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Research Article

Cortical thickness moderates intraindividual variability in prefrontal cortex activation patterns of older adults during walking

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Abstract

Objective: Increased intraindividual variability (IIV) in behavioral and cognitive performance is a risk factor for adverse outcomes but research concerning hemodynamic signal IIV is limited. Cortical thinning occurs during aging and is associated with cognitive decline. Dual-task walking (DTW) performance in older adults has been related to cognition and neural integrity. We examined the hypothesis that reduced cortical thickness would be associated with greater increases in IIV in prefrontal cortex oxygenated hemoglobin (HbO_2) from single tasks to DTW in healthy older adults while adjusting for behavioral performance. **Method:** Participants were 55 healthy community-dwelling older adults (mean age = 74.84, standard deviation (*SD*) = 4.97). Structural MRI was used to quantify cortical thickness. Functional near-infrared spectroscopy (fNIRS) was used to assess changes in prefrontal cortex HbO_2 during walking. HbO_2 IIV was operationalized as the *SD* of HbO_2 observations assessed during the first 30 seconds of each task. Linear mixed models were used to examine the moderation effect of cortical thickness throughout the cortex on HbO_2 IIV across task conditions. **Results:** Analyses revealed that thinner cortex in several regions was associated with greater increases in HbO_2 IIV from the single tasks to DTW ($ps < .02$). **Conclusions:** Consistent with neural inefficiency, reduced cortical thickness in the PFC and throughout the cerebral cortex was associated with increases in HbO_2 IIV from the single tasks to DTW without behavioral benefit. Reduced cortical thickness and greater IIV of prefrontal cortex HbO_2 during DTW may be further investigated as risk factors for developing mobility impairments in aging.

Keywords: multitasking behavior; neuroimaging; aging; gait; NIR spectroscopy; cognition

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Walking performance is a robust predictor of adverse outcomes in aging (Studenski et al., 2011) including dementia (Quan et al., 2017). Furthermore, gait is dependent on cognitive control of cortical resources (Paraskevoudi et al., 2018; Yogev-Seligmann et al., 2008); notably, gait speed has been associated with attention and executive functions (Atkinson et al., 2007).

Dual-task walk designs, combining walking with a cognitive interference task, have been used to experimentally manipulate resources of executive control of walking by imposing competing task demands (Holtzer et al., 2012, 2014). Poor dual-task walking, in particular, predicts progression to dementia (Montero-Odasso et al., 2017), frailty, disability, and mortality (Verghese et al., 2012) in aging. Further, dual-task designs provide greater ecological validity than single-task walking as multisensory interference is present in natural environments. The prefrontal cortex (PFC) is implicated in cortical control of attention and executive functions (Koechlin et al., 2003), and has been shown to increase in activation from single-tasks to dual-task walking (Holtzer et al., 2015). Consistent with the key role of the PFC in executive functions, functional near-infrared spectroscopy (fNIRS) has been used extensively to quantify changes in oxygenated hemoglobin (HbO_2) in the PFC during walking. Specifically, a recent consensus guide (Menant et al., 2020) and meta-analysis (Bishnoi et al., 2021) demonstrated reliable increases in fNIRS-derived HbO_2 in the PFC in dual compared to single-task walking conditions.

Central tendency measures of change in HbO_2 levels from single-tasks to dual-task walking have been examined most often, however, variability in brain activation may provide additional information (Holtzer et al., 2020). Intraindividual variability (IIV) is psychometrically distinct from central tendency measures (Nesselroade & Salthouse, 2004) and has been associated with poor clinical outcomes in aging (Costa et al., 2019). Much of the literature on IIV has focused on variability in cognitive performance, showing that cognitive IIV increases in aging and is predictive of cognitive decline (Haynes et al., 2017). However, IIV in gait performance is also increased in aging (Smith et al., 2017) and associated with negative outcomes (Moon et al., 2016).

Research on neural IIV is limited and less conclusive (Dinstein et al., 2015; Dubois & Adolphs, 2016; MacDonald et al., 2006; Uddin, 2020). Traditional functional neuroimaging measurements of the hemodynamic response utilize an average signal which does not consider variability of activity within individuals (Garrett et al.,

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2010). While some studies show increased IIV associated with better performance (Garrett et al., 2013), other studies show negative or differential associations between neural IIV and behavior (Boylan et al., 2021; Guitart-Masip et al., 2016). The mixed findings may underscore distinctive relationships between neural IIV and cognitive domain, task difficulty, age, and disease (Armbruster-Genç et al., 2016; Garrett et al., 2013; Grady & Garrett, 2018; Guitart-Masip et al., 2016). For instance, increased neural IIV may be adaptive in learning, but excessive IIV may have negative associations (Boylan et al., 2021; Dinstein et al., 2015; Steinberg et al., 2022). We have previously found that increased neural IIV in the PFC from single-tasks to dual-task walking was greater in men and people with cognitive impairment (Holtzer et al., 2020).

Greater neural activation may reflect proper engagement due to increased task difficulty. However, when task-related increases are greater than expected and without accompanying increases in behavioral performance, this may reflect neural inefficiency (Haier et al., 1988; Neubauer & Fink, 2009). As healthy aging is accompanied by atrophy of gray matter in the frontal cortex and throughout the brain (Giorgio et al., 2010; Salat et al., 2004), reduced brain integrity may be related to functional changes in executive control of gait (Burzynska et al., 2012). Consistent with the neural inefficiency hypothesis, over-activation during dual-task walking may be a compensatory function to meet task demands with limited neural resources (Daselaar et al., 2015). Previous studies have shown that increased PFC activation in dual-task walking was related to reduced gray matter volume (Wagshul et al., 2019), cortical thickness (Ross et al., 2021), and white matter integrity (Lucas et al., 2018) in older adults.

