensory condition 'A' (i.e., auditory) and 'V' (i.e., vision), for any time, *t* (Colonius and Diederich, 2006; Mahoney et al., 2011).

Differences between the observed CDF distribution and the predicted CDF distribution were calculated for every participant across all percentile bins as follows (Eq. 5):

$$RT_{AV} = P\left(RT_{AV} \leq t\right) - \min\left[P\left(RT_A \leq t\right) + P\left(RT_V \leq t\right), 1\right] \quad (5)$$

When the observed CDF is less than or equal to the predicted CDF, the race model is accepted. However, the race model is violated when the observed CDF is greater than the predicted CDF. Thus, a negative value (or zero) indicates acceptance of the race model, while values greater than zero provide evidence for multisensory integration as they are indicative of race model violations (Colonius and Diederich, 2006; Mahoney et al., 2011, 2014).

To investigate if the race model inequality was violated, Gondan's permutations were computed over the fastest quartile (0–25%) of responses (Gondan, 2010; Gondan and Minakata, 2016; Mahoney and Verghese, 2019) for all sessions for both those who engaged in physical activity and reading (see Tables 4, 5 below for outcomes of Gondan's permutations for the experimental and control groups). Further, in addition to performing Gondan's permutation test of the race model (Gondan and Minakata, 2016), we also calculated the area under the curve (AUC), which served as our independent variable, to further quantify the magnitude of RMI violation over the first quartile of responses. As described in (Mahoney and Verghese, 2019), the AUC was calculated for each time bin over the 0-25th percentile, where the difference value obtained from the observed CDF and the predicted CDF from the first time bin (i.e., 0%) was summed with the difference value obtained from the second time bin (5%) and divided by two. This process was repeated for the subsequent time bins until the 25th percentile was reached. All the values obtained were summed to generate a total AUC of the CDF difference wave during the 25th percentile.

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TABLE 4 Outcome of Gondan's permutation for 8 of the sessions where data was collected for those who engaged in physical activity; the statistically significant outcome of Gondan's permutations indicate that race model inequality was violated for all the sessions.

Session	tmax	tcrit	value of p
Baseline	4.503	2.281	≤0.001
1 Pre-physical activity engagement	3.064	2.337	≤0.05
1 Post-physical activity engagement	3.605	2.260	≤0.05
2 Pre-physical activity engagement	5.807	2.208	≤0.001
2 Post-physical activity engagement	4.965	2.095	≤0.001
3 Pre-physical activity engagement	5.866	2.336	≤0.001
3 Post-physical activity engagement	4.879	2.205	≤0.001
Post-physical activity engagement	6.185	2.164	≤0.001

TABLE 5 Outcome of Gondan's permutation for 8 of the sessions where data was collected for the reading group; the statistically significant outcome of Gondan's permutations indicate that race model inequality was violated for all the sessions.

Session	tmax	tcrit	value of *p*
Baseline	5.991	2.27	≤ 0.01
1 Pre-physical activity	7.207	2.26	≤ 0.01
1 Post-physical activity	9.201	2.146	≤ 0.001
2 Pre-physical activity	3.620	2.179	≤ 0.01
2 Post-physical activity	4.773	2.094	≤ 0.001
3 Pre-physical activity	5.909	2.153	≤ 0.0001
3 Post-physical activity	6.394	2.339	≤ 0.0001
Post-physical activity	7.094	2.291	≤ 0.001

In order to assess whether participation in the physical activity engagement intervention would increase race model violations more so than participation in the reading control (hypothesis 3), a mixed-design 2 (group: engagement in physical activity or reading) × 2 (time: baseline and post-intervention) ANOVA was conducted with AUC values to compare the long-term effects of engagement in physical activity and reading interventions on the AUC. Additionally, an exploratory mixed-design 2 (group: engagement in physical activity or reading) × 6 (time: pre-, post-week 1; pre-, post-week 3; pre-, post-week 5) ANOVA was conducted with AUC values to compare the acute effects of engagement in physical activity and reading interventions on the AUC.

To further investigate the data, difference scores were computed for the AUC by subtracting baseline AUC from post-intervention AUC to assess long-term changes and by subtracting the pre-session AUC from post-session AUC for sessions 1, 2, and 3 to assess acute changes. These were compared using mixed-design ANOVAs. Exploratory independent t-tests were computed to compare the difference score obtained from post-intervention and baseline sessions between participants who engaged in physical activity versus reading interventions. Moreover, an exploratory 2 (group) × 3 (time: post-session 1 - pre-session 1, post-session 2 - pre-session 2, post-session 3 - pre-session 3) mixed-design ANOVA was conducted to assess acute effects of intervention on multisensory processing. Mauchly's test of sphericity was conducted, and Greenhouse–Geisser corrections were applied if necessary. Pairwise comparisons were also made to assess the differences between time and experimental group.

Results

The results revealed that the reading group (mean age = 74.83, s.e. = 1.48) was significantly older compared to those who engaged in physical activity ($p < 0.001$; mean age = 68.46, s.e. = 1.34) and there were significantly more females in the reading as compared to those who engaged in physical activity. No further differences were found.

SIFI: audiovisual conditions

A 2 (group) × 2 (time) × 4 (conditions) mixed-design ANOVA was conducted to investigate the effects of long-term exposure to physical activity and reading on the SIFI. The analysis revealed a significant interaction between time and condition (F (3, 69) = 9.004, $p < 0.001$; $\eta^2_p = 0.281$). Planned pairwise comparisons showed that compared to accuracy on the illusory trials at baseline, the accuracy was higher for all conditions at both baseline and post-intervention, including the accuracy in the illusory condition at the time of post-intervention ($p < 0.001$). Additionally, the results indicated that compared to overall accuracy achieved at baseline, the accuracy was higher for all other conditions (i.e., 1-flash/1-beep, 2-flashes/2-beeps, 1-flash/2-beeps) at both baseline and post-intervention ($p < 0.05$), except for the accuracy achieved for the illusory condition from the post-intervention session (see Table 6 for more information). Note that Levene's test for Equality of Variance was violated for time and condition; thus, non-parametric Friedman tests were conducted, revealing a main effect of time ($\chi 2$ (1) = 6.570, $p = 0.010$) and a main effect of condition ($\chi 2$ (3) = 70.024, $p < 0.001$).Conover's post-hoc pairwise comparisons investigating the main effect of condition revealed that the main effect was driven by significantly higher accuracy for the 1-flash/1-beep condition compared to the illusory ($p = 0.002$) and overall accuracy conditions ($p = 0.019$). The pairwise comparison investigating the main effect of time failed to reveal a significant difference between accuracy obtained at baseline and post-intervention ($p = 0.254$), suggesting a lack of power to differentiate where the effect arose from. Finally, the analysis did not find a significant effect of group (F (1, 23) = 2.711, $p = 0.113$; $\eta^2_p = 0.105$). See Figure 5 and Supplementary Figure S2 for long-term accuracy scores obtained from those who engaged in physical activity and reading interventions. The results used to assess hypothesis 1 are concluded; what follows are exploratory analyses that investigate potential acute changes, difference scores, and changes in unimodal perception.

