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Research Article

Cognitive Reserve Moderates the Efficiency of Prefrontal Cortex Activation Patterns of Gait in Older Adults

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Abstract

Background: Cognitive reserve (CR) protects against cognitive decline, but whether CR influences the efficiency of cortical control of gait has not been reported. The current study addressed this important gap in the literature. Specifically, we determined the role of CR in moderating the efficiency of functional near-infrared spectroscopy (fNIRS)-derived oxygenated hemoglobin (HbO_2) in the prefrontal cortex (PFC) assessed during active walking. We hypothesized that higher CR would be associated with more efficient brain activation patterns.

Methods: Participants were 55 (mean age = 74.84; %female = 49.1) older adults who underwent the combined walking/fNIRS protocol and had magnetic resonance imaging data. We used an established dual-task walking paradigm that consisted of 3 task conditions: single-task walk (STW), single-task alpha (STA, cognitive task), and dual-task walk (DTW). Using the residual approach, CR was derived from a word-reading test score by removing variance accounted for by sociodemographic variables, tests of current cognitive functions, and a measure of structural brain integrity.

Results: CR moderated the change in fNIRS-derived HbO_2 in the PFC across tasks. Higher CR was associated with smaller increases in fNIRS-derived HbO_2 from the single tasks to dual-task walking (CR × DTW compared with STW: estimate = 0.183; $p < .001$; CR × DTW compared with STA: estimate = 0.257; $p < .001$). The moderation effect of CR remained significant when adjusting for multiple covariates and concurrent moderation effects of measures of gait performance, current cognitive functions, and structural integrity of the brain.

Conclusion: The current study provided first evidence that higher CR was associated with better neural efficiency of walking in older adults.

Keywords: Cognitive reserve, Gait, Neural efficiency, Prefrontal cortex

Cognitive reserve (CR) refers to a latent construct designed to measure individual differences in the ability to adapt and optimize task performance vis-a-vis brain aging, pathology, or insult (1). Stated differently, CR serves as a buffer against the negative effect of age-related neuropathology or insult on cognitive function and decline. Proxy measures of CR are variable and include sociodemographic measures, objective cognitive tests of reading and verbal IQ, or functional brain networks that optimize performance and processing efficiency (2,3). The concept of CR makes intuitive sense, and a recent review and meta-analytic study clearly demonstrated that higher CR levels were protective against cognitive decline (4). How to measure CR, however, is not without controversy. Specifically, commonly used CR measures, whether treated as single or composite variables, include extraneous variance that is accounted for by environmental and individual confounders. The residual approach aims to address this limitation by removing the variance in CR explained by extraneous variables (3,5). Larger residuals suggest that more CR remains after accounting for measures of neuropathology and other confounding variables. In contrast to the extensive literature concerning CR and cognition, the role of CR in gait is poorly understood.

Cognition and walking are interrelated in aging (6–8), and strong evidence supports the key role of attention and executive functions in cognitive control of gait (9,10). Dual-task methodology, utilized to quantify the resultant cognitive cost of allocating attention

resources concomitantly to competing task demands, is considered a unique facet of the executive functions that is sensitive to the deleterious effect of aging (11,12). Recent reviews and meta-analyses of dual-task gait studies have shown that taxing attention and executive resources resulted in significant and reliable negative effects on walking performance (13,14). Whereas evidence for meaningful associations between executive functions and gait have been well established, much less is known about the role of CR in gait and mobility outcomes. Higher CR, assessed using a composite measure of verbal IQ, was related to lower odds of reporting recurrent falls (15). Furthermore, the protective effects of executive functions and memory on gait speed decline were stronger among individuals with higher CR, the latter was assessed using the vocabulary test (16). A recent study found that slower gait under single- and dual-task conditions was associated with increased risk of incident mobility impairments among older adults with lower CR (measured using a word-reading test) (17). To the best of our knowledge, the role of CR in functional cortical control of gait has not been established.

Due to the limitations inherent in traditional neuroimaging methods, the literature concerning the functional brain systems of walking has been relatively scarce (18). However, recent studies using functional near-infrared spectroscopy (fNIRS) have begun to shed light on the functional brain correlates of active walking (19,20). Moreover, a recent meta-analytic study (21) found reliable and significant increases in fNIRS-derived oxygenated hemoglobin (HbO_2) in the prefrontal cortex (PFC) in dual-task walk (DTW) compared with single-task walk (STW) conditions in older adults and disease populations. Previous work also revealed that poor white matter integrity (22), lower gray matter volume (23), and thinner cortex (24) were associated with higher and inefficient activation patterns in the PFC during dual-task walking. The role of CR in determining the efficiency of cortical control of gait, however, has not been reported.

