The effect of fear of falling on prefrontal cortex activation and efficiency during walking in older adults

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Abstract Neural inefficiency is inferred when higher brain activations are associated with similar or worse performance. Improved neural efficiency is achieved when task-related brain activations are reduced after practice. No information is available on the effect of fear-of-falling (FOF) on brain activation during walking. We hypothesized that the presence of FOF would be associated with neural inefficiency and with a delay in improving neural efficiency during dual-task walking. Task conditions included single-task walk (STW), Alpha (cognitive interference), and dual-task walk (DTW). Functional near-infrared spectroscopy (fNIRS)-derived HbO₂ in the prefrontal cortex (PFC) was used to quantify task-related changes in brain activation. Practice included three repeated counterbalanced trials for each task. Participants with FOF ($n = 19$; mean age = 79.84 ± 6.01 years; %female = 68.42) and without FOF ($n = 56$; mean age = 76.73 ± 6.39 years; %female = 44.64) were included. The presence of FOF was associated with

slower stride velocity (estimate = -12.354 ; $p = 0.0154$) and with greater increases in PFC HbO₂ from STW to DTW (estimate = 0.303 , $p = 0.0009$) and from Alpha to DTW (estimate = 0.387 , $p < 0.0001$). Compared to controls, participants reporting FOF demonstrated an attenuated decline in PFC HbO₂ from the first to the second DTW trials (estimate = 0.264 ; $p = 0.0173$). In contrast, compared to controls, participants with FOF demonstrated greater decline in Alpha PFC HbO₂ from trial 1 to trial 2 (estimate = -0.419 , $p < 0.0001$) and from trial 1 to 3 (estimate = -0.281 , $p = 0.0006$). The change in PFC HbO₂ over repeated STW trials was not significant and was not moderated by FOF status. The presence of FOF was associated with higher and inefficient PFC activation during DTW in older adults.

Keywords Fear-of-falling · Dual-task walking · Prefrontal cortex, neural efficiency, functional-near-infrared spectroscopy

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Introduction

Fear-of-falling (FOF) has been defined as an exaggerated concern about falling or as low perceived self-efficacy at avoiding falls (Lach and Parsons 2013; Tinetti et al. 1994, 1986). Prevalence rates of FOF are high but variable ranging from 20 to 83% in community-dwelling older adults (Friedman et al. 2002; Scheffer et al. 2008). FOF can develop after falls but is also a risk factor for incident falls in healthy older adults with low to moderate mobility limitations (Litwin

et al. 2018). FOF in older adults has been associated with activity restriction (Bruce et al. 2002; Cumming et al. 2000; Howland et al. 1998), decline in physical function and loss of functional independence (Delbaere et al. 2004; Deshpande et al. 2008) as well as admissions to nursing homes (Cumming et al. 2000).

Dual-task walking, which requires attention and executive functions (Holtzer et al. 2012b, 2014b), is an established risk factor for incident frailty, disability, and mortality in community-residing older adults (Verghese et al. 2012). Whereas FOF, with or without activity restriction, was associated with worse gait, the variance in dual-task walking costs (i.e., the difference in walking performance between single and dual-task conditions) was not associated with FOF (Donoghue et al. 2013; Reelick et al. 2009). The “posture-first” hypothesis posits that older adults are more likely to prioritize balance or gait over cognitive task performance under dual-task conditions (Li et al. 2001). This hypothesis, however, received mixed support in the literature. A recent study, using functional near-infrared-spectroscopy (fNIRS) to quantify changes in activation patterns in the prefrontal cortex (PFC) during dual-task walking revealed that, compared to controls, older adults with neurological gait abnormalities were more likely to direct brain resources toward maintaining their walking and, in turn, compromised their cognitive interference task performance (Holtzer et al. 2016a). This finding offered a refinement to the posture-first hypothesis suggesting that it may be demonstrated among older adults with mobility limitations. It is noteworthy that changes in attentional control, measured behaviorally, have been associated with FOF, such that more attentional resources were allocated to postural control under dual-task conditions (Gage et al. 2003). Furthermore, those with FOF appear to use stiffening strategies, a hallmark of cautious gait in the presence of a postural threat, when no postural threat is present (Young and Mark Williams 2015). The mechanisms for these stiffening behaviors in individuals with FOF are poorly understood as of yet but may be associated with a posture-first strategy and the shifting of attentional control to postural maintenance.