A 2 (group) × 6 (time) × 4 (conditions) mixed-design ANOVA investigating the acute effects of engagement in physical activity and reading revealed a significant main effect of group (F (1, 18) = 5.051,

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TABLE 6 *Post-hoc* comparisons for the audiovisual condition of the SIFI during baseline and post-intervention sessions.

Time*Condition	Time*Condition	Mean Difference	SE	*t*	Cohen's *d*	*p*bonf.
B, Overall	PI, Overall	−0.147	0.037	−3.966	−0.833	0.005
	B, Illusion	0.143	0.043	3.347	0.812	0.031
	B, 2 flash	−0.191	0.043	−4.467	−1.083	< 0.001
	PI, 2 flash	−0.203	0.047	−4.329	−1.154	< 0.001
	B, 1 flash	−0.285	0.043	−6.682	−1.620	< 0.001
	PI, 1 flash	−0.350	0.047	−7.454	−1.986	< 0.001
PI, Overall	B, Illusion	0.29	0.047	6.173	1.645	< 0.001
	PI, 1 flash	−0.203	0.043	−4.754	−1.153	< 0.001
B, Illusion	PI, Illusion	−0.228	0.037	−6.152	−1.293	< 0.001
	B, 2 flash	−0.334	0.043	−7.814	−1.895	< 0.001
	PI, 2 flash	−0.346	0.047	−7.375	−1.965	< 0.001
	B, 1 flash	−0.428	0.043	−10.029	−2.432	< 0.001
	PI, 1 flash	−0.493	0.047	−10.499	−2.798	< 0.001
PI, Illusion	B, 1 flash	−0.201	0.047	−4.276	−1.139	0.001
	PI, 1 flash	−0.265	0.043	−6.207	−1.505	< 0.001
B, 2 flash	PI, 1 flash	−0.159	0.047	−3.389	−0.903	0.027
PI, 2 flash	PI, 1 flash	−0.147	0.043	−3.433	−0.833	0.023

Results indicate higher accuracy for all conditions at both baseline and post-intervention compared to the illusory condition at baseline ($p < 0.001$). Higher accuracy was found for all conditions compared to overall accuracy at baseline ($p < 0.05$), except for the illusory condition during post-intervention. Only significant results are presented.

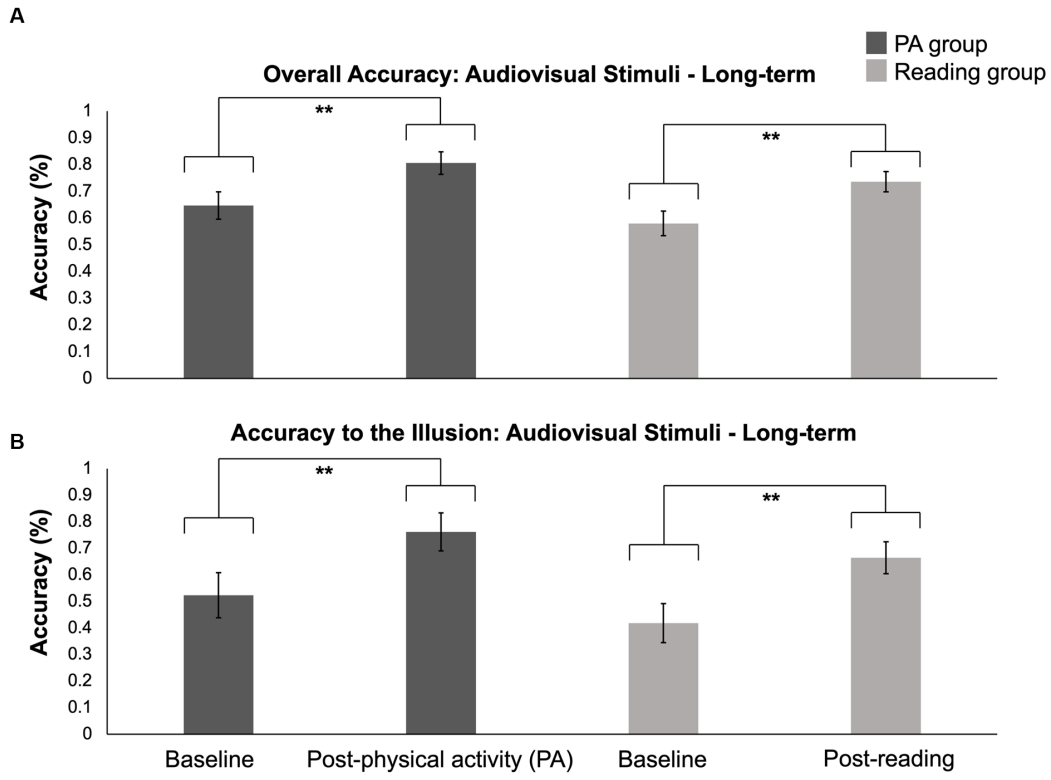

FIGURE 5
Accuracy for overall and illusory conditions during baseline and post-intervention sessions in the physical activity (PA) and reading interventions. **(A)** Overall accuracy at baseline and post-intervention. **(B)** Illusory condition accuracy at baseline and post-intervention. Error bars represent SEM. A main effect of time was found ($p = 0.010$), but pairwise comparison between baseline and post-intervention was not significant ($p = 0.254$).

$p = 0.037$; $\eta^2_p = 0.219$). Pairwise comparisons found that participants in the physical activity intervention (mean accuracy = 85.6%) were significantly more accurate compared to those in the reading group (mean accuracy = 78.2%; $p = 0.037$). Additionally, a significant interaction between time and condition (F (15, 270) = 1.753, $p = 0.041$; $\eta^2_p = 0.089$) was found. Pairwise comparisons investigating the interaction between time and condition revealed multiple significant outcomes (refer to Supplementary Table S2 for details). Of primary interest, the results showed that compared to pre-intervention accuracy for the illusion in session 1, accuracy was higher for both pre- ($p = 0.001$) and post-sessions ($p = 0.047$) of session 3. Moreover, the results demonstrated that participants achieved higher accuracy on the 1-flash/1-beep trials at all times that SIFI was administered as compared to overall accuracy ($p < 0.01$) and the accuracy achieved for the illusory condition ($p < 0.05$). Additionally, accuracy for the 1-flash/1-beep condition was also higher than the 2-flash/2-beep condition, primarily during sessions 2 and 3. Note that Levene's test for Equality of Variance was violated for time and condition, so non-parametric Friedman tests were conducted, revealing a main effect of condition ($\chi 2$ (3) = 138.972, $p < 0.001$), but no main effect of time ($\chi 2$ (5) = 3.282, $p = 0.657$). Pairwise comparisons investigating the main effect of condition found that accuracy for the 1-flash/1-beep condition was significantly higher than all the other conditions, including accuracy for the overall condition ($p = 0.003$), illusory condition ($p = 0.003$), and 2-flashes/2-beeps condition ($p = 0.014$). See Figure 6 and Supplementary Figure S3 for acute accuracy scores obtained during the 6-week intervention from those who engaged in physical activity and reading. Given that there was a significant difference in age between the exercise and reading groups, we reran these analyses using age as a covariate. When age was added as a covariate, the analysis revealed no main effect of group (F (1, 17) = 0.4706, $p = 0.412$; $\eta^2_p = 0.040$) and there were no other subsequent effects. What this indicates is that the effects reported above related to engagement in physical activity for the SIFI task may be due to the fact that the participants in the physical activity intervention were younger than those in the reading group and therefore less susceptible to the SIFI.