Current Study

The current study aimed to determine the role of CR in moderating the efficiency of fNIRS-derived HbO_2 in the PFC assessed during active walking. We used an established dual-task walking paradigm that consisted of 3 task conditions: STW, single-task alpha (STA; cognitive task), and DTW. CR was derived using the residual approach removing variance on *The Wide Range Achievement Test*, 3rd edition (WRAT-3) (25), a common marker of CR, accounted for by demographic variables, a composite measure of current cognitive functions that are sensitive to aging, and gray matter volume in the frontal cortex. Neural inefficiency was defined in the context of behavioral performance: an individual with an inefficient brain response would exhibit higher brain activations coupled with similar or worse performance compared to an individual with efficient brain responses (26). Conversely, lower brain activations, coupled with similar or better behavioral performance, are indicative of less energy utilized to support performance and suggest greater neural efficiency. We hypothesized that higher CR would be associated with more efficient brain activation patterns, evidenced by smaller increases in fNIRS-derived HbO_2 in the PFC from single- to dual-task conditions. To determine CR effects on the efficiency of PFC activation patterns across task conditions, models accounted for and directly examined the concurrent moderating effects of gait (stride velocity) and cognitive task (reciting alternate letters of the alphabet) performances on the changes in fNIRS-derived HbO_2 across task conditions. To further elucidate the influence of CR on PFC activation efficiency during active walking, models also accounted for current cognitive functions and measures of structural brain integrity.

Method

Participants

Participants in "Central Control of Mobility in Aging" (CCMA) who had completed the combined fNIRS dual-task walking paradigm and also underwent a magnetic resonance imaging (MRI) protocol were included in the current study. CCMA procedures were previously described (10,27). Briefly, potential participants were identified from population lists of lower Westchester County, NY. Verbal assent and initial eligibility were obtained via structured phone interviews that included cognitive screens and questionnaires concerning medical and psychological history as well as mobility function. Testing procedures included structured interviews, comprehensive neuropsychological, psychological, functional, and mobility assessments as well as questionnaires that covered multiple domains of function. The lcombined fNIRS and dual-task walking protocol was completed in 1 session. Cognitive status was determined at consensus diagnostic case conferences (28). Exclusion criteria were as follows: dementia, current or history of severe neurological or psychiatric disorders, inability to ambulate independently, significant loss of vision and/or hearing, and recent or anticipated medical procedures that may affect ambulation. The neuroimaging subsample included 73 participants without standard MRI contraindications (eg, pacemaker, other nonremovable metal implants or body piercings, claustrophobia). Of these, 55 participants had the combined walking and fNIRS measures and MRI data collected within 1 year. The work described in this manuscript has been executed in adherence with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Participants signed written informed consents at the first in-person study visit. The Institutional Review Board of Albert Einstein College of Medicine approved this study.

Measures

Walking protocol

In the single-task walk (STW) condition, participants were asked to walk around an electronic walkway at their "normal pace." The cognitive interference task, single-task alpha (STA), required participants to stand still while reciting alternate letters of the alphabet (A, C, E…) for 30 seconds out loud. The DTW condition required participants to perform the 2 single tasks at the same time. To minimize task prioritization effects during DTW, the participants were instructed to pay equal attention to both single tasks. Participants walked on the instrumented walkway in 3 continuous loops that consisted of 6 straight walks and 5 left-sided turns, separately, under the STW and DTW conditions. To minimize task order effects, the 3 test conditions were counterbalanced using a Latin-square design. Reliability and validity for this walking paradigm have been well established (9,10).

Quantitative gait assessment

A 4 × 20 foot Zeno electronic walkway was used to measure stride velocity, based on the location and mathematical parameters between footfalls, under the STW and DTW conditions (Zenometrics, LLC; Peekskill, NY). ProtoKinetics Movement Analysis Software technology (PKMAS) determined, algorithmically, entry and exit points under both task conditions (29). Stride velocity was computed based on the entire walking protocol in each task condition, which

consisted of 3 complete counterclockwise laps on the walkway (ie, of 6 straight walks and 5 left-handed turns). Split-half intraclass correlations in both walking conditions were greater than .95 revealing excellent internal consistency in quantitative gait assessment (30).

fNIRS system

Similar to our previous studies, fNIRS Imager 1100 (fNIR Devices, LLC, Potomac, MD) was used in the current investigation to collect brain-imaging data during active walking. The device collects data at a sampling rate of 2 Hz. The fNIRS sensor consists of 4 LED light sources and 10 photodetectors that cover the forehead using 16 optodes, with a source-detector separation of 2.5 cm. The light sources on the sensor (Epitex Inc. type L4 × 730/4 × 805/4 × 850-40Q96-I) contain 3 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 based on landmarks from the international 10–20 system.

