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Brain control of dual-task walking can be improved in aging and neurological disease

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Associated Data

Supplementary Materials

Data Availability Statement

Abstract

Go to:

The peak prevalence of multiple sclerosis has shifted into older age groups, but co-occurring and possibly synergistic motoric and cognitive declines in this patient population are poorly understood. Dual-task-walking performance, subserved by the prefrontal cortex, and compromised in multiple sclerosis and aging, predicts health outcomes. Whether acute practice can improve dual-task walking performance and prefrontal cortex hemodynamic response efficiency in multiple sclerosis has not been reported. To address this gap in the literature, the current study examined task- and practice-related effects on dual-task-walking and associated brain activation in older adults with multiple sclerosis and controls. Multiple sclerosis (n = 94, mean age = 64.76 ± 4.19 years) and control (n = 104, mean age = 68.18 ± 7.01 years) participants were tested under three experimental conditions (dual-task-walk, single-task-walk, and single-task-alpha) administered over three repeated counterbalanced trials. Functional near-infrared-spectroscopy was used to evaluate task- and practice-related changes in prefrontal cortex oxygenated hemoglobin. Gait and cognitive performances declined, and prefrontal cortex oxygenated hemoglobin was higher in dual compared to both single task conditions in both groups. Gait and cognitive performances improved over trials in both groups. There were greater declines over trials in oxygenated hemoglobin in dual-task-walk compared to single-task-walk in both groups. Among controls, but not multiple sclerosis participants, declines over trials in oxygenated hemoglobin were greater in dual-task-walk compared to single-task-alpha. Dual-task walking and associated prefrontal cortex activation efficiency improved during a single session, but improvement in neural resource utilization, although significant, was attenuated in multiple sclerosis participants. These findings suggest encouraging brain adaptability in aging and neurological disease.

Supplementary Information

The online version contains supplementary material available at 10.1007/s11357-023-01054-3.

Keywords: Aging, Multiple sclerosis, Walking, Cognition, Functional near-infrared-spectroscopy

Introduction

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Mobility decline [1] and cognitive impairment [2] are common in aging and multiple sclerosis (MS). There is further evidence that mobility and cognitive functions are interrelated or coupled in aging [3] and MS [4]. As the peak prevalence of MS has shifted into older age groups [5], co-occurring and possibly synergistic declines in both domains of function may present challenges for assessment and treatment procedures in older adults with MS [6]. Thus, this supports the application of innovative experimental paradigms that simultaneously delineate the interplay between cognitive and mobility performances and associated brain activation in older adults with MS.

Dual-task methodology represents an experimental paradigm for evaluating cognitive control of gait as evidenced by recent literature review and meta-analytic studies [7]. Dual-task methodology involves monitoring and comparing gait during single-task-walk (STW) and dual-task-walk (DTW) conditions, with a diminution in gait during DTW compared with STW. Because the effects of attention and executive demands on gait are experimentally manipulated in such paradigms, it is possible to make inferences about causal effects attributed to taxing cognitive resources and underlying brain regions and functional circuits, notably the prefrontal cortex (PFC), on walking and other mobility outcomes [8].

Recent literature review [9] and meta-analytic [10] studies using functional near-infrared spectroscopy (fNIRS) have demonstrated increased involvement of the PFC in DTW compared with STW conditions in aging and neurological samples. The increase in PFC activation is expected in tasks that are both novel and cognitively demanding, and variability in the magnitude of such brain responses may indicate important differences in resource utilization and efficiency among groups or individuals. For example, neural inefficiency [11] occurs in persons exhibiting higher brain activation, but equivalent or worse gait performance than counterparts.

Burst measurement designs involve repeated administration of the same task within a relatively brief time period and have been applied to the assessment of within person changes in cognitive function [12] and stress response [13] in older adults. Burst measurement, evaluated over repeated trials of the same cognitive task, could be used to delineate the influence of MS on learning and performance [14]. However, whether within session practice improves brain resources utilization implicated in walking in aging and MS has not been established.

In the current study, we combined burst measurement, fNIRS, and dual-task methodology to determine task- and practice-related effects on brain activation levels during walking [15]. We specifically evaluated fNIRS-derived activations in the PFC during DTW, STW, and single-task-alpha (STA: cognitive interference) assessed over three repeated counterbalanced trials in older adults with and without MS. We hypothesized that (1) PFC activations would be higher in DTW compared to STW and STA conditions and (2) brain efficiency of walking and cognition would be improved due to within session practice. That is, within the context of improved walking and cognitive performances, fNIRS-derived activation levels in the PFC would decrease over trials, notably under DTW; (3) the presence of MS would attenuate practice-related effects on PFC activation efficiency implicated in walking and cognition.