Although relatively limited in scope and number, human studies using fNIRS have begun to shed light on the functional brain correlates of active walking (Gramigna et al. 2017). These studies revealed that the PFC plays a critical role in mobility in healthy individuals (Mihara et al. 2008; Miyai et al. 2001; Suzuki et al.

2008), older adults (Harada et al. 2009; Mirelman et al. 2017), and patients with stroke (Mihara et al. 2007), multiple sclerosis (Hernandez et al. 2016), and Parkinson’s disease (Maidan et al. 2017; Maidan et al. 2016). Notably, HbO₂ in the PFC increased from single-task walk (STW) to dual-task walk (DTW) conditions in older adults due to increased attention demands in the latter condition (Holtzer et al. 2011, 2015, 2016a, b, 2017). A recent study required participants to repeatedly walk under STW and DTW conditions while changes in activation patterns in their PFC were monitored using fNIRS (Holtzer et al. 2018b). This experimental paradigm was designed to determine behavioral and HbO₂ trajectories of learning while walking. Key findings revealed that gait performance improved and PFC HbO₂ declined under DTW but not STW conditions suggesting that task-specific improvement in PFC efficiency could be accomplished in one experimental session (Holtzer et al. 2018b). The effect of FOF on PFC efficiency of walking has not been reported in the literature.

Current study Using well-established dual-task walking procedures and fNIRS, we aimed to determine the effect of FOF on PFC activation and efficiency during walking. Consistent with prior literature, neural inefficiency is inferred when higher brain activations are associated with similar or worse performance. Improved brain efficiency is observed when task-related brain activation is reduced after practice (Neubauer and Fink 2009). We hypothesized that: (a) the presence of FOF would be associated with inefficient (i.e., greater) increases in PFC HbO₂ from STW and Alpha to DTW conditions; and (b) FOF would be associated with a delay in improving PFC efficiency (i.e., reduced HbO₂) after repeated DTW trials.

Methods

Participants

A subsample of “Central Control of Mobility in Aging” (CCMA) study that recently completed a combined dual-task walking burst measurement protocol (Holtzer et al. 2018b) was included in the current study. CCMA procedures were previously described (Holtzer et al. 2014a, b). In brief, potential participants were identified

from population lists of lower Westchester County, NY. Verbal assent and initial eligibility were obtained via structured phone interviews, which were followed by two annual in-person study visits. Testing procedures included comprehensive neuropsychological, psychological, functional, and mobility assessments. The combined fNIRS, dual-task walking, and burst measurement protocol was completed in one session. Dementia diagnoses were assigned at consensus diagnostic case conferences (Holtzer et al. 2008). Exclusion criteria were 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 study was in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Participants signed written informed consents in the first in-person study visit. The Institutional Review Board approved this study.

Measures

Experimental procedure

In STW, participants were asked to walk around the electronic walkway at their “normal pace” for three consecutive loops. The cognitive interference task, Alpha, required participants to stand still while reciting alternate letters of the alphabet (A, C, E...) for 30 s out loud. In DTW, participants were instructed to perform the two single tasks (STW and Alpha) at the same time. Specifically, participants walked around the walkway for three consecutive loops at their normal pace while reciting alternate letters of the alphabet. Participants were instructed to pay equal attention to both tasks to minimize task prioritization effects (Holtzer et al. 2012b, 2014b). Reliability and validity for this walking paradigm have been well established (Holtzer et al. 2012a; Verghese et al. 2012).