The current study was designed to address an important gap in the literature concerning the interaction between structural brain integrity and IIV in cortical activation of gait in older adults. Specifically, we examined the moderating effect of cortical thickness in the PFC and other regions on IIV in PFC activation from single-tasks to dual-task walking, while adjusting for behavioral performance to capture neural efficiency. We focused on cortical thickness as it is related to executive functioning, gait, and brain atrophy in aging (Burzynska et al., 2012; Maidan et al., 2021; Salat et al., 2004). Cortical thickness is genetically and phenotypically distinct from gray matter volume measurement and is suggested to be more sensitive to age-related change (Hutton et al., 2009; Winkler et al., 2010). Our primary aim was to examine cortical thickness in the PFC as a moderator of IIV from single-tasks to dual-task walking. Our secondary aim was to examine the moderating effect of cortical thickness in other cortical regions. We hypothesized that increased neural IIV in the PFC from single to dual-task walking would be associated with thinner cortex in the PFC and in other brain regions implicated in cortical control of walking. While previous findings have implicated task-related changes to integrity of cortical regions involved in sensory, motor, and cognitive processing (Ross et al., 2021), we predicted that the examination of IIV rather than central tendency measures would provide novel additional information regarding the complex interaction of structural and functional brain correlates of gait.

Method

Participants

A subset of participants from "Central Control of Mobility in Aging" (CCMA) who completed an MRI protocol were included. Procedures for the CCMA study were described previously (Holtzer et al., 2014). Briefly, older adults were identified from population lists in Westchester country, New York, USA. After being mailed a letter, potential participants were contacted by telephone during which verbal consent and initial eligibility were obtained via structured interview. Screening included assessment of cognitive, medical, psychological, and physical status. Eligible participants (age ≥ 65 years) completed in-person visits comprised of comprehensive psychological, mobility, functional, and neuropsychological assessments. Written informed consent was obtained the first study visit. The dual-task walking protocol was completed within one session, while the MRI protocol was completed on a separate visit.

Exclusion criteria were: current or history of severe neurological or psychiatric disorder, significant impairment in vision or hearing, dementia, inability to speak English, inability to ambulate independently, and current or anticipated medical procedures that would hinder ambulation. Additional MRI exclusion criteria were left-handedness and MRI contraindication (e.g., presence of metal in the body and tolerance of the MRI procedure). A total of 73 right-handed older adults completed the MRI protocol. All study procedures were in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments and approved by the institutional review board of Albert Einstein College of Medicine.

Measures

Dual-task walking protocol

The walking protocol included three task conditions: single-task walk (STW), single-task alpha (STA), and dual-task walk (DTW). All tasks were completed on a 4 × 20 foot electronic walkway. For the STW condition, participants were instructed to walk at their normal pace, walking three continuous counterclockwise loops. For the STA condition, participants were instructed to stand in place while reciting alternate letters of the alphabet out loud (A, C, E, . . .) for 30 seconds. For the DTW condition, participants were instructed to perform the two tasks simultaneously and pay equal attention to both tasks to minimize task prioritization. Task order was counterbalanced across participants using a Latin square design. This walking protocol has been well-validated (Holtzer et al., 2014).

Quantitative gait assessment. Gait was assessed using a 4 × 20 foot Zeno electronic walkway (Zenometrics, LLC, Peekskill, NY) in conjunction with ProtoKinetics Movement Analysis Software (PKMAS). Entry and exit points of footfalls were determined algorithmically under single and dual-task walk conditions, allowing for extraction of stride velocity and walk time (England et al., 2015). Split-half intra-class correlations of quantitative gait measurements in both walking conditions were greater than 0.95, revealing excellent internal consistency (Holtzer et al., 2015).

Functional near-infrared spectroscopy. As in previous studies, the fNIRS Imager 1100 (fNIR Devices, LLC, Potomac, MD) measured oxygenated (HbO_2) and deoxygenated (Hb) hemoglobin levels in the PFC during all DTW protocol tasks (Bunce et al., 2006; Holtzer et al., 2015). The fNIRS sensor contains four light-emitting diode light sources and 10 photoreceptors 2.5 cm apart, allowing for 16 channels of data collection placed using the standard international 10–20 system (Ayaz et al., 2006). Light sensors

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emitted peak wavelengths at 730, 805, and 850 nm and data were collected at a 2-Hz sampling rate.

fNIRS preprocessing and hemodynamic signal extraction methods have been previously described (Izzetoglu & Holtzer, 2020). Briefly, this included identification and elimination of saturation, dark current conditions, or extreme noise artifacts through visual inspection. Daubechies 5 (db5) wavelet for spiky noise suppression was applied to remove motion artifacts from 730 and 850 nm wavelengths (Molavi & Dumont, 2012). The modified Beer–Lambert law was used to calculate changes from artifact removed measurements, and account for age and wavelength adjusted differential pathlength factor (DPF) and wavelength and chromophore dependent molar extinction coefficients (ϵ) (Izzetoglu & Holtzer, 2020; Kim & Liu, 2007; Scholkmann & Wolf, 2013). Finally, baseline and physiological artifacts were removed by applying spline filtering (Scholkmann et al., 2010) followed by a finite impulse response low-pass filter with cutoff frequency at 0.08 Hz.

Data points were extracted separately for each task at all 16 channels. E-Prime 2.0 software (Psychology Software Tools, Inc.) synchronized fNIRS signal extraction with PKMAS data. Participants were instructed to stand still, counting silently, with a fixed gaze to compare task-related changes to a baseline measure of HbO_2 (Holtzer et al., 2015). For the current study, we used HbO_2 as the measure of neural activation in the PFC instead of Hb due to its better reliability and sensitivity to locomotion-related cerebral activity (Miyai et al., 2001).

Measurement of Intraindividual Variability. IIV of PFC activation was operationalized by calculating standard deviation (SD) of fNIRS-derived HbO_2 during the first 30 seconds of each task. This time period ensured comparability across task conditions, as walking time under STW and DTW depended on participants' gait speed, and STA was fixed at 30 seconds. This resulted in 61 data points for each channel, as data was collected every 0.5 seconds (2-Hz sampling rate). IIV could not be calculated using relative measures of dispersion (e.g., coefficient of variation) because several participants' mean HbO_2 approached zero (i.e., no increase from the individual baseline to the experimental condition), most often under STW which imposes significantly less cognitive demands. Analyses adjusted for mean HbO_2 to address this potential limitation.

Magnetic resonance imaging

Magnetic resonance imaging was performed at Albert Einstein College of Medicine's Gruss Magnetic Resonance Research Center (Bronx, NY) in a 3T Philips scanner (Achieva TX; Philips Medical Systems, Best, the Netherlands) equipped with a 32-channel head coil. Cortical thickness was extracted from T1-weighted images (MPRAGE – TE/TR/TI = 4.6/9/8/900 ms, voxel size 1 mm isotropic, SENSE acceleration factor 2.6).