Materials and methods

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Participants

Older adults diagnosed with MS (n = 94, mean age = 64.76, % female = 69.15) and healthy controls (n = 104, mean age = 68.19, %female = 64.42) enrolled in an ongoing study titled "Brain Predictors of Mobility and Falls in Older Adults with Multiple Sclerosis" [16]. Participants in the current study were tested between September 2019 and August 2023 and had complete cognitive, mobility, psycho-social, and fNIRS assessments. Of 212 participants evaluated during this time interval, 9 received a diagnosis of dementia and 5 had missing data; those participants were removed for a total study sample of n = 198. MS diagnoses, determined using the revised McDonald criteria [17], were physician-confirmed. Extensive review of medical records was used to evaluate relevant health history and confirm participants were on stable disease-modifying-therapy (DMT) for at least 6 months prior to study visits. MS participants were recruited from regional treatment centers and patient registry lists. Publicly available population lists stratified by zip code, age, and sex were used to recruit control participants with similar demographic characteristics. Healthy controls were first mailed a letter followed by a phone call introducing the study. Both MS and control cohorts were screened using a structured telephone interview to obtain verbal consent, assess medical and psychological history, and screen for dementia, mobility, and functional abilities to determine study eligibility. Following completion of the telephone interview, participants were scheduled for two in-person study visits in the medical center. The first visit consisted of a battery of neuropsychological tests, mobility protocols including the combined burst measurement, fNIRS, dual-task walking paradigm, and questionnaires. The second visit included an MRI of the brain and additional questionnaires. Cognitive status was determined via established clinical case conference procedures [18]. Diagnosis of any major neurological, psychiatric, or medical disease (excluding MS), inability to ambulate independently with or without a single point cane, contraindication to MRI, impairment of vision or hearing that would negatively impact testing served as exclusion criteria. All participants reviewed and signed a written informed consent form in the first study visit. The work described in this manuscript has been executed in adherence with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The study was approved by the IRB of Albert Einstein College of Medicine (Protocol #2019–10049).

Measures

Walking paradigm There were two single task conditions: (1) single-task-walk (STW) and (2) single-task-alpha (STA — cognitive interference task). In STW, participants were asked to walk on the electronic walkway at their "normal pace" (i.e., typical walking speed in natural environment) wearing comfortable footwear for three consecutive loops. In STA, participants were required to stand still while reciting alternate letters of the alphabet for 30-s out loud. In dual-talk-walk (DTW) participants were instructed to walk around the walkway for three consecutive loops at their normal pace while reciting alternate letters of the alphabet. Participants started reciting alternate letters starting with the letter A or B, which was randomized across STA and DTW conditions. Participants were instructed to pay equal attention to both tasks. The three test conditions were presented in a counterbalanced order using a Latin-square design. Reliability and validity for this walking paradigm have been established [19].

Burst measurement Three repeated trials, each comprised of three task conditions (i.e., STW, STA, DTW), were administered in one experimental session to determine the influence of short-term practice effects on PFC activation as well as gait and cognitive performances [15]. Participants received a 5-min break between each of the repeated trials.

Gait assessment A 4 × 20-foot electronic walkway using ProtoKinetics Movement Analysis Software was utilized to measure quantitative gait parameters during STW and DTW (Zenometrics, LLC; Peekskill, NY). Stride velocity, cm/sec, served as the gait outcome in the current study. Split-half intra-class correlations (ICC) for stride velocity in STW and DTW were greater than 0.95 revealing excellent internal consistency [19]. While multiple quantitative gait measures were available, analysis was restricted to stride velocity to reduce the number of dependent measures. Further, in addition to exhibiting excellent psychometric properties across numerous studies, gait speed is considered a robust proxy of health outcomes [20] and has been characterized as the sixth vital sign [21].

Cognitive assessment Participants had to verbalize every other letter of the alphabet. The number of correct letters was computed for each participant under the STA (performed while standing) and DTW conditions. To allow for across task comparisons, the number of correct letters generated under STA was divided by 30 (task length is 30 s) and the number of correct letters generated during DTW was divided by the time (in sec) it took each participant to complete the task. Both ratio measures were then multiplied by 60 to derive a common and easily interpretable measure corresponding to the number of correct letters generated per minute in each task condition.

fNIRS system The methods, reliability, and validity of the fNIRS data processing and analyses were detailed in a previous paper [22]. Briefly, fNIRS measures changes in cortical oxygenated hemoglobin (HbO) levels using light–tissue interaction properties of light within the near infrared range. fNIRS has been validated against traditional neuroimaging methods and is better able to handle motion artifacts [23]. Changes in hemodynamic activity in the PFC were assessed using fNIRS Imager 1100 (fNIRS Devices, LLC, Potomac, MD). The system collects data at a sampling rate of 2 Hz. The fNIRS sensor consists of 4 LED light sources and 10 photodetectors, which cover the

forehead using 16 voxels, with a source-detector separation of 2.5 cm. The light sources on the sensor (Epitex Inc. type L4X730/4X805/4X850-40Q96-I) contain three built-in LEDs having peak wavelengths at 730, 805, and 850 nm, with an overall outer diameter of 9.2 ± 0.2 mm. The photodetectors (Bur Brown, type OPT101) are monolithic photodiodes with a single supply transimpedance amplifier. We implemented a standard sensor placement procedure [19].