Quantitative gait assessment

A 4 × 20 ft Zeno electronic walkway was used to assess stride velocity (cm/s), based on the location and mathematical parameters between footfalls, under STW and DTW conditions (Zenometrics, LLC; Peekskill, NY). ProtoKinetics Movement Analysis Software technology (PKMAS) was used to assess quantitative measures of gait (stride velocity the purpose of this investigation)

and determine, algorithmically, entry and end points under STW and DTW conditions (England et al. 2015). Split-half intra-class correlations (ICC) for stride velocity (cm/s) in both walking conditions were greater than 0.95 revealing excellent internal consistency (Holtzer et al. 2015).

Repeated measurement A total of three trials were administered separated by 5-min time intervals allowing participants to rest. In the first trial, the three test conditions (Alpha, STW, DTW) were presented in a counterbalanced order using a Latin-square design to minimize task order effects on the outcome measures. Then the same test order was maintained for each participant for the second and third trials (Holtzer et al. 2018b).

fNIRS system

The system used in the current study, fNIRS Imager 1100 (fNIRS Devices, LLC, Potomac, MD), has been validated (Izzetoglu et al. 2005). Methodological issues such as motion artifacts, removal algorithms, and use of optimal baseline procedures were discussed in previous publications (Holtzer et al. 2015, 2016a, 2017; Izzetoglu et al. 2005). The system collects data at a sampling rate of 2 Hz. The fNIRS sensor consists of four LED light sources and ten 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 based on landmarks from the international 10–20 system (Ayaz et al. 2006).

Preprocessing and hemodynamic signal extraction Raw data at 730- and 850-nm wavelengths were inspected for excessive noise, saturation, or dark current conditions. To eliminate possible respiration, heart rate signals and unwanted high frequency noise raw intensity measurements at 730 and 850 nm were low-pass filtered with a finite impulse response filter of cut-off frequency at 0.14 Hz (Izzetoglu et al. 2005). Saturation or dark current conditions were excluded. Oxygenated hemoglobin (HbO₂), calculated using

modified Beer-Lambert law, was used as proxy for PFC activation as it is more reliable and sensitive than other fNIRS-derived measures (e.g., Hb) to locomotion-related changes in cerebral oxygenation (Harada et al. 2009; Miyai et al. 2001). Proximal 10-s baselines were administered prior to each experimental condition determine relative task-related changes in HbO₂ concentrations (Holtzer et al. 2015, 2016a, b, 2017).

Epoch and feature extraction Individual mean HbO₂ data were extracted separately for each task. Gait and fNIRS data acquisition were synchronized using a central “hub” computer with E-Prime 2.0 software as previously described (Holtzer et al. 2015, 2016a, b, 2017).

Reliability of fNIRS measurements Split-half intra-class correlations within each task were high for STW (0.830), Alpha (0.864), and DTW (0.849) revealing excellent internal consistency of HbO₂ measurements (Holtzer et al. 2015).

Assessment of FOF

Consistent with previous studies (Arfken et al. 1994; Murphy et al. 2003; Vellas et al. 1997), a single-item question was used to assess FOF. Specifically, the question stated: “Did you have fear of falling in the last 2 months or since the last interview?” Binary responses (yes or no) were recorded. This single-item question has been used in previous research with good test–retest reliability ($\kappa = 0.72$) (Oh-Park et al. 2011).

Covariates

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was used to assess overall level of cognitive function (Duff et al. 2008). The Geriatric Depression Scale (GDS) was used to assess depressive symptoms (Yesavage et al. 1982). A comorbidity summary score (range 0–10) including the presence of diabetes, chronic heart failure, arthritis, hypertension, depression, stroke, Parkinson’s disease, chronic obstructive lung disease, angina, and myocardial infarction was used to characterize disease burden (Holtzer et al. 2008). Anxiety was assessed with the Beck Anxiety Inventory (BAI) (Beck et al. 1988). Falls history was assessed via structured questionnaire, specifically the question of whether a participant had ever fallen was used as a covariate for the current study.