Details concerning our fNIRS signal processing methods were provided in a previous publication (31). Briefly, data were visually inspected to identify and eliminate saturation, dark current conditions, or extreme noise. We then applied a wavelet denoising with Daubechies 5 (db5) wavelet to the raw intensity measurements at 730- and 850-nm wavelengths for spiky noise suppression. Using the modified Beer–Lambert law (MBLL), we calculated changes in HbO_2 from these artifact-removed raw intensity measurements. In MBLL, we accounted for wavelength- and chromophore-dependent molar extinction coefficients (ε) and age- and wavelength-adjusted differential pathlength factor. We applied Spline filtering followed by a finite impulse response low-pass filter with cutoff frequency at 0.08 Hz to remove possible baseline shifts and to suppress physiological artifacts such as respiration and Mayer waves. HbO_2 served as a single marker for PFC activation as we have shown in a separate study using the same paradigm that deoxygenated hemoglobin (Hb) was redundant (32). Proximal 10-second baselines were administered prior to each experimental condition to determine the relative task-related changes in HbO_2 concentrations (30,33). Individual mean HbO_2 data were extracted separately for each task and optode. We used a central "hub" computer with E-Prime 2.0 software to synchronize gait and fNIRS events. Internal consistency of HbO_2 measurements within each task was excellent as determined by split-half intraclass correlations ($r > .830$) (30).

Assessment of CR

The WRAT-3 word-reading performance is relatively stable over time in older adults and commonly used as a marker of CR (34). Using the residual approach to measure CR, the WRAT-3 served as the outcome variable in a linear regression model with years of education, ethnicity, sex, a composite measure of current cognitive functions, and volume of the left rostral middle frontal region (leftRMF) entered as predictors. Predictors were selected based on both a priori considerations and individual correlations with the WRAT-3. The standardized residuals derived from the regression model were used to operationalize CR in the current study.

Magnetic Resonance Imaging

Details concerning the MRI procedures were provided in previous publications (22,23). Magnetic resonance imaging was performed in a 3T Phillips scanner equipped with a 32-channel head coil (Achieva TX, Philips Medical Systems, Best, The Netherlands) at the Gruss Magnetic Resonance Research Center of Albert Einstein College of Medicine. The FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/) was used to extract the regional cortical volume and thickness measures from T1-weighted images (MPRAGE – TE/TR/TI = 4.6/9.8/900 ms, voxel size 1 mm isotropic, SENSE acceleration factor 2.6). Image preprocessing methods has been described previously (35–37). Briefly, this includes nonbrain tissue removal, Talairach transformation, subcortical segmentation, tessellation of gray–white matter boundaries, and atlas registration. FreeSurfer's cortical parcellation identified 34 regions in each hemisphere (38), which were visually inspected for accuracy by overlaying the segmentation on each participant's T1 image in FSLeyes. Finally, FreeSurfer's "mri_segstats" was used to extract regional cortical gray matter volumes. Cortical thickness measurements underwent surface-based smoothing at FWHM = 5 mm prior to extraction.

Diffusion Tensor Imaging

DTI raw images used a single shot spin echo EPI sequence (TE/TR = 65/10,000 ms, voxel size 3 mm isotropic, SENSE acceleration factor 2.8), were inspected for artifact, and were corrected for eddy currents and motion. DTI and high-resolution T1-weighted structural images were extracted using the FSL FMRIB Structural Toolkit (39). T1-weighted images were segmented into gray, white, and cerebrospinal fluid (CSF) components using FSL's FAST (40), and whole-brain white matter masks were then generated by thresholding the white matter output at 50% and eroding with a 3-pixel kernel to avoid the gray–white interface. DTI-derived maps of fractional anisotropy (FA) were obtained using the FSL FMRIB Diffusion Toolkit (41), followed by distortion correction using the B0 field maps. Whole-brain FA measures were obtained in T1 space by registering the FA maps to the participant's T1 image (42), multiplying the FA maps by the white matter mask, and calculating mean FA over the white matter mask.

Covariates and Moderators

Magnetic resonance imaging

The left RMF volume, selected based on its role in language (43), associations with executive functions and motor performance in older adults (44) and robust correlation with WRAT-3 scores in the current sample, served as a covariate and as a moderator of changes in fNIRS-derived HbO_2 across task conditions. Whole-brain gray matter volume, whole-brain FA, and mean cortical thickness served as covariates and moderators in separate supplemental analyses.

Composite measure of current cognitive functions

Scores on 3 commonly used neuropsychological tests (Digit Symbol Modalities Test, Free and Cued Selective Reminding Test, Letter Fluency—FAS) that assess speed of processing and working memory, episodic verbal memory, and language and executive functions were Z transformed based on sample distribution and then averaged to create a composite Z score of cognitive functions known to be sensitive to aging and disease (45).