To further investigate the data, difference scores were computed by subtracting baseline accuracy from post-intervention accuracy to assess long-term changes and by subtracting pre-session accuracy from post-session accuracy for sessions 1, 2, and 3 to assess acute changes. A 2 (group) × 1 (time: post-intervention - baseline) × 4 (condition) mixed-design ANOVA investigating the effects of long-term exposure to physical activity and reading revealed a main effect of condition (F (3, 72) = 8.070, $p < 0.001$; $\eta^2_p = 0.252$). Pairwise comparisons were conducted to investigate the main effect of condition, which revealed that the difference in accuracy for the illusory condition was significantly higher than that for the 2-flashes/2-beeps ($p < 0.001$) and 1-flash/1-beep conditions ($p = 0.005$). This indicates that susceptibility to the illusion not only decreased after 6 weeks of both engagement in physical activity and reading interventions, but also showed greater improvement compared to the control conditions. Further, the pairwise comparisons revealed that the difference in overall accuracy was significantly higher than that for the 2-flashes/2-beeps condition ($p = 0.035$). The ANOVA failed to find a main effect of group (F (1, 24) = 0.225, $p = 0.639$; $\eta^2_p = 0.009$) or a significant interaction between condition and group (F(3, 72) = 0.223, $p = 0.880$; $\eta^2_p = 0.009$). See Supplementary Figures S4, S5 for a comparison of difference scores obtained by subtracting baseline accuracy from post-intervention accuracy scores for the physical activity and reading interventions.

A 2 (group) × 3 (time: post-session 1 - pre-session 1, post-session 2 - pre-session 2, post-session 3 - pre-session 3) × 4 (condition) analysis was conducted to investigate the acute effects of time, condition, and intervention. The analysis failed to reveal significant effects for group (F(1, 20) = 1.606, $p = 0.220$; $\eta^2_p = 0.074$), time (F(2, 40) = 0.433, $p = 0.652$; $\eta^2_p = 0.021$), and condition (F(3, 60) = 0.017, $p = 0.997$; $\eta^2_p < 0.001$). Additionally, no significant interactions were found for group and time ($p = 0.837$), group and condition ($p = 0.818$), or time, condition, and group ($p = 0.996$). See Supplementary Figures S6, S7 for a comparison of the acute difference scores between the physical activity and reading interventions.

See Supplementary Figures S8–S11 for unimodal (control) condition analysis for the SIFI. To summarize, we did not find any significant differences between the two groups. Of interest, accuracy for auditory cues during the post-intervention session was significantly higher than at baseline ($p = 0.011$). Additionally, when an independent t-test was conducted to examine the long-term effects of physical activity and reading on the visual condition, the results revealed a near-significant difference between the two groups ($t(25) = -1.837$, $p = 0.078$; *Cohen's d* = − 0.707), with the reading group demonstrating a larger difference in accuracy compared to those who engaged in physical activity.

Simultaneity and temporal order judgment tasks

Initially, a mixed-design ANOVA (2 × 2 × 2) was conducted for TBW, considering group (engagement in physical activity or reading), task (SJ or TOJ), and time (baseline and post-intervention). Due to a violation of Levene's test for Equality of Variance, Friedman tests were performed, revealing a significant main effect of task ($\chi 2(1) = 13.365$, $p < 0.001$) but not of time ($\chi 2(1) = 2.504$, $p = 0.114$). Pairwise comparisons indicated wider TBWs for the SJ task ($p = 0.021$) and wider TBWs at baseline compared to post-intervention. No significant effect of group (F (1, 21) = 0.055, $p = 0.816$; $\eta^2_p = 0.003$) or interaction between group, time, and task (F (1, 21) = 0.054, $p = 0.818$; $\eta^2_p = 0.003$) was found. See Supplementary Figure S12 (average Gaussian [SJ] function) and Supplementary Figure S13 (average Logistic [TOJ] function).

The following exploratory analyses investigated long-term intervention effects on TBW, PSS and amplitude. Difference scores were used to assess the long-term effects of engagement in physical activity and reading on SJ and TOJ tasks. A mixed-design ANOVA (2 × 2) with difference scores for TBW and PSS did not reveal any significant main effects or interactions for either TBW or PSS. An independent t-test investigating amplitude differences between the physical activity and reading interventions did not reveal a significant difference. See Supplementary Figure S14 for a graphical representation of the difference scores obtained for the SJ and TOJ tasks for both groups, and Supplementary Figure S15 for the amplitude difference scores.