Preprocessing and hemodynamic signal extraction Initially, data from each of the sixteen fNIRS channels for all participants were visually inspected to identify and eliminate saturation, dark current conditions, or extreme noise, which could happen due to incorrect sensor placement. Next, wavelet denoising with Daubechies 5 (db5) wavelet was applied to the raw intensity measurements at 730 and 850 nm wavelengths for spiky noise suppression [24]. Changes in HbO were calculated from those artifact-removed raw intensity measurements using modified Beer-Lambert law (MBLL) as previously described [22]. In MBLL, we used the previously published wavelength and chromophore-dependent molar extinction coefficients (ε) by Prahl, and age and wavelength adjusted differential pathlength factor (DPF) [22]. To remove possible baseline shifts and to suppress physiological artifacts such as respiration and Mayer waves, we first applied spline filtering [25] followed by a finite impulse response low-pass filter with cut-off frequency at 0.08 Hz [22]. In our analysis, HbO was used as a proxy for PFC activation as it is more reliable and sensitive than other fNIRS-derived measures (e.g., deoxygenated hemoglobin - HbR) to locomotion-related changes in cerebral oxygenation [26]. To determine the relative task-related changes in HbO concentrations, data epochs in STW, STA, and DTW were corrected relative to 10-s baselines administered immediately prior to each experimental condition as previously described [22].

Individual mean HbO data were extracted separately for STW, STA, and DTW. E-prime synchronized gait and fNIRS events to the millisecond. Internal consistency of HbO determined by split-half intra-class correlations within each task, was excellent for STW (0.830), STA (0.864), and DTW (0.849) [19].

Covariates

Age, sex, education, global health status (GHS), and the repeatable battery for the assessment of neuropsychological status (RBANS) served as covariates to account for possible effects of confounders and overall cognition. The GHS, a comorbidity measure, computes a total score based on the presence/absence of the following clinical conditions: diabetes, chronic heart failure, arthritis, hypertension, depression, stroke, Parkinson's disease, chronic obstructive lung disease, angina, and myocardial infarction score (range 0–10) [18]. The RBANS has been extensively researched and normed in aging [27] and MS [28]. The RBANS assesses five cognitive domains (Immediate Memory, Visuospatial/constructional, Language, Attention, and Delayed Memory) with a total scale score ranging from 40 to 160. Its utility as a single measure of cognitive function has been well-validated [29].

Statistical analysis

Descriptive statistics were used to summarize all study measures (mean ± SD for continuous measures, count and percent for categorical variables) and tabulated per group. Linear mixed effects models (LMMs) with participant-specific random intercept were employed as the main strategy for data analysis to account for correlations among measurements within the same participant to compare stride velocity, cognitive performance, and PFC HbO between participants with MS and controls during STW, STA, and DTW, and across trials. Task and trial conditions served as the within-participant repeated measures, and group status (MS vs. control) was the two-level between-group variable. Separate LMMs were conducted for stride velocity (STW, DTW), cognitive performance (STA, DTW), and PFC HbO levels (STW, STW, DTW). In all models, DTW served as the reference task condition; trial 1 served as a reference for trials 2 and 3 to evaluate practice effects. Analyses were first run unadjusted and then adjusted for covariates. To examine moderation effects, two-way interactions of task × trial, group × task, and group × trial were conducted as well as three-way interactions of group × task × trial. Stratified models by group status followed significant three-way interactions to facilitate interpretation of the results. Continuous covariates were median-centered based on sample distribution when adjusted for in LMMs. Estimated means in stride velocity, cognitive performance, and PFC HbO over trials stratified by task and group were visually presented by histograms. Between-trial comparisons stratified by task and group were additionally conducted to clarify within-session practice effects on stride velocity, cognitive performance, and PFC HbO. Tests of statistical significance were two-sided, and p value < 0.05 was considered statistically significant. Data were analyzed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA) statistical software.

Results

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Participants

Participant characteristics were stratified per group (Table 1). There were more female than male participants in the MS (69.15%) and control (64.42%) groups. Mean age was lower in MS (64.76 ± 4.19 years) compared to controls (68.19 ± 7.1 years). Mean RBANS total score in MS (90.32 ± 12.63) and controls (92.46 ± 15.57) was comparable and indicative of cognitive status within the normal range. On average, both samples had college education (MS = 15.04 ± 2.37 years; control = 16.23 ± 2.37 years). MS subtypes and disease duration, based on the year of first physician's formal diagnosis of MS, are presented in Table 1.

Table 1

Sample characteristics stratified by group

Variable	MS (n = 94)		Control (n = 104)		p value
	Mean	SD	Mean	SD	
Age (years)	64.76	4.19	68.19	7.1	0.0016
Education (years)	15.04	2.37	16.23	2.37	0.0006
GHS (0–10)	1.3	1.17	1.22	.87	0.9937
RBANS: total scale score	90.32	12.63	92.46	15.57	0.2871
Baseline stride velocity (cm/sec)	81.21	21.40	90.60	19.03	0.0013
Disease duration (years)	22.41	11.28			
	Number	Percent	Number	Percent	
Females	65	69.15	67	64.42	0.4812
MS subtypes					

Relapsing remitting	58	61.07
Secondary progressive	21	22.34
Primary progressive	6	6.38
Undetermined	9	9.57

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MS multiple sclerosis, *RBANS* repeatable battery for the assessment of neuropsychological status, *GHS* global health status

Wilcoxon rank-sum test was used for group differences on age, education, and GHS. *T*-test was used for group differences on RBANS total scale score and stride velocity. Chi-square test was used for group differences in gender distribution