Dual-task performance

Stride velocity and the rate of correct letter generation under DTW were used to quantify DTW performance. The composite cognitive Z score, DTW stride velocity, and DTW rate of correct letter generation served as covariates and moderators of task-related changes in fNIRS-derived HbO_2.

Other covariates included were age, sex, and a Global Health Status score (GHS; range 0–10). The GHS included the following 10 conditions, which were determined as present or absent: diabetes, chronic heart failure, arthritis, hypertension, depression, stroke, Parkinson's disease, chronic obstructive lung disease, angina, and myocardial infarction (28).

Statistical Analysis

Descriptive statistics of all study measures (mean ± *SD* for continuous measures) were examined and tabulated for the entire sample. Separate linear mixed-effects models were used to examine task effects on gait and cognitive performance. Then 5 separate linear mixed-effects models (LMEMs) were conducted to determine the moderating effects of CR on the change in fNIRS-derived HbO_2 across task conditions. Moderation effects were defined as the interaction terms within the context of the LMEMs wherein levels in one variable influenced the change in the outcome measure (fNIRS-derived HbO_2) across the 3-level within-subject repeated-measures task condition (ie, STW, STA, DTW). Analyses were first run unadjusted (model 1) and then adjusted for covariates including age, GHS score, sex, DTW stride velocity and rate of correct letter generation (model 2). Stride velocity and the rate of correct letter generation under DTW were entered in model 2 as covariates and concurrent moderators, which was critical for interpretating the moderating effect of CR on PFC efficiency across task conditions. In model 3, the mean composite cognitive *Z* score was entered as a covariate and moderator to further elucidate the effect of CR on study outcomes. Model 4 included the leftRMF volume as a covariate and moderator. Finally, model 5 included both the composite cognitive *Z* score and leftRMF volume as covariates and concurrent moderators. Additionally, in separate supplemental analyses, whole-brain gray matter volume, whole-brain FA, and mean cortical thickness were entered as covariates and moderators in separate models. SPSS statistical software package (version 25; SPSS, Inc., Chicago, IL) was used for statistical analysis, and *p*-values were considered significant at $p < .05$.

Table 1. Descriptive Statistics of the Study Sample ($N = 55$)

Variable	M (*SD*) or *N* (%)
Age (y)	74.84 (4.97)
Sex	
Male	28 (50.9%)
Female	27 (49.1%)
Education (y)	15.49 (3.37)
Ethnicity	
Caucasian	36 (65.5%)
Not Caucasian (Black, Hispanic, Asian, other)	19 (34.5%)
GHS (0–10)	1.36 (1.08)
WRAT-3 Raw Score (0–42)	36.11 (5.15)
WRAT-3 Standard Score	110.29 (8.37)
STW velocity (cm/s)	72.46 (15.43)
DTW velocity (cm/s)	62.53 (13.55)
STW letter generation rate (letter/s)	0.53 (0.22)
DTW letter generation rate (letter/s)	0.59 (0.19)
HbO_2 STW (μM)	0.29 (0.62)
HbO_2 STA (μM)	0.63 (0.55)
HbO_2 DTW (μM)	0.90 (0.81)
Left rostral middle frontal volume (mm^3)	12 596.47 (1 821.15)
Total gray matter volume (mm^3)	506 089.49 (51 261.60)
Mean cortical thickness (mm)	2.29 (0.08)
Mean FA	0.35 (0.02)
Verbal Fluencies FAS Total Raw Score	43.95 (12.86)
Free and Cued Selective Reminding Test Raw Score	29.60 (10.03)
Digit Symbol Modalities Test Total Raw Score	57.55 (14.12)

Notes: DTW = dual-task walk; FA = fractional anisotropy; GHS = Global Health Score; HbO_2 = oxygenated hemoglobin; STA = single-task alpha; STW = single-task walk; WRAT-3 = *The Wide Range Achievement Test*, 3rd edition. GHS ranges from 0 to 10 with higher values indicating the presence of more comorbidities; WRAT-3 raw score ranges from 0 to 42, with higher values indicating better performance; velocity measured in cm/s, with higher values indicating faster walking; letter generation rate measured in letters/s, with higher values indicating better performance; for verbal fluency raw score, free and cued selective reminding raw score, and digit symbol modalities raw score, higher values indicate better performance.

Results

Descriptive statistics of demographic, behavioral, and HbO_2 data were summarized for the entire sample in Table 1. The participants (mean age in years = 74.84 ± 4.97; %female = 49.1) were relatively healthy as indicated by their average GHS score (1.36 ± 1.08) and had estimated intellectual function in the average range as determined by their WRAT-3 score (Standard Score = 110.29 ± 8.37). LMEMs revealed that stride velocity declined significantly from STW to DTW (estimate = −9.923; $p < .001$; 95% CI = −13.997 to −5.870), but the change in the rate of correct letter generation from STA to DTW was not statistically different (estimate = 0.050; $p > .05$; 95% CI = −0.002 to 0.103).