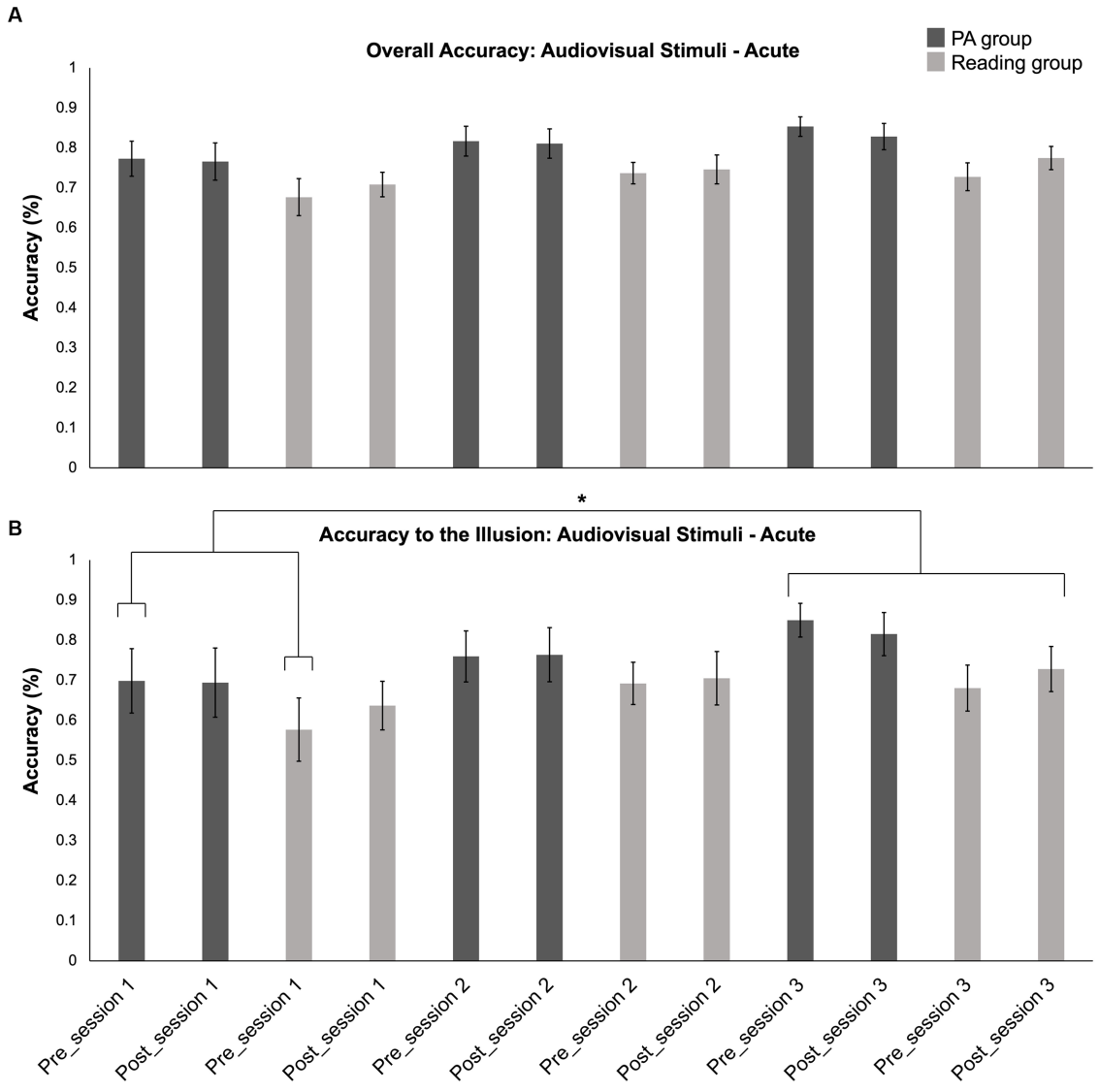

FIGURE 6
Acute accuracy for overall and illusory conditions during sessions 1, 2, and 3 in the physical activity (PA) and reading interventions. **(A)** Overall acute accuracy. **(B)** Illusory condition acute accuracy. Those who engaged in physical activity had significantly higher accuracy than the reading group (p = 0.037). Error bars represent SE.

Response time

A 2 (group) × 2 (time: baseline and post-intervention) × 3 (modality: auditory, visual, or audiovisual) mixed-design ANOVA was conducted to determine the long-term effects of participation in the two interventions. The analysis revealed significant main effects of group (F (1, 24) = 7.318, p = 0.012; η^2_p = 0.234) and modality (F (1.445, 34.673) = 67.898, p < 0.001; η^2_p = 0.739). Pairwise comparisons showed longer response times for the reading group compared to those who engaged in physical activity (p = 0.012), and both auditory (p < 0.001) and visual (p < 0.001) stimuli had significantly longer response times than audiovisual stimuli. No significant main effect of time (F (1, 24) = 0.907, p = 0.350; η^2_p = 0.036) or interaction between group, time, and modality (F (1.684, 40.417) = 0.593, p = 0.556; η^2_p = 0.024) was found. Figure 7 presents mean response time data for baseline and post-intervention sessions for both groups. Hypothesis 3 analyses on mean response time are followed by exploratory analyses investigating potential acute changes and difference scores from longitudinal and acute sessions. Just as the main effect of group was investigated above for the SIFI due to a significant difference in age between the exercise and reading groups, we re-ran these analyses using age as a covariate. When age was added as a covariate, the analysis revealed no main effect of group (F (1, 23) = 0.707, p = 0.409; η^2_p = 0.030). We did however find a significant interaction between group and time (F (1, 22) = 5.00, p = 0.035; η^2_p = 0.179), a main effect of time (F (1, 23) = 4.360, p = 0.048; η^2_p = 0.159), and a main effect of age (F (1, 23) = 5.140, p = 0.033; η^2_p = 0.183). The lack of a main effect of group and a main effect of age indicate that the effects reported above related to those in the reading group as having longer response times may be due to the fact that the participants in the reading group were older than those who engaged in physical activity and therefore had slower response times.

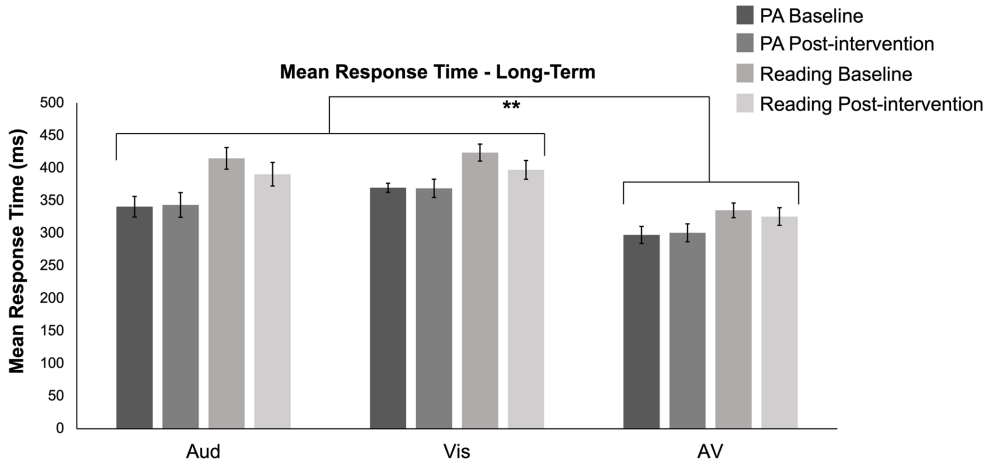

FIGURE 7
The mean response time for baseline (darker shade) and post-intervention (lighter shade) sessions in both the physical activity (PA; dark grey) and reading (light grey) groups across auditory, visual, and audiovisual trials. The reading group displayed longer response times (mean = 381.305, s.e. = 16.832) compared to those who engaged in physical activity (mean = 336.9172, s.e. = 12.954, p = 0.012). Moreover, response times for audiovisual stimuli (mean = 314.792, s.e. = 9.275) were significantly faster than auditory (mean = 372.524, s.e. = 18.195; $p < 0.001$) and visual (mean = 390.0177, s.e. = 13.047; $p < 0.001$) modalities. Aud, auditory stimuli; Vis, visual stimuli; AV, audiovisual stimuli; pre, baseline; post, post-intervention. Error bars indicate the SEM.

A 2 (group: experimental or control) × 6 (time: pre-, post-week 1; pre-, post-week 3; pre-, post-week 5) × 3 (modality: auditory, visual, or audiovisual) mixed-design ANOVA was conducted to determine the acute impact of physical activity engagement versus reading. The analysis revealed a significant main effect of group (F (1, 23) = 9.127, p = 0.006; η^2_p = 0.284), with longer response times for the reading group compared to those who engaged in physical activity (p = 0.006). Due to a violation of the Levene's test for Equality of Variance, a Friedman test was conducted, revealing a significant main effect of modality ($\chi 2$(2) = 134.776, $p < 0.001$). Pairwise comparisons showed longer response times for both auditory ($p < 0.001$) and visual ($p < 0.001$) stimuli compared to audiovisual stimuli. No significant main effect of time ($\chi 2$(5) = 8.246, p = 0.143) or interaction between group, time, and modality (F (4.692, 107.914) = 1.052, p = 0.389; η^2_p = 0.044) was found. See Supplementary Figure S16 for mean response time data for acute conditions. Just as the main effect of group was investigated above, here too we re-ran these analyses using age as a covariate. When age was added as a covariate, the analysis revealed no main effect of group (F (1, 22) = 0.759, p = 0.393; η^2_p = 0.033). We did however find a significant main effect of age (F (1, 22) = 5.289, p = 0.031; η^2_p = 0.194). Similar to the results presented above, this lack of a main effect of group and the significant main effect of age indicate that the effects reported above of those in the reading group having longer response time may be explained by the age difference between the two groups.