Cortical thickness measures and cortical segmentation was extracted from all participants using the FreeSurfer image analysis suite (https://surfer.nmr.mgh.harvard.edu) (Fischl, 2012). Preprocessing included brain extraction, Talairach transformation, subcortical segmentation, identification of gray-white matter boundaries, and atlas registration. These methods were detailed previously (Dale et al., 1999; Fischl et al., 2002; Fischl et al., 2004). The 68 regions identified by FreeSurfer's cortical parcellation tools (Desikan et al., 2006) were visually inspected in FSLeyes by overlaying the segmentation on each subject's T1 image (Smith et al., 2004). Surface-based smoothing was applied at FWHM = 5 mm prior to extraction, and cortical thickness values at each region were mean centered prior to statistical analysis.

Covariates

We adjusted for factors that may impact DTW performance, cognition, and brain integrity, and for behavioral performance to evaluate inefficiency. Covariates were age, sex, global cognitive functioning, global health, and correct letter generation performance and walking performance under the DTW condition. Global cognitive functioning was measured using the total score from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998). Global Health Score (GHS) is a summary score ranging from zero to 10, indicating presence or absence of 10 health conditions (diabetes, chronic heart failure, arthritis, hypertension, depression, stroke, Parkinson's disease, chronic obstructive lung disease, angina, and myocardial infarction) taken via self-reported interview (Holtzer et al., 2008). Cognitive performance under DTW was assessed by dividing the correct letters generated by time walked, and walking performance was measured as stride velocity extracted from the PKMAS system. Statistical models were further adjusted for mean DTW HbO_2.

Statistical analysis

Analyses were performed utilizing SPSS statistical software package (version 26; SPSS, Inc., Chicago, IL). Linear mixed models (LMEMs) were used to examine the main effects of task and cortical thickness on HbO_2 IIV, as well as the moderating effect of cortical thickness. These models included data from all 16 channels and accounted for correlations across repeated measures within the DTW paradigm. The outcome was HbO_2 IIV, with task entered as fixed effects, channel entered as random effects, and task by channel entered as repeated effects. A compound symmetry covariance structure was selected to account for the correlation between HbO_2 measured among channels within task within each person.

Sixty-eight LMEMs were run, one for each cortical region, to examine the moderating effect of cortical thickness across the cortex on the change in HbO_2 IIV from STW and STA to DTW. The moderating effect of cortical thickness, entered as a covariate, on the change in fNIRS-derived HbO_2 IIV across task conditions was assessed via three-level 2-way interactions of regional cortical thickness by task. For all models, DTW HbO_2 IIV was the reference group. Analyses adjusted for all covariates described above. False discovery rate (FDR) was used to adjust for multiple comparisons (Benjamini & Hochberg, 1995).

Results

A total of 73 participants completed the MRI protocol. Participants were excluded for the following reasons: more than one year between MRI and fNIRS ($n = 8$), poor quality fNIRS data ($n = 7$), and data exploration outliers (e.g., unusually high variance in gait velocity or HbO_2; $n = 3$). Thus, 55 participants (mean age = 74.84 ± 4.97 years; % female = 49.1) had complete data available for both the DTW and MRI protocols and were included in analyses. Participants were relatively healthy (GHS mean = 1.36 ± 1.08) with average global cognitive functioning (RBANS total score

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Table 1. Demographic characteristics of the study sample

Variable	Mean (*SD*) or *N* (%)
Age (years)	74.84 (4.97)
Sex (female)	27 (49.1%)
Education (years)	15.49 (3.34)
Global Health Score (GHS)	1.36 (1.08)
RBANS total score	92.71 (11.28)
STW velocity (cm/second)[a]	72.45 (15.43)
DTW velocity (cm/second)[a]	62.53 (13.55)
STA letter generation rate	0.53 (0.22)
DTW letter generation rate	0.59 (0.19)
HbO_2 SD STW (μM)	0.29 (0.13)
HbO_2 SD STA (μM)	0.33 (0.17)
HbO_2 SD DTW (μM)	0.36 (0.19)

Note. $N = 55$. RBANS = repeatable battery for the assessment of neuropsychological status; STW = single-task-walk; STA = single-task-alpha; DTW = dual-task-walk; HbO_2 = oxygenated hemoglobin.
[a]$N = 53$ for stride velocity measures.

Table 2. Cortical thickness of the study sample

	Left hemisphere			Right hemisphere		
Region[a]	*M*	*SD*	Range	*M*	*SD*	Range
Banks of the superior temporal sulcus	2.36	0.16	2.03–2.73	2.37	0.15	1.98–2.71
Caudal anterior cingulate	2.59	0.26	2.11–3.30	2.48	0.23	2.01–3.16
Caudal middle frontal	2.33	0.14	1.98–2.59	2.33	0.14	2.00–2.57
Cuneus	1.85	0.13	1.58–2.16	1.85	0.12	1.57–2.12
Entorhinal	2.84	0.36	1.93–3.57	2.90	0.36	1.71–3.62
Frontal pole	2.50	0.31	1.97–3.39	2.52	0.27	2.04–3.30
Fusiform	2.48	0.11	2.25–2.79	2.42	0.12	2.16–2.64
Inferior parietal	2.31	0.12	1.97–2.54	2.27	0.10	2.05–2.55
Inferior temporal	2.48	0.10	2.26–2.66	2.39	0.10	2.16–2.65
Insula	2.74	0.17	2.36–3.13	2.72	0.15	2.37–3.05
Isthmus cingulate	2.19	0.19	1.78–2.69	2.22	0.17	1.87–2.58
Lateral occipital	2.04	0.13	1.68–2.33	2.05	0.11	1.80–2.25
Lateral orbitofrontal	2.42	0.14	2.19–2.81	2.38	0.13	2.11–2.62
Lingual	1.93	0.10	1.70–2.14	1.96	0.11	1.59–2.16
Medial orbitofrontal	2.32	0.18	2.00–3.00	2.40	0.17	2.12–3.03
Middle temporal	2.60	0.13	2.28–3.00	2.56	0.13	2.29–2.84
Paracentral	2.30	0.13	2.03–2.63	2.31	0.13	2.04–2.56
Parahippocampal	2.43	0.25	1.90–2.83	2.38	0.16	2.01–2.73
Pars opercularis	2.38	0.12	2.10–2.75	2.38	0.13	2.08–2.69
Pars orbitalis	2.41	0.14	2.10–2.71	2.44	0.15	2.11–2.74
Pars triangularis	2.23	0.11	1.90–2.46	2.24	0.11	2.01–2.53
Pericalcarine	1.60	0.10	1.37–1.84	1.62	0.11	1.41–2.04
Postcentral	1.97	0.12	1.70–2.26	1.92	0.09	1.73–2.14
Posterior cingulate	2.31	0.17	1.86–2.68	2.32	0.14	2.09–2.79
Precentral	2.38	0.14	1.93–2.61	2.36	0.11	2.07–2.63
Precuneus	2.24	0.12	1.96–2.49	2.25	0.12	1.93–2.47
Rostral anterior cingulate	2.65	0.22	2.15–3.19	2.80	0.28	2.24–3.77
Rostral middle frontal	2.19	0.12	1.90–2.39	2.23	0.11	1.97–2.51
Superior frontal	2.43	0.13	2.08–2.72	2.47	0.12	2.19–2.69
Superior parietal	2.10	0.14	1.70–2.42	2.06	0.12	1.70–2.31
Superior temporal	2.50	0.15	2.19–2.79	2.48	0.14	2.20–2.79
Supramarginal	2.38	0.11	2.13–2.61	2.32	0.13	2.00–2.56
Temporal pole	3.10	0.30	2.08–3.74	3.13	0.31	2.48–3.71
Transverse temporal	2.31	0.22	1.82–2.83	2.27	0.24	1.76–2.73