Statistical analysis

Separate linear mixed effects models (LME) were used to determine the effects of task (STW, Alpha, and DTW) and trials (1–3), stratified by experimental condition, on HbO₂, stride velocity and rate of correct letter generation. The moderating effects of FOF on task and trials in the above statistical models were examined via two-way interactions. In the LME models using HbO₂ as the outcome variable, individual optode data (1–16) were treated as random effects. Analyses controlled for gender, age, education, depressive symptoms, anxiety symptoms, disease comorbidity, falls history, and total RBANS index score. Finally, sensitivity analyses included stride velocity as a covariate in the separate models examining the effect of task (STW vs. DTW) and DTW trials and their interactions with FOF on HbO₂. All statistical analyses were carried out by package lme4 in R (R3.4.2, <https://www.R-project.org/>) (Bates et al. 2015) and p values were considered significant at $p < 0.05$.

Results

Participants ($n = 75$; mean age = 77.52 ± 6.41 ys; mean education = 14.99 ± 3.04 ys; %female = 50.57) who had completed the burst measurement protocol and had responded to the FOF question were included in the current study. The mean RBANS Index score (94.09 ± 11.85) was indicative of average overall cognitive function. Mean GHS (0.84 ± 0.50) and GDS (4.21 ± 3.18) scores were low indicating the sample was relatively healthy and with minimal depressive symptoms, respectively. The mean BAI score was also low (3.07 ± 4.75) indicating that anxiety symptoms were minimal. A positive falls history was reported by 62.67% of the sample. Analyses stratified by FOF status revealed that the covariates, with the exception of falls history, were not significantly different between the two groups. Demographic information and descriptive statistics were summarized and stratified by FOF status in Table 1.

FOF: HbO₂ patterns across tasks and repeated trials

Task effects LME revealed significant FOF $\times$ task interactions whereby participants with FOF demonstrated

Table 1 Sample characteristics

	Total sample (<i>n</i> = 75)	FOF (<i>n</i> = 19)	NFOF (<i>n</i> = 56)	<i>p</i>
Age years	77.52 (± 6.41)	79.84 (± 6.01)	76.73 (± 6.39)	0.0671
Gender (%female)	38 (50.57%)	13 (68.42%)	25 (44.64%)	0.1270
GHS	0.84 (± 0.50)	1.11 (± 1.29)	0.75 (± 0.98)	0.2116
Education years	14.99 (± 3.04)	14.37 (± 2.22)	15.20 (± 3.26)	0.3078
RBANS (total scale index)	94.09 (± 11.85)	91.53 (± 12.51)	94.96 (± 11.61)	0.2776
GDS score	4.21 (± 3.18)	4.53 (± 3.10)	4.11 (± 3.23)	0.6234
Fall history (%fallen ever)	47 (62.67%)	17 (89.47%)	0.011730 (53.57%)	0.0117*
BAI score	3.07 (± 4.75)	3.84 (± 6.83)	2.80 (± 3.84)	0.4135

GHS, Global Health Status score; *FOF*, fear of falling; *NFOF*, no fear of falling; *RBANS*, Repeatable Battery for the Assessment of Neuropsychological Status; *BAI*, Beck Anxiety Inventory; *GDS*, Geriatric Depression Scale. *P* values indicate significance values for group comparisons on the covariates

greater increases in HbO₂ from STW to DTW (estimate = 0.303, $p = 0.0009$) and from Alpha to DTW (estimate = 0.387, $p < 0.0001$) compared to controls. The complete LME model is presented in Table 2; Fig. 1 depicts the moderating effect of FOF status on the change in HbO₂ across task conditions.