To further investigate the data, difference scores were used to assess long-term and acute effects. A 2 (group) × 3 (modality) mixed-design ANOVA was conducted to assess long-term intervention effects on multisensory processing using difference scores. No significant main effect of group (F (1, 24) = 1.356, p = 0.256; η^2_p = 0.053), modality (F (2, 48) = 1.086, p = 0.346; η^2_p = 0.043), or interaction between group and modality (F (2, 48) = 0.593, p = 0.556; η^2_p = 0.024) was found. Additionally, a 2 (group) × 3 (time: post-session 1 - pre-session 1, post-session 2 - pre-session 2, post-session 3 - pre-session 3) × 3 (modality) mixed-design ANOVA was conducted to assess acute intervention effects on multisensory processing. This analysis did not reveal significant main effects of group (F (1, 23) = 3.445, p = 0.076; η^2_p = 0.130), modality (F (2, 46) = 2.206, p = 0.122; η^2_p = 0.088), or time (F (2, 46) = 1.726, p = 0.189; η^2_p = 0.070). However, a significant interaction between time and modality (F (2.957, 68.002) = 3.157, p = 0.018; η^2_p = 0.121) was found. Pairwise comparisons investigating the interaction between time and modality revealed that the interaction was driven by the auditory modality exhibiting a larger difference when pre-session 3 scores were subtracted from post-session 3 scores (i.e., greater improvement; mean = −27.54, s.e. = 19.86) compared to the session 3 difference scores obtained for the audiovisual modality (p = 0.027; mean = −1.768, s.e. = 4.363). Although not significant, the main effect of group approached significance, and post-hoc pairwise comparisons revealed that those in the reading condition showed a larger difference in performance (mean = −27.25, s.e. = 4.84) compared to those who engaged in physical activity (mean = −3.63, s.e. = 2.55). Figure 8 displays both acute (panel a) and long-term (panel b) difference scores. Here for the acute sessions, a significant interaction between time and modality was found, potentially driven by a larger difference for the auditory modality compared to the audiovisual modality over session 3 (p = 0.027). Although not significant, the reading group showed a larger difference in performance (i.e., greater improvement) compared to those who engaged in physical activity. No other significant effects or interactions were found. As we did not expect reading to positively affect performance, we suspected that here too the nearing-significant effect of group was driven by age, and indeed when age was added as a covariate, the analysis revealed no main effect of group (F (1, 22) = 2,273, p = 0.146; η^2_p = 0.094). No other effects were significant. These results indicate that the effect of reading leading to a greater difference in performance (i.e., greater improvement) may be explained by age. Those in the reading group may have exhibited greater improvement as there is greater room for improvement with older age.

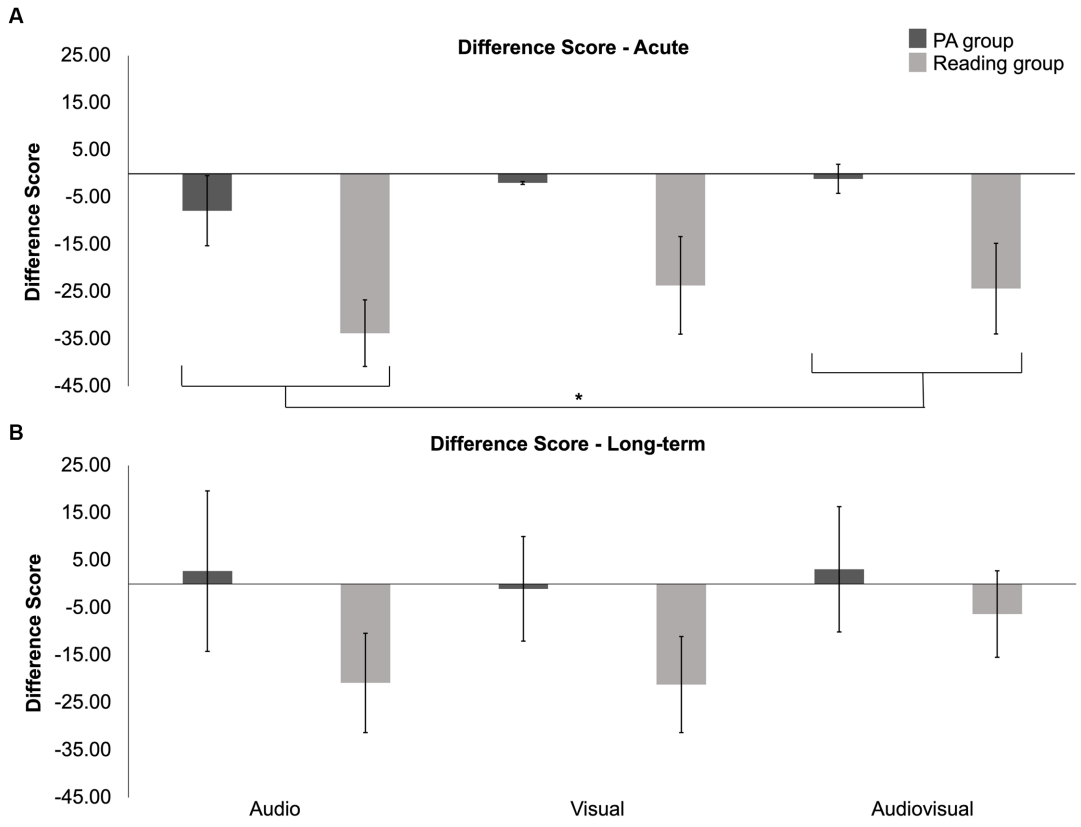

FIGURE 8
Scores calculated by subtracting pre-session response time for auditory, visual, and audiovisual stimuli from post-session response time. Response times are collapsed across 3 times (session 1 post - pre-session 1, session 2 post - pre-session 2, and session 3 post - pre-session 3) in panel **(A)** and 1 time (post - baseline) in panel **(B)**. Error bars indicate the SEM.

See Supplementary material for analyses conducted with median response times that confirm and supplement our findings from mean response times.

Area under the curve

To investigate the long-term effects of the interventions, a 2 (group) × 2 (time) mixed-design ANOVA was conducted. This analysis revealed a near-significant effect of time (F (1, 25) = 3.526, p = 0.072; η^2_p = 0.124) but did not show a main effect of group (F (1, 25) = 0.859, p = 0.363; η^2_p = 0.033) or a significant interaction between group and time (F (1, 25) = 0.10, p = 0.923; η^2_p < 0.001). Pairwise comparisons investigating the near-significant effect of time revealed an increase in the area under the curve post-intervention compared to baseline, indicating increased violations post-intervention. See Figures 9 and 10 for the probability difference waves. This section concludes the analyses used to assess the effects of intervention on race model violations (hypothesis 3). The following exploratory analyses investigate potential acute changes and difference scores obtained from longitudinal and acute sessions.