Unadjusted and adjusted analyses were not materially different for all LMMs. Therefore, analyses that fully adjusted for all covariates (age, gender, education, GHS, RBANS) were presented.

fNIRS-derived activations

The overall LMM revealed significant effects of trial ($p < 0.0001$), task ($p < 0.0001$), trial × task interaction ($p < 0.0001$), trial × group interaction ($p = 0.0033$), task × group ($p < 0.0001$), and a three-way interaction of group × task × trial ($p = 0.0251$). The overall significant three-way interaction indicated that group status moderated task-related changes in HbO over trials (summary of the model is presented in supplemental Table 1). Therefore, subsequent LMMs were stratified by group.

fNIRS-derived activations: control participants

The overall LMM revealed significant effects of trial ($p < 0.0001$), task ($p < 0.001$), and trial × task interaction ($p < 0.0001$). Specifically, significant declines in PFC HbO levels in DTW were observed from trial 1 to trial 2 ($p < 0.0001$) and from trial 1 to trial 3 ($p < 0.0001$). Task effects in trial 1 demonstrated significantly higher PFC HbO levels in DTW compared to both STW ($p < 0.0001$) and STA ($p < 0.0001$). Significant trial × task interactions revealed that the decline in PFC HbO levels from trial 1 to 2 was greater in DTW compared to STW ($p < 0.0001$) and STA ($p = 0.0176$); similarly greater decline in PFC HbO levels from trial 1 to 3 was observed in DTW compared to STW ($p < 0.0001$) and STA ($p = 0.0374$). Detailed summary of these analyses is presented in Table 2 panel A.

Table 2

Linear mixed effects model examining main effects and interactions of group, trial, and task as well as covariates on fNIRS-derived HbO

Variable	Estimate	SE	*p* value	95%CI lower	95%CI upper
Panel A: Control participants					
Intercept	1.2854	0.08751	< .0001	1.1117	1.459
Trial 1 vs. Trial 2	− 0.3147	0.0397	< .0001	− 0.3925	− 0.2369
Trial 1 vs. Trial 3	− 0.4296	0.0394	< .0001	− 0.5068	− 0.3523
DTW vs. STW	− 1.1933	0.0396	< .0001	− 1.2709	− 1.1156
DTW vs. STA	− 0.3294	0.0396	< .0001	− 0.4071	− 0.2518
Trial 1 vs. Trial 2*DTW vs. STW	0.2994	0.0559	< .0001	0.1898	0.4089
Trial 1 vs. Trial 2*DTW vs. STA	0.1331	0.0560	0.0176	0.0231	0.243
Trial 1 vs. Trial 3*DTW vs. STW	0.4045	0.0556	< .0001	0.2955	0.5135
Trial 1 vs. Trial 3*DTW vs. STA	0.1161	0.0557	0.0374	0.0067	0.2254
Gender	− 0.1108	0.1109	0.3177	− 0.3283	0.1066
Age (years)	0.0136	0.0078	0.0833	− 0.0017	0.029
Education (years)	− 0.0142	0.0209	0.4954	− 0.0552	0.0267
GHS	0.0308	0.05722	0.5894	− 0.0812	0.143
RBANS total score	− 0.002	0.0033	0.5478	− 0.0085	0.0045
Panel B: MS participants					
Intercept	1.3013	0.0831	< .0001	1.1362	1.4665
Trial 1 vs. Trial 2	− 0.2957	0.0395	< .0001	− 0.3733	− 0.2182

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MS multiple sclerosis, *DTW* dual-task-walk, *STW* single-task-walk, *STA* single-task-alpha, *GHS* global health status, *RBANS* repeatable battery for the assessment of neuropsychological status, *SE* standard error, *CI* confidence interval
Continuous variables (age, education, GHS, and RBANS total scores) are median-centered

fNIRS-derived activations: MS participants

The overall LMM revealed significant effects of trial ($p < 0.0001$), task ($p < 0.001$), trial × task interaction ($p < 0.0001$). Specifically, significant declines in PFC HbO levels in DTW were observed from trial 1 to trial 2 ($p < 0.0001$) and from trial 1 to trial 3 ($p < 0.0001$). Task effects in trial 1 demonstrated significantly higher PFC HbO levels in DTW compared to both STW ($p < 0.0001$) and STA ($p = 0.0313$). Significant trial × task interactions revealed that the decline in PFC HbO levels from trial 1 to 2 was greater in DTW compared to STW ($p < 0.0001$) but not STA ($p = 0.5457$); similarly greater decline in PFC HbO levels from trial 1 to 3 was observed in DTW compared to STW ($p < 0.0001$) but not STA ($p = 0.4917$). Detailed summary of these analyses is presented in Table 2 (panel B). Visual depiction of HbO levels per trial, task, and group is provided in Fig. 1.