Derivation of CR Residuals

A linear regression model was carried out with WRAT-3 raw scores as the outcome variable, and years of education, ethnicity, sex, composite cognitive *Z* score, and leftRMF volume as the predictors. The regression model was statistically significant ($R = .801$, $R^2 = .642$, $p < .001$). The standardized residuals extracted from the model were used to operationalize CR. A summary of the model is presented in Table 2.

Moderating Effects of CR on the Change in fNIRS-Derived HbO_2 Across Task Conditions

Key results will be quoted in this section as (estimate; *p*-value). Model 1: Consistent with the study hypothesis, higher CR was associated with smaller increases in fNIRS-derived HbO_2 from STW (0.186; $p < .001$) and STA (0.227; $p < .001$) to the DTW condition. Model 2: The moderating effects of CR remained significant (CR × DTW compared with STW: 0.146; $p = .003$; CR × DTW compared with STA: 0.173; $p < .001$) even when adjusting for the significant moderating effects of DTW stride velocity on the change from STW to DTW (0.015; $p < .001$) and DTW rate of letter generation from STA to DTW (1.466; $p < .001$). Model 3: The moderating effects of CR on the change in fNIRS-derived HbO_2 remained significant (CR × DTW compared with STW: 0.187; $p < .001$; CR × DTW compared with STA: 0.228; $p < .001$) when adjusting for the significant moderating effect of the composite cognitive *Z* score (composite cognitive *Z* score × DTW compared with STW: 0.385; $p < .001$; composite cognitive *Z* score × DTW compared with STA: 0.612; $p < .001$). Model 4: The moderating effect of CR remained significant (CR × DTW compared with STW: 0.184; $p < .001$; CR × DTW compared with STA: 0.259; $p < .001$) when adjusting for the moderating effect

Table 2. Derivation of Cognitive Reserve Residuals

Variable	Estimate	*SE*	*t*	*p*	LLCI	ULCI
Constant	21.41	3.87	5.54	<.001	13.63	29.19
Left rostral middle frontal volume	0.001	0.00	2.55	.014	0.00	0.001
Composite cognitive functioning	1.78	0.73	2.43	.019	0.30	3.25
Sex	−2.01	1.12	−1.78	.081	−4.27	0.26
Ethnicity	−1.82	0.72	−2.52	.015	−3.26	−0.37
Education (y)	0.64	0.18	3.67	.001	0.29	1.00

Notes: LLCI = lower limit confidence interval; ULCI = upper limit confidence interval.

of the leftRMF volume (leftRMF volume × DTW compared with STW: 0.199; $p < .001$; leftRMF volume × DTW compared with STA: 0.163; $p < .001$). Model 5: The moderating effects of CR remained significant (CR × DTW compared with STW: 0.183; $p < .001$; CR × DTW compared with STA: estimate = 0.257; $p < .001$) when adjusting for the concurrent moderating effects of the composite cognitive *Z* score (composite cognitive *Z* score × DTW compared with STW: 0.329; $p < .001$; composite cognitive Z score × DTW compared with STA: 0.597; $p < .001$) and leftRMF volume (leftRMF volume × DTW compared with STW: estimate = 0.127; $p = .005$; leftRMF volume × DTW compared with STA: estimate = 0.033; $p = .463$). These results, summarized in Table 3, models 1–5, consistently demonstrated that higher CR was associated with more efficient activation patterns in the PFC across task conditions, irrespective of the covariates and moderators that were included in the different models. The moderating effect of CR on the change in fNIRS-HbO_2 across task conditions is visually depicted in Figure 1.

Supplemental Analyses

To further examine the moderating effects of CR on the efficiency of PFC activation during active walking, we used 3 measures of structural integrity of the brain (total gray matter volume, whole-brain FA, mean cortical thickness) as covariates and moderators in 3 separate LMEM models. Results revealed that CR remained a significant moderator of PFC efficiency (CR × DTW compared with STW: 0.175; $p < .001$; CR × DTW compared with STA: 0.255; $p < .001$) when controlling for the moderating effect of total gray matter volume (total gray matter volume × DTW compared with STW: 0.136; $p = .003$; total gray matter volume × DTW compared with STA: 0.084; $p = .068$). CR also remained a significant moderator of PFC efficiency (CR × DTW compared with STW: 0.176; $p < .001$; CR × DTW compared with STA: 0.245; $p < .001$) when controlling for the moderating effects of whole-brain FA (whole-brain FA × DTW compared with STW: 9.930; $p < .001$; whole-brain FA × DTW compared with STA: 11.170; $p < .001$). Finally, CR remained a significant moderator of PFC efficiency (CR × DTW compared with STW: 0.215; $p < .001$; CR × DTW compared with STA: 0.258; $p < .001$) when controlling for mean cortical thickness (cortical thickness × DTW compared with STW: estimate = 0.249; $p < .001$; cortical thickness × DTW compared with STA: 0.098; $p = .030$). The complete analyses are presented in Supplementary Tables 1–3.