A 2 (group) × 6 (time) mixed-design ANOVA investigating the acute effects of intervention on AUC revealed no significant effect of group (F (1, 23) = 1.332, p = 0.260; η^2_p = 0.055) or time (F (3.531, 81.209) = 1.913, p = 0.124; η^2_p = 0.077). Additionally, no significant interaction between group and time was found (F (3.531, 81.209) = 0.931, p = 0.442; η^2_p = 0.039). See Supplementary Figures S11, 12 for the graphical representation of the acute and long-term area under the curve for the physical activity and reading interventions, respectively.

To further investigate the long-term effects of intervention on AUC using difference scores, an independent t-test was conducted, which did not reveal a significant difference between the two groups (t (25) = 0.098, p = 0.923; *Cohen's d* = 0.038). Difference scores were also used to assess acute effects. A 2 (group) × 3 (time: post-session 1 - pre-session 1, post-session 2 - pre-session 2, and post-session 3 - pre-session 3) mixed-design ANOVA investigating acute effects failed to reveal a significant main effect of group (F (1, 24) = 0.039, p = 0.846; η^2_p = 0.002) or time (F (2, 48) = 1.829, p = 0.172; η^2_p = 0.071). Furthermore, no significant interaction between group and time was found (F (2, 48) < 0.01, p = 0.999; η^2_p < 0.001). See Supplementary Figure S17 for both the acute (panel A) and long-term (panel B) difference scores from those in the physical activity and reading interventions.

Discussion

Our study aimed to investigate the effects of a physical activity intervention in a VR setting on perceptual processing compared to a

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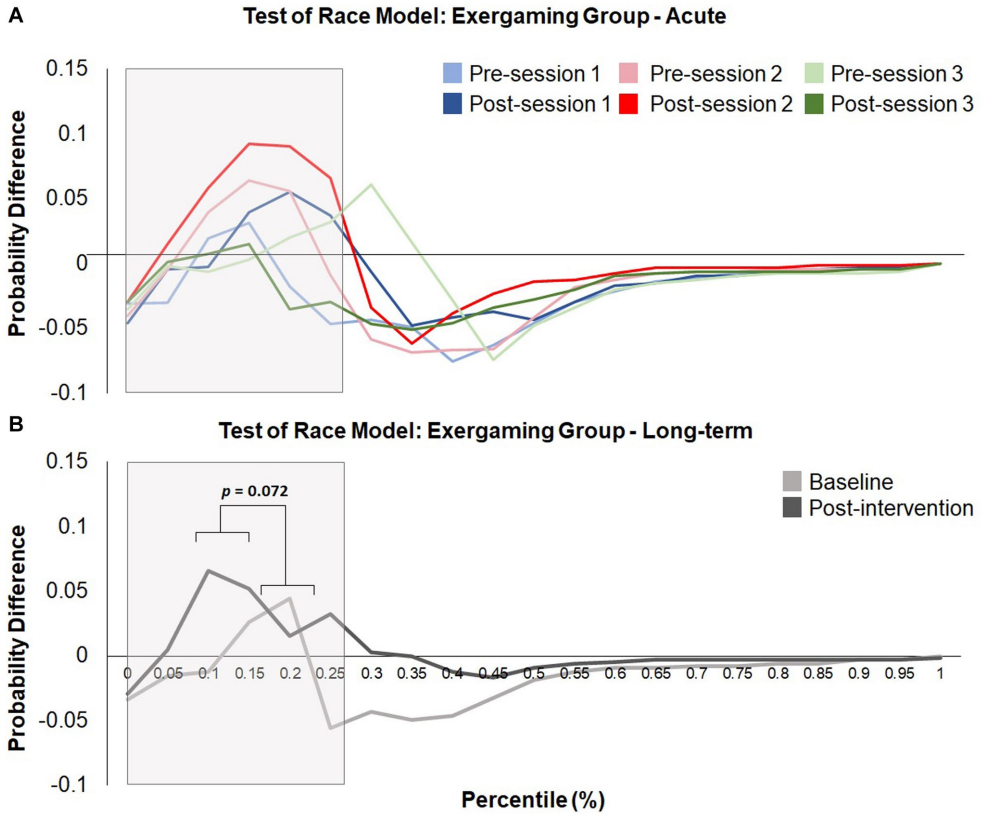

FIGURE 9
Test of the race model for those who engaged in physical activity showing the probability difference wave, where the predicted CDF is subtracted from the observed CDF for **(A)** acute changes (sessions 1, 2, and 3) and **(B)** long-term differences (i.e., baseline and post-intervention). The grey box indicates the area analyzed. A near-significant effect of time from the acute analysis revealed that the area under the curve increased after both interventions ($p = 0.072$). No further significant effects or interactions were found.

reading control condition. Initial analyses revealed that those who engaged in physical activity in a VR environment exhibited higher accuracy scores on the SIFI task (acute effect) and faster response times on the audiovisual RT task (both chronic and acute effect). The significant improvements in perceptual processing in both the experimental and control groups suggest that these interventions may positively impact multisensory processing.

Apart from group differences, time was also a significant factor of interest as data was collected across multiple sessions (baseline and post-intervention for all tasks and three additional pre- and post-sessions for the RT and SIFI tasks in between) to investigate chronic and acute effects of physical activity in VR or reading on multisensory processing. Starting with the chronic effects observed for the SIFI, we found that accuracy to the illusory condition was significantly lower at baseline as compared to post-intervention, suggesting that susceptibility to the illusory condition can decrease either because of repetition effects or because of the interventions that each group was exposed to. Further, the difference score analysis revealed that difference in accuracy to the illusory condition was larger than that for the 2 flash 2-beep condition suggesting that repetition or exposure to our experimental and control conditions is more likely to impact components of perceptual performance that have greater potential for improvement. Further evidence for such a process is provided by the near-significant effect of group for the visual-only trials of the SIFI, where those in the reading group showed a larger difference in performance after 6 weeks of intervention. Our acute-analysis results from the RT task also indicate larger differences on trials with greater room for improvement, where although the mean response times to audiovisual trials were significantly faster than auditory and visual trials across time, the auditory modality showed a larger difference in performance as compared to the audiovisual modality. Additionally, both mean and median response time difference scores investigating acute and long-term effects also revealed that those in the reading group showed larger improvement (i.e., greater difference score) as compared to those in the experimental group. As the reading group had significantly longer response times to all modalities and showed a greater reduction in response time as compared to the experimental group, this finding further suggests the potential of our interventions or repetition to target areas or populations that are most in need of improvement.