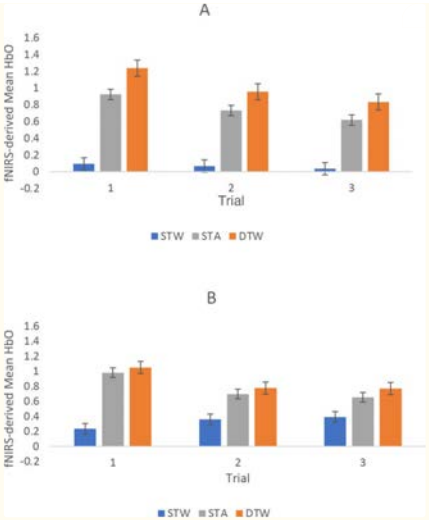

Fig. 1

Mean fNIRS-derived HbO per trial (1–3), task condition (STW, STA, DTW), and group (MS vs. control). **A** Control participants. **B** MS participants. STW, single-task-walk; STA, single-task-alpha; DTW, dual-task-walk; MS, multiple sclerosis

Gait: stride velocity

The overall LMM revealed significant effects of trial ($p < 0.0001$), task ($p < 0.001$), group ($p = 0.0023$; slower stride velocity in MS compared to control participants), trial × task interaction ($p < 0.0345$), and task × group interaction ($p = 0.0059$). The three-way interaction of group × task × trial, however, was not significant ($p = 0.409$) indicating that group, task, and trial did not moderate any two-way interactions. Among healthy controls, DTW gait velocity improved from trial 1 to trial 2 ($p < 0.0001$) and from trial 1 to trial 3 ($p < 0.0001$). Task effects in trial 1 among healthy controls demonstrated significantly slower gait velocity in DTW compared to STW ($p < 0.0001$). A significant trial × task interaction revealed that differences between DTW and STW were reduced from trial 1 to trials 3 in the same group indicating greater improvements in DTW compared to STW ($p = 0.0094$). In trial 1, MS participants walked slower in DTW compared to controls ($p = 0.0312$). A significant group × task interaction revealed that the decrease in stride velocity between DTW and STW was smaller in MS compared to control participants in trial 1 ($p = 0.0162$). Detailed summary of these analyses is presented in Table 3. Visual depiction of stride velocity per trial, task, and group status is provided in Fig. 2.

Table 3

Linear mixed effects model examining main effects and interactions of group, trial, and task as well as covariates on stride velocity

Variable	Estimate	SE	*p* value|	95% CI lower	95% CI upper
Intercept	78.1978	2.7697	< .0001	72.7347	83.6608
Trial 1 vs. Trial 2	5.7256	1.0268	< .0001	3.7105	7.7408
Trial 1 vs. Trial 3	7.1798	1.0313	< .0001	5.156	9.2037
DTW vs. STW	14.801	1.0305	< .0001	12.7787	16.8234
Group (MS vs. control)	− 6.723	3.1162	0.0312	− 12.8385	− 0.6075
Trial 1 vs. Trial 2* DTW vs. STW	− 2.7673	1.4296	0.0532	− 5.5729	0.0383
Trial 1 vs. Trial 3* DTW vs. STW	− 3.7537	1.4433	0.0094	− 6.5862	− 0.9213
Trial 1 vs. Trial 2* Group (MS vs. control)	− 1.2778	1.472	0.3856	− 4.1666	1.6109
Trial 1 vs. Trial 2* Group (MS vs. control)	− 2.2224	1.4777	0.1329	− 5.1225	0.6776
DTW vs. STW * Group (MS vs. control)	− 3.5587	1.4767	0.0162	− 6.4567	− 0.6606
Trial 1 vs. Trial 2* DTW vs. STW * Group (MS vs. control)	0.9583	2.0663	0.6429	− 3.0969	5.0135
Trial 1 vs. Trial 3* DTW vs. STW * Group (MS vs. control)	2.7348	2.0774	0.1883	− 1.3421	6.8117
Gender	− 1.4805	3.0388	0.6262	− 7.4442	4.4832
Age (years)	− 0.4222	0.251	0.0928	− 0.9147	0.0703
Education (years)	0.0201	0.5816	0.9724	− 1.1212	1.1614
GHS	− 1.5671	1.344	0.2439	− 4.2048	1.0706

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MS multiple sclerosis, *DTW* dual-task-walk, *STW* single-task-walk, *STA* single-task-alpha, *GHS* global health status, *RBANS* repeatable battery for the assessment of neuropsychological status, *SE* standard error, *CI* confidence interval. Continuous variables (age, education, GHS, and RBANS total scores) are median-centered

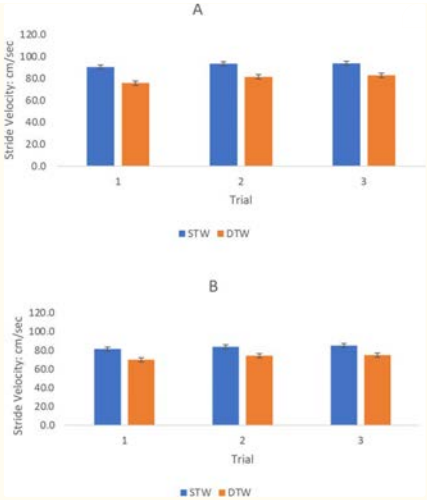

Fig. 2

Mean stride velocity per trial (1–3), task (STW, DTW), and group (MS vs. control). **A** Control participants. **B** MS participants. STW, single-task-walk; DTW, dual-task-walk; MS, multiple sclerosis