Trial effects LME revealed that HbO₂ declined over repeated trials DTW (trial 2 vs. trial 1: estimate = −.309, $p < 0.0001$; trial 3 vs. trial 1: estimate = −0.243, $p < 0.0001$). The interaction of FOF × trials revealed a significant moderation effect on the change in HbO₂ from trial 1 to trial 2 (estimate = 0.264, $p = 0.0173$) whereby participants who endorsed FOF demonstrated an attenuated decline in

HbO₂ compared to participants who did not endorse FOF. Alpha HbO₂ declined from trial 1 to trial 2 (estimate = −0.1521, $p = 0.0002$) and from trial 1 to 3 (estimate = −0.1033, $p = 0.0133$). Compared to controls, participants with FOF demonstrated greater decline in Alpha HbO₂ from trial 1 to trial 2 (estimate = −0.4191, $p < 0.0001$) and from trial 1 to 3 (estimate = −0.2809, $p = 0.0006$). The effect of trial on HbO₂ under STW was not significant nor was the moderation effect of FOF. Detailed summary of these findings is presented in Table 3. Figure 2a–c demonstrates the significant but opposite moderation effects of FOF on HbO₂ across DTW (a) and Alpha (b) trials as well as the non-significant moderating effect of FOF on STW trials (c).

Table 2 Linear mixed-effects model examining the effects of task, presence of FOF, and their interaction on PFC oxygenation ($N = 75$)

Variable	Estimate	<i>t</i>	95% CI	<i>p</i> value
STW vs. DTW	0.635	−13.72	[−0.73, −0.54]	< 0.0001
Alpha vs. DTW	0.108	2.33	[0.02, 0.20]	0.0198
FOF presence	0.411	2.79	[0.12, 0.70]	0.0052
STW vs. DTW × FOF	0.304	3.31	[0.48, 0.12]	0.0009
Alpha vs. DTW × FOF	0.387	4.22	[0.57, 0.21]	< 0.0001
Age	−0.010	−1.10	[−0.03, 0.01]	0.2727
GHS	0.035	0.61	[−0.08, 0.15]	0.5408
Gender	−0.201	−1.68	[−0.43, 0.03]	0.0923
Education years	0.011	0.60	[−0.03, 0.05]	0.5477
RBANS	0.013	2.62	[0.00, 0.02]	0.0089
GDS	−0.013	−0.62	[−0.05, 0.03]	0.5342
Fall history	0.089	0.70	[−0.16, 0.34]	0.4823
BAI	0.000	0.00	[−0.03, 0.03]	0.9993

STW, single-task walk; *DTW*, dual-task walk; *Alpha*, cognitive interference task; *FOF*, fear of falling; *GHS*, Global Health Status; *RBANS*, Repeatable Battery for the Assessment of Neuropsychological Status; *BAI*, Beck Anxiety Inventory; *GDS*, Geriatric Depression Scale

Fig. 1 Mean prefrontal cortex (PFC) oxygenated hemoglobin (HbO₂) per task stratified by fear of falling (FOF) status. Single asterisk indicates significant interaction effects, where $p < 0.05$. STW vs. DTW $\times$ FOF $p = 0.0009$; Alpha vs. DTW $\times$ FOF $p < 0.0001$.

FOF: changes in stride velocity and rate of letter generation across tasks and trials

Task effects Stride velocity declined significantly from STW to DTW (estimate = -13.6449 , $p = 0.0002$). FOF was associated with slower stride velocity (estimate = -12.3536 , p value = 0.0154) but did not moderate the change in stride velocity from STW to DTW (estimate = 5.0202 , $p = 0.1475$, for detailed summary of the LME model see supplementary Table 1 panel A). The rate of correct letter generation was higher in Alpha compared to DTW (estimate = 0.0853 , $p = 0.0222$) but FOF did not moderate this change (estimate = 0.0133 , $p = 0.6323$; for detailed summary, see supplementary Table 1 panel B).