[a]Cortical Parcellation based on the Desikan-Killiany atlas (Desikan et al., 2006).

mean = 92.71 ± 11.28). Complete descriptive statistics of the sample are included in Table 1. Descriptive statistics of regional cortical thickness values extracted from FreeSurfer's cortical parcellation tools are included in Table 2.

HbO_2 IIV increased from STW to DTW (estimate = −0.07 μM, $p < .001$, 95% CI [−0.09, −0.05]) and from STA to DTW (estimate = −0.03 μM, $p = .005$, 95% CI [−0.04, −0.01]). Split-half intra-class correlations revealed excellent internal consistency of HbO_2 IIV in each task (STA = 0.82; STW = 0.84; DTW = 0.87).

After confirming the main effect of task on HbO_2 IIV, full models including the main and moderating effects of task and cortical thickness were run for each region. The primary analyses with the 12 prefrontal regions, the caudal middle frontal, rostral middle frontal, frontal pole, superior frontal, lateral orbitofrontal, and medial orbitofrontal regions (left and right), are displayed in Table 3. All PFC regions moderated the task effect of HbO_2 IIV except for the bilateral orbitofrontal cortex, both lateral and medial regions.

Secondary analyses examined the 54 remaining regions of the cortex. All models were FDR-corrected ($p < .02$). Models in which the moderating effects of cortical thickness outside the PFC were significant are included in Table 4. In summary, 16 regions of the left hemisphere and 21 regions of the right hemisphere significantly moderated task effects of HbO_2 IIV. Full models including covariates and nonsignificant effects can be found in Supplementary Table 1. In all models, the effect of sex was significant (estimate ~ 0.09, $p < .05$), showing that males had higher HbO_2 IIV across tasks.

To display the distinct and overlapping regions, pictorial representations of the results are shown in figures. Regions where cortical thickness significantly moderated the task effect of HbO_2 IIV from STW to DTW are shown in Figure 1, and from STA to DTW in Figure 2. Significant regions spanned the cortex: PFC: bilateral caudal middle frontal, bilateral rostral middle frontal, bilateral superior frontal, bilateral frontal pole; non-PFC frontal lobe: left caudal anterior cingulate, left pars orbitalis, bilateral pars triangularis, right pars opercularis, right precentral; parietal lobe: bilateral precuneus, bilateral superior parietal, right inferior parietal, right isthmus; temporal lobe: bilateral banks of the superior temporal sulcus, bilateral inferior temporal, bilateral temporal pole, right fusiform, right middle temporal, bilateral superior temporal; occipital lobe: left cuneus, left lingual, bilateral pericalcarine, right lateral occipital, right lingual; and right insula.

In all models the main effect of task was negative, indicating that HbO_2 IIV increased from single-tasks to DTW. For the majority of cortical regions, the main effect of thickness was negative and the interaction effects of task by thickness were positive, indicating that increased HbO_2 IIV in the PFC was associated with thinner cortex and that HbO_2 IIV increased more from single-tasks to DTW when individuals had thinner cortex in these regions. However, a number of regions showed a positive main effect of thickness on HbO_2 IIV and a negative interaction effect of task by thickness, indicating that higher HbO_2 IIV and an attenuated increase from STW to DTW were associated with greater thickness in these regions (left banks of the superior temporal sulcus, left superior temporal gyrus, bilateral temporal poles, right isthmus, right middle temporal gyrus, and right insula). Finally, a few regions demonstrated positive thickness main effect and interaction effects, indicating that higher IIV and a greater increase from single to dual task were associated with greater thickness in these regions (STA vs. DTW: left cuneus, right banks of the superior temporal sulcus, right middle temporal, and right pars opercularis models; STW vs. DTW: left pericalcarine).

Discussion

We examined the moderating effects of regional cortical thickness on changes in PFC activation IIV from single-tasks to DTW.