Cognition: correct letter generation

The overall LMM revealed significant effects of trial ($p < 0.0001$) and task ($p < 0.0001$). The effect of group or two and three-way interactions of task, trial, and group was not significant. Among control participants, DTW correct letter generation improved from trial 1 to trial 2 ($p < 0.0001$), and from trial 1 to trial 3 ($p < 0.0001$). Task effects in trial 1 in the same group demonstrated significantly lower number of correctly generated letters in DTW compared to STA ($p < 0.0001$). A significant trial (1 vs. 3) × task interaction revealed that differences between DTW and STA among controls were reduced due to practice ($p = 0.0152$). Detailed summary of these analyses is presented in Table 4. Visual depiction of cognitive performance per trial, task, and group status is provided in Fig. 3.

Table 4

Linear mixed effects model examining main effects and interactions of group, trial, and task as well as covariates on correct letter generation

Variable	Estimate	SE	*p* value	95% CI lower	95% CI upper
Intercept	29.8857	1.107	< .0001	27.7024	32.0691
Trial 1 vs. Trial 2	3.3821	0.7369	< .0001	1.9359	4.8282
Trial 1 vs. Trial 3	5.8592	0.7404	< .0001	4.4062	7.3122
DTW vs. STA	5.4112	0.7335	< .0001	3.9718	6.8506
Group (MS vs. control)	− 0.6094	1.2991	0.6391	− 3.1588	1.94
Trial 1 vs. Trial 2* DTW vs. STA	− 1.0551	1.0226	0.3024	− 3.0619	0.9516
Trial 1 vs. Trial 3* DTW vs. STA	− 2.4938	1.0251	0.0152	− 4.5055	− 0.4821
Trial 1 vs. Trial 2* Group (MS vs. control)	− 0.6847	1.057	0.5173	− 2.7591	1.3897
Trial 1 vs. Trial 3* Group (MS vs. control)	− 1.0505	1.0612	0.3225	− 3.1331	1.0322
DTW vs. STA * Group (MS vs. control)	− 1.0574	1.0529	0.3155	− 3.1237	1.0089
Trial 1 vs. Trial 2* DTW vs. STA * Group (MS vs. control)	1.3365	1.4751	0.3652	− 1.5584	4.2314
Trial 1 vs. Trial 3* DTW vs. STA * Group (MS vs. control)	2.5923	1.4789	0.08	− 0.31	5.4946
Gender	− 0.2958	1.1233	0.7924	− 2.5002	1.9086
Age (years)	− 0.0566	0.09285	0.5419	− 0.2389	0.1256
Education (years)	0.2049	0.215	0.3407	− 0.2169	0.6268
GHS	− 0.6549	0.4968	0.1878	− 1.6298	0.3201

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MS multiple sclerosis, *DTW* dual-task-walk, *STW* single-task-walk, *STA* single-task-alpha, *GHS* global health status, *MS* multiple sclerosis, *RBANS* repeatable battery for the assessment of neuropsychological status, *SE* standard error, *CI* confidence interval. Continuous variables (age, education, GHS, and RBANS total scores) are median-centered

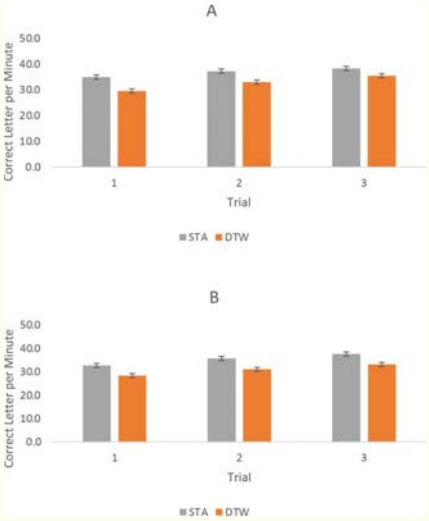

Fig. 3

Mean correct letters per trial (1–3), task (STA, DTW), and group (MS vs. control). **A** Control participants. **B** MS participants. STA, single-task-alpha; DTW, dual-task-walk; MS, multiple sclerosis

Within session practice effects stratified by task and group

To further clarify within session practice effects on fNIRS-derived HbO, stride velocity, and cognition (letter generation), effect sizes and their corresponding *p* values were extracted from the LMMs for trial comparisons stratified by task and group. These results are summarized in Table 5. Overall, significant improvements in stride velocity and cognitive performances were observed in both groups over trials under single and dual-task conditions. Declines in HbO were observed in STA and DTW in both groups. Under STW, changes in HbO were significant in MS but not control participants due to low levels that were maintained in the latter group in all trials.