Discussion

Walking ability is a robust measure of health and a predictor of multiple adverse outcomes among older adults (46). Hence, it is of interest to identify mechanisms of gait and mobility outcomes that are potentially modifiable. The current study determined the moderating effect of CR on the neural efficiency of active walking, operationalized via fNIRS-derived HbO_2, across conditions that experimentally manipulated cognitive demands. We found that higher CR was associated with a more efficient PFC hemodynamic response. Specifically, increases in fNIRS-derived HbO_2 from the single tasks to dual-task walking were attenuated as a function of higher CR when adjusting for covariates and moderating effects of a priori identified variables on study outcomes. These findings are discussed in detail below.

The literature concerning the relationship between CR and mobility outcomes has been relatively scarce (17). To the best of our knowledge, this is the first study to report on the effect of CR on the neural efficiency of active walking. Confirming the study hypothesis, we found in a cohort of community-residing older adults that higher CR was associated with better fNIRS-derived HbO_2 efficiency when recruiting brain resources to support the cognitive demands of dual-task walking. To interpret the results in the context of neural efficiency, it was imperative to evaluate gait and cognitive performance. Our analytic approach both adjusted for behavioral performance and further examined the concurrent moderating effects of gait and cognitive performance during DTW on changes in fNIRS-derived HbO_2 activation patterns. In this analysis (model 2), the effect of CR was not diminished, providing support to the notion that individuals with higher CR required less brain resources to support the increase in cognitive demands of dual-task walking while taking into account gait and cognitive performance. Notably, the concurrent moderating effects of gait and cognition during DTW were task-contrast specific. That is, faster stride velocity was associated with a smaller increase in fNIRS-derived HbO_2 from STW to DTW, whereas higher rate of correct letter generation was associated with a smaller increase in fNIRS-derived HbO_2 from STA to DTW. Hence, those individuals who demonstrated better performance during DTW showed smaller increases in fNIRS-derived HbO_2 from the single tasks to dual-task walking, suggesting more efficient usage of brain resources.

A significant advantage of the residual approach is the removal of extraneous variance from the measurement of CR. The operational definition of CR in the current study removed the variance accounted for by measures of current cognitive functions and brain morphology that both correlated with WRAT-3 scores and have also been established as sensitive to the deleterious effect of aging (47,48). Moreover, adjusting for the concurrent moderating effects of the composite cognitive *Z* score and left RMF allowed us to assess the role of CR in the neural efficiency of locomotion even more stringently. Our findings provided strong evidence that, above and beyond the concurrent associations of current cognitive functions and brain morphology with the changes in fNIRS-derived HbO_2 in the PFC across task conditions, higher CR levels appeared protective against inefficient recruitment of the brain resources utilized to support the cognitive demands of dual-task walking. Furthermore, sensitivity analyses adjusting for the moderating effects of whole-brain gray

Table 3. Moderating Effects of Cognitive Reserve, on the Change in fNIRS-Derived HbO_2 Across Task Conditions