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Table 3. Adjusted main and interaction effects of PFC thickness and task HbO_2 IIV

		Left hemisphere				Right hemisphere			
Region	Variable	Estimate	95% CI	*t*	*p*	Estimate	95% CI	*t*	*p*
Caudal middle frontal	Task (STW vs. DTW)	−0.05	[−0.06, −0.03]	−4.81	<.001	−0.04	[−0.06, −0.03]	−4.66	<.001
	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−2.10	.036	−0.02	[−0.04, 0.00]	−1.96	.050
	Thickness	−0.35	[−0.59, −0.11]	−2.96	.005	−0.54	[−0.79, −0.30]	−4.43	<.001
	STW vs. DTW × thickness	0.35	[0.22, 0.47]	5.43	<.001	0.43	[0.30, 0.57]	6.33	<.001
	STA vs. DTW × thickness	0.29	[0.16, 0.41]	4.49	<.001	0.45	[0.32, 0.58]	6.59	<.001
Rostral middle frontal	Task (STW vs. DTW)	−0.05	[−0.06, −0.03]	−4.81	<.001	−0.05	[−0.06, −0.03]	−4.83	<.001
	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−2.08	.037	−0.02	[−0.04, 0.00]	−2.08	.038
	Thickness	−0.43	[−0.71, −0.14]	−3.00	.004	−0.36	[−0.66, −0.05]	−2.36	.022
	STW vs. DTW × thickness	0.42	[0.26, 0.57]	5.26	<.001	0.41	[0.25, 0.57]	5.08	<.001
	STA vs. DTW × thickness	0.36	[0.20, 0.51]	4.52	<.001	0.51	[0.35, 0.67]	6.34	<.001
Superior frontal	Task (STW vs. DTW)	−0.05	[−0.06, −0.03]	−4.74	<.001	−0.05	[−0.06, −0.03]	−4.83	<.001
	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−1.97	.049	−0.02	[−0.04, 0.00]	−2.07	.038
	Thickness	−0.44	[−0.70, −0.17]	−3.33	.002	−0.45	[−0.72, −0.18]	−3.38	.001
	STW vs. DTW × thickness	0.38	[0.24, 0.52]	5.21	<.001	0.30	[0.16, 0.45]	4.10	<.001
	STA vs. DTW × thickness	0.41	[0.26, 0.55]	5.58	<.001	0.40	[0.26, 0.55]	5.46	<.001
Frontal pole	Task (STW vs. DTW)	−0.05	[−0.06, −0.03]	−4.75	<.001	−0.05	[−0.06, −0.03]	−4.75	<.001
	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−2.09	.037	−0.02	[−0.04, 0.00]	−2.09	.037
	Thickness	−0.11	[−0.22, 0.01]	−1.87	.067	−0.06	[−0.19, 0.07]	−0.87	.388
	STW vs. DTW × thickness	0.17	[0.11, 0.23]	5.67	<.001	0.16	[0.09, 0.23]	4.60	<.001
	STA vs. DTW × thickness	0.16	[0.10, 0.21]	5.22	<.001	0.11	[0.04, 0.17]	3.10	.002
Lateral orbitofrontal	Task (STW vs. DTW)	−0.05	[−0.06, −0.03]	−4.71	<.001	−0.05	[−0.06, −0.03]	−4.73	<.001
	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−2.04	.041	−0.02	[−0.04, 0.00]	−2.07	.039
	Thickness	0.03	[−0.21, 0.26]	0.22	.828	0.07	[−0.18, 0.32]	0.56	.580
	STW vs. DTW × thickness	−0.05	[−0.18, 0.08]	−0.81	.416	−0.05	[−0.19, 0.09]	−0.72	.470
	STA vs. DTW × thickness	0.03	[−0.10, 0.16]	0.46	.643	0.10	[−0.04, 0.25]	1.44	.150
Medial orbitofrontal	Task (STW vs. DTW)	−0.05	[−0.06, −0.03]	−4.71	<.001	−0.04	[−0.06, −0.03]	−4.66	<.001
	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−2.04	.041	−0.02	[−0.04, 0.00]	−2.06	.039
	Thickness	−0.01	[−0.20, 0.17]	−0.13	.898	−0.08	[−0.27, 0.11]	−0.88	.385
	STW vs. DTW × thickness	0.02	[−0.08, 0.13]	0.45	.653	−0.05	[−0.15, 0.06]	−0.84	.403
	STA vs. DTW × thickness	0.07	[−0.03, 0.17]	1.33	.183	0.06	[−0.04, 0.17]	1.15	.248

Note. DTW is the reference group. For all results, including covariates, see supplemental materials. HbO_2 = oxygenated hemoglobin; IIV = intraindividual variability; STW = single-task-walk; STA = single-task-alpha; DTW = dual-task-walk.

Findings revealed that thinner cortex in the PFC, and in specific regions in all cerebral lobes, was related to greater increases in fNIRS-derived HbO_2 IIV in DTW compared to STA and STW. This supported our hypothesis that lower cortical thickness would be related to increased IIV and poor dual-task PFC efficiency. As we controlled for gait and cognitive performance, the moderation of HbO_2 IIV by cortical thickness suggests inefficient PFC response.

While previous literature on IIV in aging suggests that greater variability is indicative of poor outcomes (Costa et al., 2019), the literature on neural IIV is less conclusive. It is important to note that neural IIV can be measured as hemodynamic (e.g., fNIRS or fMRI) or electrophysiological (e.g., EEG) and different findings arise depending on the method used, likely reflecting different physiological processes (Kumral et al., 2020). Greater IIV in the hemodynamic response has been associated with greater task difficulty, greater variability in movement, and cognitive impairments (Haar et al., 2017; Holtzer et al., 2020). Neural IIV has been suggested to be task and region-dependent (Armbruster-Genç et al., 2016; Boylan et al., 2021; Guitart-Masip et al., 2016). It has been postulated that neural IIV may follow a u-shaped curve, with some variability necessary for learning but too much variability being disadvantageous and associated with clinical disorders (Dinstein et al., 2015). Indeed, one study showed that increased neural IIV during DTW was associated with cognitive impairments and greater behavioral IIV (Holtzer et al., 2020). A recent study, however, found that people with Parkinson's disease demonstrated greater neural IIV during normal walking and that this IIV did not increase from single- to DTW. Over repeated learning trials, DTW neural IIV increased in Parkinson's disease and decreased in healthy controls (Maidan et al., 2022). In sum, recent research supports the notion that a degree of neural IIV is adaptive, but that excessive IIV may be indicative of inefficiency.

Most models in the current study followed the pattern of lower cortical thickness associated with greater DTW PFC IIV. However, in five models of the frontal, temporal, and occipital lobes, greater thickness in these regions was associated with greater increases in DTW IIV. This is in line with previous studies showing regional differences in neural variability (Armbruster-Genç et al., 2016; Boylan et al., 2021; Guitart-Masip et al., 2016). Further, it is important to note that the statistical analyses examined regional thickness measurements as distinct, when in fact these regions are not independent from one another (Habeck & Stern, 2007). Given the suspected differential cost-benefit implications of neural IIV and the complex networks involved in task-related activation in DTW, it is not surprising that all regions did not show the same patterns.