Table 5

Effect sizes for between trial comparisons stratified by task and group

	Task	Trial	ES Estimate	SE	*P*-value
Panel A: HbO					
Control	STW	2 vs 1	−0.0252	0.0338	0.4559
		3 vs 1	−0.0582	0.0336	0.0834
	STA	2 vs 1	−0.1917	0.0290	< .0001
		3 vs 1	−0.3055	0.0289	< .0001
	DTW	2 vs 1	−0.2817	0.0375	< .0001
		3 vs 1	−0.4033	0.0372	< .0001
MS	STW	2 vs 1	0.1259	0.0359	0.0005
		3 vs 1	0.1584	0.0363	< .0001
	STA	2 vs 1	−0.2841	0.0301	< .0001
		3 vs 1	−0.3274	0.0301	< .0001
	DTW	2 vs 1	−0.2738	0.0376	< .0001
		3 vs 1	−0.2806	0.0380	< .0001
Panel B: Stride velocity					
Control	STW	2 vs 1	2.9377	0.5453	< .0001
		3 vs 1	3.4054	0.5536	< .0001
	DTW	2 vs 1	5.7741	0.6848	< .0001
		3 vs 1	7.1181	0.6875	< .0001

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MS multiple sclerosis; *DTW* dual-task-walk; *STW* single-task-walk; *STA* single-task-alpha

Discussion

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We evaluated within session practice effects on neural efficiency assessed during single and dual-task walking conditions in older adults with and without MS. In the context of improved gait and cognitive performances over trials, fNIRS-derived activation in the PFC declined, notably under DTW, suggesting improved utilization of brain resources. Robust practice-related improvements in brain efficiency were observed in both groups, but appeared attenuated in the older adults with MS. These findings are discussed in detail below.

Results from LMMs revealed declines in gait and cognitive performances under DTW compared to STW and STA, respectively, in both groups. These findings are consistent with prior studies in other populations [7, 30] confirming the key role attention and executive functions have in coordinating cognitive resources to support dual-task walking [8, 19]. Participants demonstrated robust improvements over trials in cognitive performance. A significant trial × task interaction further

clarified these practice effects revealing that improvements in correct letter generation from trial 1 to 3 were greater in DTW compared to STA. Similarly, while stride velocity was slower in older adults with MS compared to controls, participants showed significant improvements in gait performance over trials. Trial × task interactions further clarified these practice effects revealing that improvements were marginally (trial 1 to 2) and significantly (trial 1 to 3) greater in DTW compared to STW. Additional between-trial comparisons, stratified by task and group, supported significant practice effects on both gait and cognitive performances across tasks in older adults with and without MS.

The LMM using fNIRS-derived HbO as the outcome measure revealed a significant three-way interaction of group × trial × task indicating that changes over trials in task-related PFC activation were moderated by the presence of MS. Therefore, follow-up analyses were stratified by group to facilitate the interpretation of the results. Consistent with our first hypothesis, group-stratified analysis revealed that fNIRS-derived HbO increased in DTW compared to STW and STA in both cohorts confirming the key role of the PFC in allocating cognitive resources to support walking under attention-demanding conditions [10].

Comparisons of fNIRS-derived HbO in the first trial to the second and third trials revealed significant declines in PFC activation levels suggesting an overall reduced utilization of neural resources across task conditions. Given that performances in both gait and cognition improved over trials, these findings support the second study hypothesis predicting improved neural efficiency in the PFC due to within session practice. These results, however, were further explained by trial × task interactions that differed as a function of group. Specifically, among healthy controls, differences in HbO levels between DTW and both single task conditions were reduced in the second and third trials as compared to the first trial. This effect is attributed to greater declines in fNIRS-derived HbO during DTW compared to both STW and STA over trials. Among older adults with MS, however, greater declines over trials in HbO levels during DTW were observed in comparison to STW but not STA. Hence, in the context of practice-related improvement in gait and cognitive performances, the corresponding declines over trials in PFC activation levels suggest improved utilization of neural resources, notably under DTW, that varied due to the presence of MS. This supports the third study hypothesis indicating that practice related improvement in DTW, the condition imposing the most cognitive demands, was attenuated in older adults with MS compared to healthy controls. Additional analysis examining effects sizes for trial comparisons stratified by task and group supported the above findings revealing declines in HbO under STA and DTW in both groups. Under STW, changes in HbO were significant in MS but not control participants due to low levels that were maintained in the latter group over trials suggesting that walking under single task conditions may have been more cognitively demanding for older adults with MS compared to controls; this is consistent with the inefficiency hypothesis proposing that more neural resources are utilized by individuals with reduced brain integrity for relatively simple tasks [11].

To our knowledge, this study is the first to demonstrate within session practice-related improvements in the efficiency of neural resource utilization that support attention-demanding walking in both normal aging and MS. The ability of participants in both groups to adapt to cognitively demanding tasks within a single experimental session is noteworthy given the deleterious effects of aging and neurological disease on structural and functional brain integrity. These findings are consistent with and extend a recent meta-analysis of fMRI studies of cognitively demanding tasks, suggesting the PFC is optimal for probing practice effects on brain efficiency [31]. We suggest that due to brain adaptation to the novelty and high cognitive demands imposed by DTW, performance became less effortful allowing for greater automaticity in task performance that could be further supported by striatal brain regions [32]. Possible implications for treatments designed to optimize walking and associated brain function are discussed under study limitations and future directions.