Trial effects The effect of trial on DTW stride velocity was significantly demonstrating improvement from trial 1 to 2 (estimate = 1.948 , $p = 0.0059$) and from trial 1 to 3 (estimate = 2.755 , $p = 0.0001$). FOF, however, did not moderate the improvement in stride velocity from trial 1 to 2 (estimate = -0.2951 , $p = 0.8364$) or from trial 1 to 3 (estimate = -1.3746 , $p = 0.3364$; for detailed summary of the results, see supplementary Table 2 panel A). The effect of trial (trial 1 to 2: estimate = 0.5480 , $p = 0.4708$; trial 1 to 3: estimate = -0.4223 , $p = 0.5785$): or the moderation effect of FOF on trial (trial 1 to 2: estimate = 0.9606 , $p = 0.5236$; trial 1 to 3: estimate = 1.1058 , $p = 0.4627$) under STW stride velocity were not significant (for detailed summary of the results, see supplementary Table 2 panel B). The effect of trial on the rate of correct letter generation in Alpha was significant demonstrating improvement from trial 1 to 2 (estimate = 0.0610 , $p = 0.0020$) and from trial 1 to 3 (estimate = 0.0689 , $p = 0.0005$). FOF, however, did not moderate the

improvement in the rate of correct letter generation from trial 1 to 2 (estimate = -0.0329 , $p = 0.3943$) or from trial 1 to 3 (estimate = -0.0233 , $p = 0.5468$; see supplementary Table 2 panel C). The effect of trial on DTW rate of correct letter generation was significant demonstrating improvement from trial 1 to 2 (estimate = 0.0695 , $p = 0.0001$) and from trial 1 to 3 (estimate = 0.0864 , $p < 0.0001$). FOF, however, did not moderate the improvement in the rate of correct letter generation from trial 1 to 2 (estimate = -0.0249 , $p = 0.4864$) or from trial 1 to 3 (estimate = -0.0096 , $p = 0.7894$; for detailed summary of the results see, supplementary Table 2 panel D). Supplementary Table 3 provides descriptive information for stride velocity and correct letter generation stratified by FOF status, task, and trial.

Sensitivity analysis Due to group differences in stride velocity, additional LMEs were run revealing that the moderating effect of FOF on the change in HbO₂ from STW to DTW remained significant (estimate = -0.3579 , $p < 0.0001$) even when adjusting for stride velocity and its interaction with task. Furthermore, the moderating effect of FOF on the change in HbO₂ across DTW trials remained significant (trial 1 to 2: estimate = 0.3651 , $p = 0.0018$) even when adjusting for stride velocity and its interaction with trial.

Discussion

The current study examined the effect of FOF on brain activation and efficiency patterns during walking in community residing older adults. We found that participants who endorsed FOF exhibited greater increases in

Table 3 LMEM analysis: FOF and trial effects and their interactions on the change in HbO₂ under different task conditions