The specific regions found to moderate the change in HbO_2 IIV from STW to DTW are involved in sensory, motor, and cognitive functioning. Involvement of PFC (caudal middle, rostral middle, superior middle, and frontal pole regions) thickness suggests that neural IIV expresses direct inefficiency of the PFC, and is consistent with a previous study linking prefrontal gray matter volume with task-related change in mean PFC signal (Wagshul et al., 2019). The parietal findings are likely related to spatial processing and integration (Passarelli et al., 2021) as well as attention and arousal (Leech & Sharp, 2014). Temporal lobe regions implicated are involved in auditory integration and language (Bhaya-Grossman & Chang, 2022; Herlin et al., 2021; van Kemenade et al., 2019), and highlight the processes needed with the

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Table 4. Significant adjusted interaction effects of posterior cortical thickness and task HbO_2 IIV

Region	Variable	Estimate	95% CI	*t*	*p*
Left hemisphere					
Banks of the superior temporal sulcus	Task (STW vs. DTW)	−0.04	[−0.06, −0.03]	−4.67	<.001
	Thickness	0.13	[−0.08, 0.35]	1.24	.220
	STW vs. DTW × thickness	−0.17	[−0.28, −0.06]	−2.95	.003
Caudal anterior cingulate	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−2.14	.033
	Thickness	−0.06	[−0.18, 0.07]	−0.90	.371
	STA vs. DTW × thickness	0.12	[0.05, 0.19]	3.29	.001
Cuneus	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−2.05	.041
	Thickness	0.05	[−0.23, 0.33]	0.37	.712
	STA vs. DTW × thickness	0.20	[0.05, 0.34]	2.69	.007
Inferior temporal	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−2.19	.029
	Thickness	−0.15	[−0.49, 0.18]	−0.93	.357
	STA vs. DTW × thickness	0.43	[0.25, 0.60]	4.74	<.001
Lingual	Task (STW vs. DTW)	−0.05	[−0.07, −0.03]	−4.85	<.001
	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−2.06	.039
	Thickness	−0.35	[−0.71, 0.02]	−1.92	.060
	STW vs. DTW × thickness	0.38	[0.21, 0.56]	4.29	<.001
	STA vs. DTW × thickness	0.43	[0.25, 0.61]	4.75	<.001
Pars orbitalis	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−1.95	.051
	Thickness	−0.08	[−0.32, 0.16]	−0.70	.489
	STA vs. DTW × thickness	0.17	[0.05, 0.30]	2.67	.008
Pars triangularis	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−1.95	.052
	Thickness	−0.34	[−0.65, −0.04]	−2.29	.026
	STA vs. DTW × thickness	0.26	[0.10, 0.43]	3.10	.002
Pericalcarine	Task (STW vs. DTW)	−0.05	[−0.07, −0.03]	−4.87	<.001
	Thickness	0.10	[−0.23, 0.43]	0.61	.545
	STW vs. DTW × thickness	0.33	[0.15, 0.51]	3.65	<.001
Precuneus	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−1.97	.049
	Thickness	−0.07	[−0.39, 0.25]	−0.45	.657
	STA vs. DTW × thickness	0.22	[0.06, 0.37]	2.65	.008
Superior parietal	Task (STW vs. DTW)	−0.04	[−0.06, −0.03]	−4.61	<.001
	Thickness	−0.18	[−0.43, 0.07]	−1.42	.160
	STW vs. DTW × thickness	0.30	[0.16, 0.43]	4.34	<.001
Superior temporal	Task (STW vs. DTW)	−0.05	[−0.06, −0.03]	−4.78	<.001
	Thickness	0.10	[−0.15, 0.36]	0.80	.425
	STW vs. DTW × thickness	−0.21	[−0.33, −0.08]	−3.28	.001
Temporal pole	Task (STW vs. DTW)	−0.05	[−0.06, −0.03]	−4.79	<.001
	Thickness	0.09	[−0.02, 0.20]	1.64	.106
	STW vs. DTW × thickness	−0.10	[−0.16, −0.04]	−3.38	.001
Right hemisphere					
Banks of the superior temporal sulcus	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−2.19	.028
	Thickness	0.07	[−0.16, 0.31]	0.64	.523
	STA vs. DTW × thickness	0.28	[0.15, 0.40]	4.37	<.001
Fusiform	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−2.04	.041
	Thickness	−0.14	[−0.43, 0.15]	−0.97	.339
	STA vs. DTW × thickness	0.26	[0.11, 0.42]	3.31	.001
Inferior parietal	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−1.99	.047
	Thickness	−0.11	[−0.44, 0.23]	−0.64	.524
	STA vs. DTW × thickness	0.22	[0.05, 0.40]	2.47	.014
Inferior temporal	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−2.01	.045
	Thickness	−0.01	[−0.36, 0.33]	−0.08	.937
	STA vs. DTW × thickness	0.35	[0.17, 0.52]	3.89	<.001
Isthmus cingulate	Task (STW vs. DTW)	−0.04	[−0.06, −0.03]	−4.60	<.001
	Thickness	0.12	[−0.08, 0.32]	1.23	.223
	STW vs. DTW × thickness	−0.22	[−0.33, −0.11]	−4.01	<.001
Lateral occipital	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−2.10	.036
	Thickness	−0.02	[−0.33, 0.28]	−0.14	.891
	STA vs. DTW × thickness	0.23	[0.07, 0.39]	2.85	.004
Lingual	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−2.11	.035
	Thickness	−0.14	[−0.45, 0.16]	−0.94	.351
	STA vs. DTW × thickness	0.23	[0.07, 0.39]	2.77	.006
Middle temporal	Task (STW vs. DTW)	−0.05	[−0.06, −0.03]	−4.87	<.001
	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−2.16	.031
	Thickness	0.06	[−0.20, 0.33]	0.47	.641
	STW vs. DTW × thickness	−0.20	[−0.34, −0.07]	−2.98	.003
	STA vs. DTW × thickness	0.26	[0.13, 0.39]	3.83	<.001
Pars opercularis	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−2.04	.041
	Thickness	0.03	[−0.23, 0.29]	0.22	.827
	STA vs. DTW × thickness	0.17	[0.04, 0.31]	2.47	.013
Pars triangularis	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−2.09	.037
	Thickness	−0.19	[−0.51, 0.12]	−1.22	.227
	STA vs. DTW × thickness	0.21	[0.05, 0.38]	2.54	.011