	Model 1			Model 2			Model 3			Model 4			Model 5		
Variable	Est.	95% CI	*p*	Est.	95% CI	*p*	Est.	95% CI	*p*	Est.	95% CI	*p*	Est.	95% CI	*p*
Intercept	0.93	[0.77, 1.09]	<.001	0.32	[−2.52, 3.16]	.819	0.19	[−2.24, 2.62]	.877	0.28	[−1.97, 2.53]	.804	0.18	[−2.28, 2.64]	.884
STW HbO_2 vs DTW HbO_2	−0.26	[−0.34, −0.17]	<.001	−1.43	[−1.88, −0.97]	<.001	−0.25	[−0.34, −0.17]	<.001	−0.26	[−0.35, −0.17]	<.001	−0.26	[−0.34, −0.17]	<.001
STA HbO_2 vs DTW HbO_2	−0.62	[−0.71, −0.54]	<.001	−1.60	[−2.06, −1.15]	<.001	−0.62	[−0.71, −0.54]	<.001	−0.65	[−0.73, −0.56]	<.001	−0.64	[−0.73, −0.56]	<.001
Channel	−0.003	[−0.01, 0.005]	.50	−0.002	[−0.01, 0.01]	.567	−0.003	[−0.01, 0.005]	.489	−0.002	[−0.01, 0.01]	.574	−.002	[−0.01, 0.005]	.564
CR	−0.28	[−0.43, −0.12]	.001	−0.22	[−0.39, −0.05]	.012	−0.28	[−0.44, −0.12]	=.001	−0.28	[−0.44, −0.12]	.001	−0.28	[−0.44, −0.11]	.001
STW vs DTW HbO_2 × CR	0.19	[0.10, 0.28]	<.001	0.15	[0.05, 0.24]	.003	0.19	[0.10, 0.28]	<.001	0.18	[0.09, 0.28]	<.001	0.18	[0.09, 0.28]	<.001
STA vs DTW HbO_2 × CR	0.23	[0.14, 0.32]	<.001	0.17	[0.08, 0.27]	.001	0.23	[0.14, 0.32]	<.001	0.26	[0.16, 0.35]	<.001	0.26	[0.16, 0.35]	<.001
DTW velocity (cm/s)	—	—	—	0.01	[−0.01, 0.02]	.387	—	—	—	—	—	—	—	—	—
STW vs DTW HbO_2 × DTW Vel.	—	—	—	0.02	[0.01, 0.02]	<.001	—	—	—	—	—	—	—	—	—
STA vs DTW HbO_2 × DTW Vel.	—	—	—	<0.01	[−0.01, 0.01]	.666	—	—	—	—	—	—	—	—	—
DTW letter generation rate	—	—	—	−1.13	[−1.99, −0.28]	.010	—	—	—	—	—	—	—	—	—
STW vs DTW HbO_2 × DTW letter generation	—	—	—	0.38	[−0.11, 0.86]	.131	—	—	—	—	—	—	—	—	—
STA vs DTW HbO_2 × DTW letter generation	—	—	—	1.47	[0.98, 1.95]	<.001	—	—	—	—	—	—	—	—	—
Age (y)	—	—	—	0.01	[−0.02, 0.04]	.569	0.01	[−0.03, 0.04]	.694	0.003	[−0.03, 0.03]	.848	0.004	[−0.03, 0.04]	.800
Sex	—	—	—	0.24	[−0.03, 0.52]	.082	0.23	[−0.05, 0.50]	.106	0.33	[0.003, 0.66]	.048	0.33	[0.0004, 0.66]	.050
GHS	—	—	—	−0.07	[−0.20, 0.07]	.315	−0.04	[−0.17, 0.09]	.508	−0.05	[−0.18, 0.09]	.487	−0.04	[−0.18, 0.09]	.512
Cog. function	—	—	—	—	—	—	−0.34	[−0.56, −0.13]	.002	—	—	—	−0.29	[−0.51, −0.06]	=−.013
STW vs DTW HbO_2 × cog. function	—	—	—	—	—	—	0.39	[0.27, 0.50]	<.001	—	—	—	0.33	[0.21, 0.45]	<.001
STA vs DTW HbO_2 × cog. function	—	—	—	—	—	—	0.61	[0.50, 0.73]	<.001	—	—	—	0.60	[0.48, 0.72]	<.001
LRMF volume	—	—	—	—	—	—	—	—	—	−0.23	[−0.40, −0.06]	.010	−0.17	[−0.35, 0.01]	.066
STW vs DTW HbO_2 × LRMF vol.	—	—	—	—	—	—	—	—	—	0.20	[0.11, 0.29]	<.001	0.13	[0.04, 0.22]	.005
STA vs DTW HbO_2 × LRMF vol.	—	—	—	—	—	—	—	—	—	0.16	[0.08, 0.25]	<.001	0.03	[−0.06, 0.12]	.463

Notes: Cog. function = composite *Z* score of cognitive functions; CR = cognitive reserve; DTW = dual-task walk; GHS = Global Health Score; HbO_2 = oxygenated hemoglobin; LRMF = left rostral middle frontal; STA = single-task alpha; STW = single-task walk; letter generation rate is measured in letters/s; velocity is measured in cm/s.

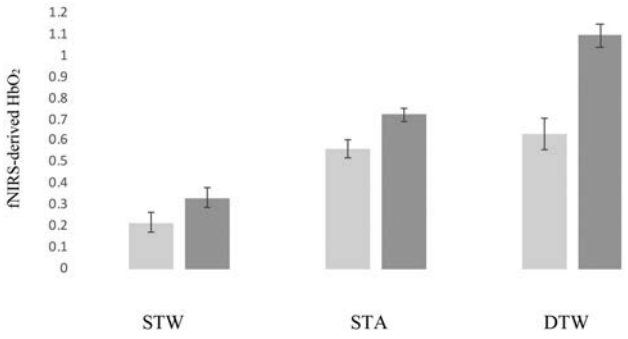

Figure 1. Moderating effects of CR (dichotomized via median split) on the change in fNIRS-derived HbO_2 across task conditions. Light gray indicates high CR; dark gray indicates low CR. Linear mixed-effect model revealed that higher CR (dichotomized via median split) was associated with smaller increases in fNIRS-derived HbO_2 from STW (.273; p = .004; 95% CI: 0.089–0.458) and STA (.335; p < .001; 95% CI: 0.151–0.519) to the DTW condition. STW = single-task walk; STA = single-task alpha; DTW = dual-task walk; CR = cognitive reserve.

matter volume, whole-brain FA, and mean cortical thickness on the change in fNIRS-derived HbO_2 in the PFC across task conditions, further bolstered the critical role of CR in determining the neural efficiency of gait in older adults.