Variable	Estimate	<i>t</i>	95% CI	<i>p</i> value
Dual-task walk				
Trial 1 vs. 2	−0.309	−5.51	[−0.42, −0.20]	<0.0001
Trial 1 vs. 3	−0.243	−4.29	[−0.35, −0.13]	<0.0001
FOF presence	0.534	1.78	[−0.05, 1.12]	0.0743
Trial 1 vs. 2 × FOF	0.264	2.38	[0.05, 0.48]	0.0173
Trial 1 vs. 3 × FOF	−0.216	−1.95	[−0.43, 0.00]	0.0516
Age (years)	−0.030	−1.60	[−0.07, 0.01]	0.1105
GHS	0.011	0.09	[−0.23, 0.25]	0.9268
Gender	0.216	0.86	[−0.28, 0.71]	0.3916
Education (years)	0.012	0.31	[−0.07, 0.09]	0.7558
RBANS	0.023	2.20	[0.00, 0.04]	0.0275
GDS	−0.031	−0.69	[−0.12, 0.06]	0.4916
Falls history	0.112	0.42	[−0.41, 0.64]	0.6765
BAI	−0.009	−0.34	[−0.06, 0.04]	0.7334
Single-task walk				
Trial 1 vs. 2	−0.075	−1.50	[−0.17, .02]	0.1325
Trial 1 vs. 3	−0.071	−1.40	[−0.17, 0.03]	0.1624
FOF presence	−0.140	−0.66	[0.56, 0.28]	0.5112
Trial 1 vs. 2 × FOF	0.164	1.66	[−0.03, 0.36]	0.0978
Trial 1 vs. 3 × FOF	0.062	0.63	[−0.13, 0.26]	0.5280
Age (years)	−0.013	−1.02	[0.04, 0.01]	0.3083
GHS	−0.011	−0.3	[−0.18, 0.16]	0.8950
Gender	−0.115	−0.65	[−0.46, 0.23]	0.5140
Education (years)	0.003	−0.10	[−0.06, 0.05]	0.9213
RBANS	0.007	0.90	[−0.01, 0.02]	0.3681
GDS	−0.006	−0.18	[−0.07, 0.06]	0.8579
Falls history	0.301	1.60	[−0.07, 0.67]	0.1088
BAI	0.030	1.55	[−0.01, 0.07]	0.1209
Alpha				
Trial 1 vs. 2	−0.152	−3.68	[−0.23, −0.07]	0.0002
Trial 1 vs. 3	−0.103	−2.47	[−0.19, −0.02]	0.0013
FOF	0.310	1.50	[−0.09, 0.71]	0.1336
Trial 1 vs. 2 × FOF	−0.419	−5.13	[−0.58, −0.26]	<0.0001
Trial 1 vs. 3 × FOF	−0.281	−3.43	[−0.44, −0.12]	0.0006
Age (years)	0.011	0.87	[−0.01, 0.04]	0.3864
GHS	0.090	1.08	[−0.07, 0.25]	0.2816
Gender	0.515	2.97	[0.18, 0.86]	0.0029
Education (years)	0.028	1.01	[−0.03, 0.08]	0.3116
RBANS	0.008	1.18	[−0.01, 0.02]	0.2363
GDS	0.003	−0.09	[−0.06, 0.06]	0.9303
Falls history	−0.095	−0.52	[−0.46, 0.27]	0.6042
BAI	−0.022	−1.16	[−0.06, 0.01]	0.2463

STW, single-task walk; *DTW*, dual-task walk; *Alpha*, cognitive interference task; *FOF*, fear of falling; *GHS*, Global Health Status; *RBANS*, Repeatable Battery for the Assessment of Neuropsychological Status; *BAI*, Beck Anxiety Inventory; *GDS*, Geriatric Depression Scale

Fig. 2 Mean prefrontal cortex (PFC) oxygenated hemoglobin (HbO₂) across task conditions. Single asterisk indicates significant interaction effects, where $p < 0.05$. **a** Dual-task walk (DTW): trial 1 vs. 2 $\times$ FOF $p = 0.0173$; **b** Alpha: trial 1 vs. 2 $\times$ FOF $p < 0.0001$; trial 1 vs. 3 $\times$ FOF $p = 0.0006$; **c** Single-task walk (STW): there were no significant interactions.

PFC HbO₂ from STW to DTW and from Alpha to DTW compared to those who did not report FOF. Because FOF was associated with slower stride velocity, these findings suggest inefficient PFC activation during dual-task walking, a condition that imposes greater demands on the attention system. Behaviorally, the dual-task manipulation produced the expected effect (i.e., significant decline in stride velocity in DTW compared to STW)

irrespective of FOF status, which is consistent with previous studies (Donoghue et al. 2013; Reelick et al. 2009) but also see (Uemura et al. 2012). This finding maybe attributed, in part, to slower STW stride velocity among participants endorsing FOF; however, it also supports our findings of reduced PFC efficiency in the FOF group under DTW conditions, given that the task manipulation produced similar behavioral effects in both groups.

The effects of repeated trials on changes in PFC activation patterns under Alpha and DTW conditions varied as a function of FOF status. Specifically, the decline in PFC activation from trials 1 to 2 under DTW was attenuated among older adults endorsing FOF compared to those who did not report FOF suggesting a delay in improving neural efficiency in the former group. In contrast, the presence of FOF was associated with greater declines in PFC activation across repeated Alpha trials suggesting improved neural efficiency due to practice among older adults who endorse FOF compared to controls on a cognitive task that does not require walking. It is critical to emphasize that behavioral performance improved across repeated trials of both task conditions irrespective of FOF status. This strongly suggests that neural inefficiency among older adults who endorse FOF is specific to attention-demanding locomotion and does not generalize to experimental conditions that require only cognitive effort. This pattern demonstrating increased allocation of brain resources toward gait under attention demanding conditions is consistent with a posture-first strategy, which appears to be employed by specific subsets of the older adults' population, such as those who report FOF.