(*Continued*)

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Table 4. (*Continued*)

Region	Variable	Estimate	95% CI	*t*	*p*
Pericalcarine	Task (STW vs. DTW)	−0.05	[−0.07, −0.03]	−4.84	<.001
	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−2.13	.033
	Thickness	−0.06	[−0.38, 0.26]	−0.36	.722
	STW vs. DTW × thickness	0.25	[0.09, 0.41]	3.00	.003
	STA vs. DTW × thickness	0.25	[0.09, 0.41]	3.06	.002
Precentral	Task (STW vs. DTW)	−0.05	[−0.06, −0.03]	−4.76	<.001
	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−1.96	.051
	Thickness	−0.34	[−0.69, 0.00]	−2.00	.050
	STW vs. DTW × thickness	0.20	[0.03, 0.37]	2.36	.018
	STA vs. DTW × thickness	0.34	[0.17, 0.51]	3.89	<.001
Precuneus	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−2.02	.044
	Thickness	−0.14	[−0.43, 0.16]	−0.92	.360
	STA vs. DTW × thickness	0.22	[0.06, 0.37]	2.70	.007
Superior parietal	Task (STW vs. DTW)	−0.04	[−0.06, −0.03]	−4.60	<.001
	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−1.95	.052
	Thickness	−0.21	[−0.50, 0.08]	−1.44	.156
	STW vs. DTW × thickness	0.30	[0.15, 0.46]	3.79	<.001
	STA vs. DTW × thickness	0.25	[0.09, 0.41]	3.11	.002
Superior temporal	Task (STA vs. DTW)	−0.02	[−0.04, 0.00]	−2.07	.039
	Thickness	−0.31	[−0.58, −0.03]	−2.19	.033
	STA vs. DTW × thickness	0.18	[0.05, 0.32]	2.63	.009
Temporal pole	Task (STW vs. DTW)	−0.05	[−0.06, −0.03]	−4.75	<.001
	Thickness	0.01	[−0.10, 0.12]	0.20	.841
	STW vs. DTW × thickness	−0.12	[−0.17, −0.06]	−3.85	<.001
Insula	Task (STW vs. DTW)	−0.05	[−0.06, −0.03]	−4.76	<.001
	Thickness	0.08	[−0.15, 0.30]	0.67	.503
	STW vs. DTW × thickness	−0.20	[−0.32, −0.08]	−3.25	.001

Note. DTW is the reference group. Only models with significant FDR-corrected interaction effects are displayed. For all results, see supplemental materials. HbO_2 = oxygenated hemoglobin; IIV = intraindividual variability; STW = single-task-walk; STA = single-task-alpha; DTW = dual-task-walk.

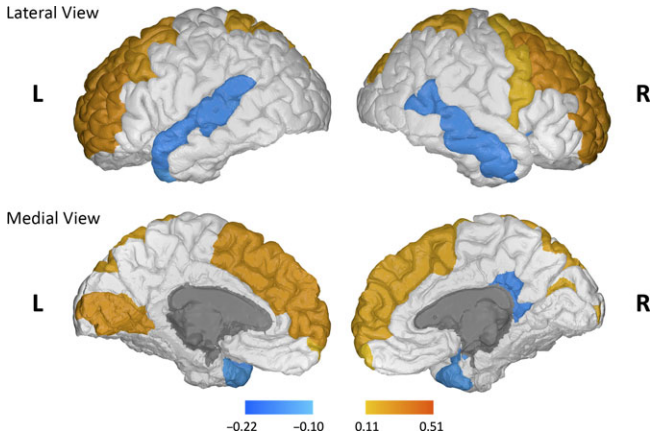

Fig. 1. Regions in which cortical thickness significantly moderated the DTW vs. STW task effect on change in HbO_2 IIV. *Note*. FDR-corrected significant regions are highlighted in color. Yellow-red colors indicate positive interaction effects, while blue color indicates negative interaction effects. STW = single-task-walk; DTW = dual-task-walk; HbO_2 = oxygenated hemoglobin; IIV = intraindividual variability. Drawings generated using BrainPainter (Marinescu et al., 2019).

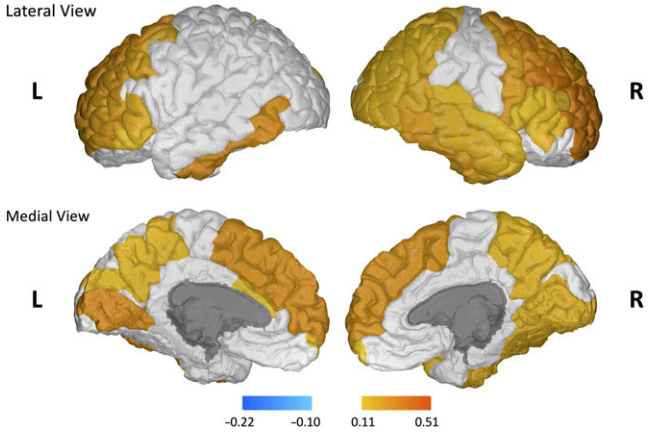

Fig. 2. Regions in which cortical thickness significantly moderated the DTW vs. STA task effect on change in HbO_2 IIV. *Note*. FDR-corrected significant regions are highlighted in color. Yellow-red colors indicate positive interaction effects, while blue color indicates negative interaction effects. STA = single-task-alpha; DTW = dual-task-walk; HbO_2 = oxygenated hemoglobin; IIV = intraindividual variability. Drawings generated using BrainPainter (Marinescu et al., 2019).

addition of the verbalized cognitive alphabet-based task. Occipital regions involved are necessary for primary visual processing (Wandell et al., 2007) and object processing (Mechelli et al., 2000), basic visual field processing needed when walking. Finally, the insula is implicated in speech, attention, and sensorimotor processing (Uddin et al., 2017).