Study Limitations, Strength, and Future Directions

The dual-task paradigm used in the current study was optimal to assess changes in neural efficiency due to its established experimental manipulation of cognitive demands and associated neural correlates of walking (30). However, it is important to note that neural efficiency was evaluated using fNIRS-derived HbO_2 levels that were restricted to the PFC. Hence, the effect of CR on neural efficiency in other brain regions was not assessed in the current study. Additionally, further research is needed to clarify the significance of CR in determining the neural efficiency of locomotion in normal aging and disease populations. At present, there is no consensus regarding the optimal measurement of CR. Although the residual approach is conceptually appealing and empirically supported (3,5), it has limitations that should be acknowledged. That is, the residuals used to operationalize CR are determined by both the outcome measure and the predictors selected to measure this latent construct. Hence, establishing the repeatability and generalizability of CR effects across studies that utilize different measures to derive the residuals of this latent construct is important. It is noteworthy that a recent meta-analysis revealed that using the residual approach to measure CR yielded stronger effects than sociodemographic proxy measures in protecting against the risk of developing MCI and dementia (4). These findings suggest that despite differences in the operational definition of CR, repeatability and generalizability could be established. Moreover, the variables used to determine the residuals that served as a marker for CR in the current study were selected based on both theoretical considerations and efforts to optimize their correlations with the outcome measure (WRAT-3). Importantly, supplemental analyses that further adjusted for multiple measures for brain integrity (ie, whole-brain FA, whole-brain gray matter, mean cortical thickness) were not materially different. We did not include chronological age in the regression used to define CR because it was not related to WRAT-3 scores. We did, however, control for the effect of chronological age in the linear mixed-effects models that evaluated the role of CR in neural efficiency of gait.

Because the sample was relatively small and consisted of healthy and dementia-free individuals, the generalizability of our findings to patient populations, especially those with neurological diseases and dementias of different etiologies should be examined in future studies. Additionally, the effects of physical fitness and activity levels on CR and neural efficiency were not assessed in the current study but should be evaluated in future research. The decline in gait but not cognitive performance from the single tasks to dual-task walking may be attributed to task prioritization and, in part, to better psychometric properties of stride velocity when compared with the letter generation task. Nonetheless, it is noteworthy that both gait and cognitive performance under DTW moderated the change in fNIRS-derived activations in the expected direction whereby better performance was associated with an attenuated increase from single- to dual-task conditions, suggesting better neural efficiency. A recent study revealed that gait performance improved and PFC fNIRS-derived HbO_2 declined after repeated DTW but not STW trials, suggesting task-specific learning and improvement in PFC efficiency due to practice (32). This finding is consistent with a meta-analytic study revealing that practice in cognitively demanding tasks resulted in reduced brain activations, notably in the PFC (49). Whether levels of CR can influence treatment effects on walking performance and its associated neural efficiency should be evaluated in future studies. CR can also be enhanced via interventions (50). It would, therefore, be of further interest to examine whether enhancing CR may also improve the neural efficiency of gait. The current study utilized a stringent approach to fNIRS data processing by applying the combined filters and differential pathlength factors previously described (31) as well as filters designed to remove motion artifacts to protect the validity of the study outcomes. Given that task effects on both oxygenated and deoxygenated hemoglobin have been reported in multiple previous publications (32), and in order to reduce the possibility of false discovery rate, we elected not to include deoxygenated hemoglobin as an additional outcome measure in the current investigation.

Conclusion

The current study provided first evidence that higher CR is associated with more efficient neural activation patterns of active walking in community-residing older adults. The implications of these findings for patient populations and interventions designed to enhance cognitive and brain control of locomotion should be examined in future research.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Author Contributions

Conceptualization: R.H.; Methodology: R.H., D.R., C.O., M.I., M.E.W.; Formal analysis: R.H.; Writing—original draft preparation: R.H.; Writing—review and editing: R.H., D.R., C.O., M.I., M.E.W.; Funding acquisition: R.H.

Conflict of Interest

M.I. has a very minor share in the company that manufactures the fNIRS device used in this study. The other authors declare no conflicts of interest. 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.

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