Although not significant, we found that those in the reading group had wider TBWs at baseline as compared to post-intervention (i.e., greater improvement) for the SJ and TOJ tasks.I. These results suggest that either reading and engaging with VR can directly affect the width of the TBW, or that exposure to, and improvement on the SIFI and RT tasks, may have beneficial transferable effects. Previous research provides some guidance related to transfer effects. A study conducted by Setti et al. (2014) aimed to determine the impact of perceptual training on older adults where they trained twenty-four individuals to judge the temporal order of auditory and visual stimuli using the TOJ task, while providing feedback after each trial, over five consecutive

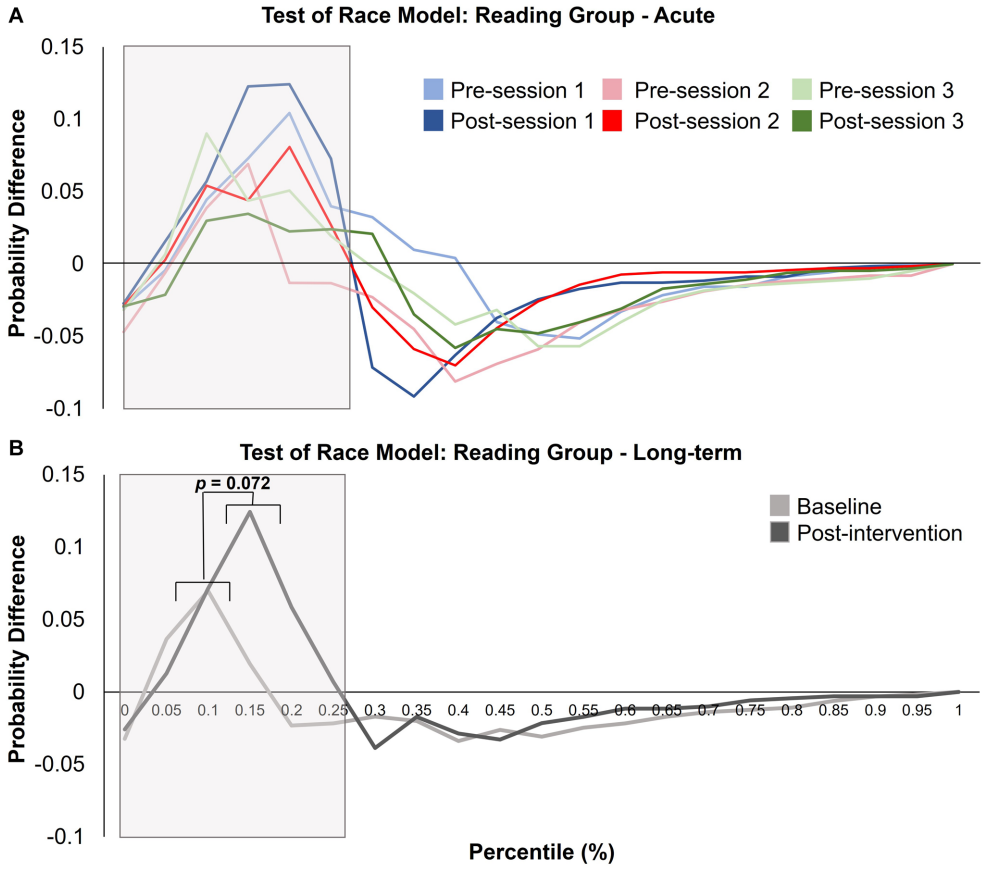

FIGURE 10
Test of the race model for the reading group showing the probability difference wave, where the predicted CDF is subtracted from the observed CDF for **(A)** acute changes (sessions 1, 2, and 3) and **(B)** long-term differences (i.e., baseline and post-intervention). The grey box indicates the area analyzed. A near-significant effect of time from the acute analysis revealed that the area under the curve increased after both interventions ($p = 0.072$). No further significant effects or interactions were found.

days. They found that the majority (eighteen of the twenty-four) of the participants were significantly more accurate on the TOJ task on the fifth as compared to the first day. Additionally, the researchers aimed to determine whether training participants on the TOJ task would reduce susceptibility to the SIFI and although training on the TOJ task did not improve susceptibility to the SIFI for all the stimulus onset asynchronies, significant improvement appeared for the longest SOA of 270 ms.

Our results additionally revealed that (prior to our covariate analysis) the control group showed greater improvement (i.e., reduction) in response time compared to the experimental group. However, when age was added as a covariate in our analysis, this difference disappeared. These results indicate that older adults are more likely to benefit from interventions, possibly due to repetition or transfer effects, because they have greater room for improvement (Powers III et al., 2009, 2016). Future research should employ a more systematic approach to participant selection, matching age and sex between intervention and control groups.

As single-bouts of exercise have been shown to impact not only higher-order cognitive function (Audiffren et al., 2008; Chang et al., 2012; McSween et al., 2018; pontifex et al., 2019) but also sensory processing (O'brien et al., 2017; Basharat and Barnett-Cowan, 2023), it is not surprising that our physical activity intervention ('Seas the Day') affected multisensory processing as assessed *via* the RT and SIFI tasks. One potential explanation for changes observed through exercise in multisensory processing could be related to increases in Gamma-aminobtyric acid (GABA), the chief inhibitory neurotransmitter in the central nervous system. GABA tends to decrease in concentration with aging and indeed, Gao et al. (2013) found that the levels of GABA are reduced in frontal and parietal regions by approximately 5% per decade of life. Such a reduction in GABA can reduce the brain's ability to ignore or inhibit the integration of erroneous cues and can potentially increase the difficulty in discriminating the temporal order of information. GABA levels have been found to increase in concentration not only with chronic exercise but also following acute bouts of exercise (Maddock et al., 2016; Li et al., 2017). Indeed, in a study conducted by Maddock et al. (2016), GABA levels were found to increase significantly after vigorous exercise (80% of predicted maximal heart rate) in 38 young adults (mean age = 26.68). It is important to note however that although there is evidence to indicate that single bouts of aerobic exercise can increase GABA concentration, which may have an impact on multisensory processing, most of the neurophysiological research has been conducted with high or moderate intensity exercise, which is unlike the intensity utilized in this intervention. The participants in this study were asked to exert

light to moderate effort and most participants reported exerting light effort. This can help to explain the lack of group differences observed for the SJ and TOJ tasks between the control and experimental groups. However, a meta-analysis conducted by Chang et al. (2012) did find that 20 min of light exercise can induce cognitive enhancement as long as cognition is tested within the first 20 min following exercise, which may help to explain the effects that were indeed observed. It is interesting however that the larger differences between the mean and median scores were observed for the reading group.