In addition to PFC regions implicated in STW to DTW change, the inferior frontal gyrus (pars triangularis, pars orbitalis, and pars opercularis) was implicated in the STA to DTW change. This contains Broca's area and is essential to speech production (Amunts & Zilles, 2012), potentially implicating competing demands of speech and walking in DTW. Similarly, the addition of the walking component in DTW implicated further areas involved in sensorimotor functioning. Significant regions found to moderate the change in HbO_2 IIV from STA to DTW included the precentral gyrus which contains the motor cortex (Lim et al., 1994), the inferior parietal lobule which is involved in sensory integration and movement (Haaland et al., 2000), the precuneus which is involved in spatially guided movement (Cavanna & Trimble,

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2006), and the fusiform and inferior temporal gyri which are involved in visual (Cohen et al., 2000; Ptak & Valenza, 2005) and object (Cant & Goodale, 2007; Grill-Spector et al., 2001) processing.

Aging is accompanied by changes in brain integrity and functioning, and there are well-documented sex differences in cognitive (Levine et al., 2021) and neurobiological aging (Kakimoto et al., 2016). All models in the current study showed a main effect of sex, specifically that males had higher HbO_2 IIV across tasks. Prior studies have found that men showed increased activation during DTW when under increased stress (Holtzer et al., 2017) and demonstrated greater increases in HbO_2 IIV from single- to dual-task-walk conditions (Holtzer et al., 2020). These findings may be related to increased PFC atrophy seen in men compared to women during aging (Curiati et al., 2009). While the moderating effect of sex was not examined in the current study, this warrants further investigation.

Previous studies reported the influence of gray and white matter integrity on PFC activation during DTW; this was the first study to examine brain integrity in relation to IIV in HbO_2 activity. We found that the regions associated with increased HbO_2 IIV were overlapping but also distinct compared to the regions associated with increased mean HbO_2 (Ross et al., 2021). This suggests that HbO_2 IIV in the PFC provides incremental information not available through central tendency measurements that may be uniquely sensitive to the effect of aging and disease on brain efficiency vis-à-vis walking, notably under attention-demanding conditions.

Strengths, limitations, and future directions

The participants were dementia-free community-dwelling older adults. Future studies should examine these findings in a larger cohort sample, as the current study, common to neuroimaging studies, included only a moderate sample size. As the current study was cross sectional, whether thinner cortex is indicative of pathological brain atrophy versus normal age-related variability cannot be unequivocally ruled out. However, the current sample underwent a consensus case conference to diagnose participants as free of dementia, and there is no evidence of neurological disease. We therefore assumed that the range of cortical thickness observed in the current study is representative of the normal aging population. Future longitudinal work may shed further light on the relationship between changes in cortical thickness, and PFC HbO_2 IIV, assessed over repeated measurements. Whether or not the current results translate into longitudinal, age-related decreases in cortical thickness is of clinical importance.

PFC IIV was measured using HbO_2, rather than deoxygenated hemoglobin (Hb). A previous study demonstrated similar task-related outcomes when examining HbO_2 and Hb (Izzetoglu & Holtzer, 2020). We used only HbO_2 in the current study to limit type two errors. The device used in the current study did not have short channels, which limited our ability to remove artifact arising from extracerebral sources. However, we applied stringent processing and filtering of the fNIRS signal to limit motion artifacts and to account for the impact of age on absorption coefficients and DPF (Scholkmann & Wolf, 2013). To further protect the validity of the current study outcomes, we adjusted for possible confounding effects of mean HbO_2 signal in each model. Additionally, we measured only PFC IIV during the first 30 seconds of each trial. This allowed us to make direct one-to-one comparisons between tasks eliminating the potential confounding effect of time on IIV estimates. Moreover, clinically validated gait assessments are often limited to short 25-foot (Motl et al., 2017) protocols, which are often completed within 30 seconds. As previous literature implicated neural variability in learning, it would be important to examine whether PFC IIV is reduced over repeated learning trials in a pattern similar to central tendency measures (Holtzer et al., 2019). Whether PFC IIV follows the pattern of traditional practice effects, and its relationship to structural integrity of the brain, would provide valuable information of potential clinical utility.

We only measured HbO_2 IIV in the PFC. Additional work is warranted to examine neural activation and IIV in more posterior regions as well, as the current findings provide a partial representation of brain control of locomotion. We elected to examine whole-brain segmented regions to compare the current findings to previous work examining cortical thickness in relation to task-related changes in the mean HbO_2 signal (Ross et al., 2021). Future studies may consider network approaches as cortical regions are not independent.

Relative measures of dispersion (e.g., coefficient of variation) could not be calculated as several participants' mean HbO_2 approached zero. Analyses using *SD* were adjusted for mean HbO_2 to address this potential limitation. Previous studies have used and validated *SD* to operationalize IIV (Costa et al., 2019; Garrett et al., 2011). Split-half intra-class correlations of HbO_2 IIV across the 30 seconds of each task were examined to ensure that findings were not simply reflective of increased noise during the course of tasks and revealed excellent internal consistency of HbO_2 IIV. An additional benefit of examining IIV as a task-related biomarker is that it eliminates the effects of relative measurements to a baseline condition. These effects are present in continuous-wave fNIRS measurements while using mean values. Thus, examining neural IIV in task-related research demonstrates both a clinical and methodological strength. Nonlinear measures of data complexity such as multi-scale entropy can provide additional information about the variability of data (Angsuwatanakul et al., 2020) and may be used in future studies. There is no current established entropy calculation method in fNIRS analysis, and many require large amounts of datapoints or other parameters not available in the current study.

Finally, there remains a lack of consensus regarding optimal neural IIV (Dinstein et al., 2015). There may be an inflection point at which neural IIV differentiates between being adaptive to disadvantageous, or the utility of IIV may be dependent on population (Maidan et al., 2022). Multimodal neuroimaging approaches provide an advantage for understanding brain mechanisms underlying healthy and disease-related aging (Sui et al., 2014). Future studies should leverage multimodal neuroimaging approaches in healthy and clinical populations to elucidate how the structural integrity of the brain and neural IIV interact to influence cognitive and motoric task performance.

Conclusion

Consistent with the neural inefficiency hypothesis, we found that thinner cortex in the PFC and specific regions throughout the cortex was associated with greater increases in neural IIV in the PFC from single-tasks to dual-task walking without behavioral gains. Cortical thickness in multiple brain regions influenced the change in PFC HbO_2 IIV across task conditions, highlighting the role of complex interactions between brain structure and function in supporting gait performance among older adults. Reduced

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cortical thickness and greater IIV of fNIRS-derived HbO_2 during dual-task walking should be further investigated as possible markers of increased risk of developing mobility impairments in aging and disease populations.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1355617723000371

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