Literature concerning mechanisms that underlie variability in brain efficiency implicated in cognitive and gait function has been limited. The efficiency of fNIRS-derived activations in the PFC during walking was related to structural integrity of the brain, measured via MRI, in normal aging. Specifically, reduced gray matter volume, notably but not exclusively in regions in the frontal cortex [33], lower whole brain fractional anisotropy [34], and thinner cortex in multiple brain regions [35] were independently associated with inefficient fNIRS-derived brain activation patterns in the PFC assessed during dual-task walking. MS influences the structural integrity of the brain [36, 37], which might explain the lower efficiency observed in patients with MS in the current study. But other potential mechanisms such as cognitive reserve which could be enhanced through lifestyle changes might influence the efficiency of fNIRS-derived activations [38]. Identifying modifiable mechanisms that explain variability in brain efficiency associated with walking has critical implications for treatment paradigms designed to improve physical and overall health in aging and neurological disease.

The ability to walk is a robust measure of health. The decline in walking performance is associated with a multitude of adverse health outcomes including higher rates of morbidity, more hospitalizations, poorer quality of life, and mortality [39–42]. Dual-task walking may better approximate locomotion in natural environments where individuals are required to continuously negotiate multiple stimuli and interferences. Poor dual-task walking is predictive of incident disability, frailty, and mortality [43] as well as fall risk [44, 45]. Furthermore, among healthy older adults, inefficient fNIRS-derived HbO, assessed during dual-task walking, predicted greater risk of incident falls [46]. Hence, improving brain efficiency associated with dual-task walking in healthy older adults and those diagnosed with neurological disease should be considered as a target for interventions designed to reduce falls.

Study strengths limitations and future directions

Older adults with MS represent a growing but significantly understudied clinical population, and the inclusion of a control group allowed for comparisons deciphering the effects of normal aging from neurological disease on study outcomes. MS and control participants were well-characterized, but due to study design and eligibility criteria requiring ambulatory capabilities, intact cognition, and MRI, generalizability of the findings to more variable and impaired samples should be evaluated in future research. Stride velocity was utilized to assess gait performance in the current study due to its excellent psychometric properties and established predictive utility of health outcomes [20, 21]. It would be of interest, however, to examine the effects of acute practice on other quantitative measures of gait, notably gait variability which is sensitive to dual-task effects [30] and cognitive impairment in clinical populations [47]. While analysis controlled for key potential confounders, the unweighted summation of 10 diseases used to derive the GHS variable provided limited adjustment for comorbidity in the current study. fNIRS is a noninvasive optics-based neuroimaging modality that has been successfully applied to assess changes in brain activation patterns in natural environments [48]. Importantly, this technology is uniquely suitable to distinguish motion artifacts that are inherent in locomotion from true brain signals [22]. It is

important to recognize, however, that the spatial resolution and depth of penetration of fNIRS are limited. The decline in fNIRS-derived HbO over trials was not be attributed to drift in measurement as data were visually inspected and proximal baselines were used before each task and trial. We have not conducted analyses on HbR in the current study to limit the number of analyses and because it is redundant with HbO in this paradigm [22]. The robust, acute practice effects observed in this study with respect to behavioral and fNIRS outcomes have critical treatment implications. But the durability of these effects should be tested in future studies with longer time intervals. Dual-task training [44] and home based gait and balance training in MS [49] improve both cognitive and motor functioning. It remains to be evaluated whether fNIRS-derived HbO could be used as a biomarker for evaluating treatment outcomes, notably improving cortical efficiency of gait control.

Conclusion

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We demonstrated that dual-task walking and the efficiency of its associated activation levels in the PFC could be improved during a single practice session in older adults with and without MS. While acute practice-related improvement in gait and cognitive performances were comparable across groups, improvement in neural resources utilization, although significant, was attenuated in older adults with MS. These findings point to encouraging brain adaptability in aging and neurological disease. Furthermore, the utility of fNIRS-derived HbO as a biomarker for treatment appears promising and should be examined in future research.

Supplementary Information

Below is the link to the electronic supplementary material.

Supplementary file1 (DOCX 20 KB)(20K, docx)

Glossary

Go to:

DTW	Dual-task-walk
STW	Single-task-walk
STA	Single-task-alpha
fNIRS	Functional near-infrared spectroscopy
GHS	Global health status
IRB	Institutional review board
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
PFC	Prefrontal cortex
RBANS	Repeatable battery for the assessment of neuropsychological status
HbO	Oxygenated hemoglobin
HbR	Deoxygenated hemoglobin

Author contribution

Go to:

RH: Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. JC: Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. RWM: Drafting/revision of the manuscript for content, including medical writing for content. FWF: Drafting/revision of the manuscript for content, including medical writing for content. MEH: Drafting/revision of the manuscript for content, including medical writing for content. MW: Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. MI: Analysis or interpretation of data, drafting/revision of the manuscript for content, including medical writing for content.

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Data availability

Go to:

Data will be provided to qualified investigators upon written request to the corresponding author.

Declarations

Go to:

Ethics approval

The work described in this manuscript has been executed in adherence with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Institutional review board

Albert Einstein College of Medicine Institutional Review Board approved this study (IRB #: 2019–10049).

Informed consent

Participants signed written informed consents in the first in-person study visit.

Conflict of interest

Dr. Izzetoglu has a minor share in fNIRS device. All other authors have no conflicts of interest to report in relation to the current article. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Footnotes

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