Although changes in multisensory processing were expected from engaging in the experimental intervention, the unexpected improvements from engaging in reading may arise from the fact that reading is thought to be a relaxing activity which has been shown to improve mental health, maintain cognitive abilities, reduce the risk of mortality, and reduce stress in young and older adults (Rizzolo et al., 2009; Bavishi et al., 2016; Levine et al., 2022). Indeed, in a study conducted by Rizzolo et al. (2009), a single session of 30 min of reading was found to reduce stress by reducing elevated systolic blood pressure, diastolic blood pressure, and heart rate in 24 young adults (mean age = 23). Most interestingly, it was found that 30-min of reading had similar effects to 30-min of yoga and watching a humorous video. In an older study, 60 min of reading was similarly found to reduce anxiety, heart rate, and blood pressure in 24 adults (mean age = 36.2), however in this study, Tai-Chi was found to have superior effects (Jin, 1992). One possible mechanism through which reading can reduce stress is *via* easing of tension in the muscles of readers, which may occur when an individual becomes immersed into the topic of interest. Another potential mechanism, not dissimilar to exercise, is the GABergic system, where reading may reduce stress through the modulation of GABA (refer to de Souza Spinosa et al., 2002 and Lydiard, 2003 that indicate an increase in GABA with a reduction in stress and anxiety). The evidence presented here and above indicates that the GABAergic system may underlie the changes in multisensory processes observed in this study and warrants further investigation.

While reading served as a control condition in our study, it may not be optimal for researchers investigating multisensory processing, as reading is considered a multisensory activity (Boerma et al., 2016; Brosch, 2018). Notably, the additional covariate analyses (with age as a factor) rendered the difference between the two groups insignificant. Future research should explore alternative control conditions less likely to engage multisensory processing and systematically investigate control conditions utilized by the exercise literature (e.g., stretching, socializing with others, disengaged, etc.; Pontifex et al., 2019). Additionally, future researchers may consider increasing the intensity of their exergaming intervention, as moderate to vigorous intensity has been found to optimally affect cognitive processing following both acute (Chang et al., 2012; McSween et al., 2018; Pontifex et al., 2019) and chronic physical exercise (Erickson et al., 2011, 2019). Finally, including the perceived enjoyment questionnaire for both groups would provide a more comprehensive comparison between the interventions.

It is crucial to interpret these results with caution, however, due to potential group differences, such as the older age of participants and higher number of females in the reading group. The age discrepancy could have provided greater potential for improvement in the reading group, as evidenced by the larger difference scores obtained for the SIFI and RT tasks. Prior research has demonstrated that the age of the perceiver directly impacts the temporal binding window (TBW) and susceptibility to illusions, which can be associated with various adverse outcomes (Poliakoff et al., 2006; Setti et al., 2011a,b; Chan et al., 2014a,b; Bedard and Barnett-Cowan, 2016; Basharat et al., 2018, 2019). To mitigate the effects of age between the control and experimental groups, we added age as a covariate each time a main effect of the group was found, revealing that age significantly affected performance in this study. An additional limitation of this study is the learning effects that may arise from repetition of the SIFI and RT tasks. Although learning effects are inevitable, especially for the RT task, future studies can consider the utilization of randomization of SOAs for each session for the SIFI task to reduce such effects from affecting their results.

In conclusion, our study aimed to demonstrate that participation in our co-designed physical activity intervention, compared to a reading control, would reduce susceptibility to the SIFI, reduce the width of the TBW for both the SJ and TOJ tasks, and reduce response time while increasing race model violations. Although we found evidence for a reduction in susceptibility to the SIFI and a reduction in response time, we did not find any evidence of change for the SJ and TOJ tasks or a change in race model violations. More importantly, we found that the older age of our participants in the reading group was the driving factor for the observed group differences. Researchers should consider alternative control conditions and ensure that age and sex are matched between intervention and control groups to provide a more accurate comparison. Regardless of this limitation, our study demonstrates that both physical activity in a VR setting and reading interventions can influence perceptual processing. Despite potential group differences and limitations, our findings contribute valuable insights into the impact of these interventions on multisensory processing.

Our research indicates that VR may be a useful tool to investigate and subsequently impact multisensory processing, while promoting physical activity. As we aimed to create an intervention that was accessible to all older adults with intact auditory and visual processing, we were therefore limited to light-to-moderate intensity of physical activity. However, researchers hoping to utilize this tool in the future may see larger effects with exercise intervention requiring a higher intensity of exertion. Future research should focus on exploring the underlying mechanisms, such as the GABAergic system, that may contribute to the observed changes in perceptual processing. Additionally, it is recommended that future researchers investigate the longer-term effects (i.e., longer than 6 weeks) of these interventions on multisensory processing and cognitive function in older adults with and without cognitive impairment.

Author's note

Physical activity plays a crucial role in maintaining and improving cognitive and perceptual processes, particularly in older adults. Perceptual processes, such as multisensory integration, refer to the ability to combine and interpret sensory information from various sources (e.g., vision, hearing, touch) to better understand and interact with the environment. Research has demonstrated that regular physical activity can enhance these perceptual processes, leading to improvements in cognitive function, motor learning, and overall well-being. In this

exploratory, pilot non-randomized control trial, we investigated the effects exergaming in a virtual reality as compared to our reading control during the COVID-19 pandemic to encourage participation in physical activity. We found that exergaming and reading interventions can influence perceptual processing as tested *via* four different tasks including the Sound-induced flash illusion. More importantly, however, we found that the older age of our participants in the reading group was the driving factor for the observed group differences. Regardless of this limitation, our study demonstrates that perceptual processes are malleable and can be influenced by both reading and exergaming interventions. Despite potential group differences and limitations, our findings contribute valuable insights into the impact of these interventions on multisensory processing.

Data availability statement

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

Ethics statement

The studies involving humans were approved by University of Waterloo's Human Research Ethics Board. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because Verbal consent was obtained from all participants in lieu of written consent.

Author contributions

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

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Conflict of interest

The authors collaborated with VR Vision to co-design the exergame entitled "Seas the Day". This exergame however has been freely published and is available at no cost in the Oculus Store.

Publisher's note

Supplementary material

The supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2023.1207651/full#supplementary-material

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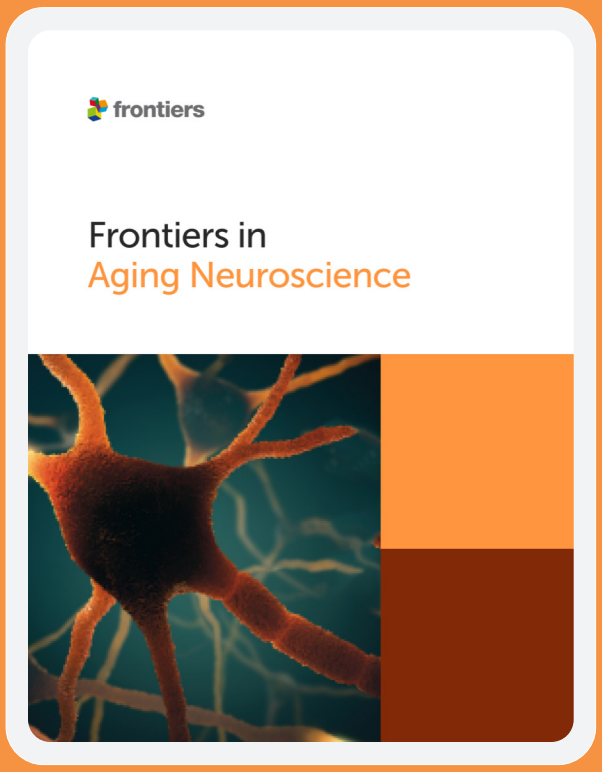

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