Clinical implications Higher and inefficient PFC activation levels, as assessed with fNIRS during dual-task walking, predicted incident falls among healthy older adults (Verghese et al. 2016). The current findings revealed that individuals who endorsed FOF demonstrated inefficient PFC activation patterns during dual-task walking as well as a delay in improving their PFC efficiency after practice. While within-session practice, as applied in this experiment, is not an intervention, it provides critical information about behavioral and neural activity that could be directly translated into rehabilitation of mobility and fall prevention for individuals endorsing FOF. Specifically, although delayed, improved PFC efficiency in dual-task walking was observed among older adults who endorsed FOF. Long-term retention of these gains as well as their transfer to proximal and more distal outcomes should be examined in future research. It is noteworthy, however, that mere repetition of walking trials under single task conditions

was not associated with improvement in behavioral performance or neural efficiency irrespective of FOF status. Hence, training should focus on improving dual-task walking performance and its associated neural activity.

Limitations, strengths, and future directions Strengths of this investigation include the novelty of our experimental procedures, careful clinical characterization of the participants and multivariate analyses accounting for several possible confounders including but not limited to history of falls and anxiety. It is noteworthy that evidence for FOF-related neural inefficiency remained even when controlling for group differences in stride velocity. The study design did not include traditional imaging in all participants that would have enabled further insights into underlying brain substrates that might influence neural activity and efficiency of walking. Literature concerning the association of FOF with brain structure and function is very limited. FOF, however, was associated with decreased gray matter volume in the left cerebellum, bilateral inferior occipital gyrus, bilateral superior frontal gyrus, and left supplementary motor area, which are important for motor control, executive functioning and visual processing (Tuerk et al. 2016). Multi-modal neuroimaging revealed greater activation levels in the context of reduced structural brain integrity (Daselaar et al. 2015). Specifically with respect to dual-task walking, we have recently demonstrated that worse white matter integrity was associated with inefficient fNIRS-derived PFC HbO₂ during dual-task walking in older adults (Lucas et al. 2018). It would be of interest to determine whether and how white matter integrity and gray matter volume moderate or possibly mediate the association of FOF with brain activation patterns during walking. The current fNIRS system offers significant advantages in terms of portability and capability to assess cortical activation during active walking. While its limitations in terms of depth of penetration and spatial resolution should be acknowledged our recent MRI fNIRS co-registration study provided further validation for this system among older adults (Chen et al. 2017). Methodological issues that are concerned with the use of fNIRS during walking have been recently reviewed (Vitorio et al. 2017). The current

study has implemented many of the procedures and recommendations detailed in the above review (Vitorio et al. 2017). It should further be emphasized that confounders such as respiration or physical fatigue could not explain the moderating effects of FOF on task and trial-related changes in fNIRS-derived activation patterns and efficiency, notably given that experimental conditions were administered in a random order and had the same walking environment and physical requirements. In addition, the statistical models controlled for covariates that could be viewed as proxies for physical fitness (e.g., GHS index and gait performance). Nonetheless, a review article provided evidence that cardiorespiratory fitness was associated with both brain volume and function (Hayes et al. 2013). With respect to fNIRS, one study reported that cardiorespiratory fitness was associated with increased HbO₂ levels during cognitive task performance among older women (Albinet et al. 2014). It would be of interest to examine in future research whether cardiorespiratory fitness influences fNIRS-derived activation patterns during walking and more specifically the moderating effects of clinically relevant variables such as FOF on these outcomes. HbO₂ is more reliable and sensitive to locomotion-related changes in cerebral oxygenation compared to deoxygenated hemoglobin (Harada et al. 2009) and was thus used in the current study. Nonetheless, we have shown in recent studies (Holtzer et al. 2018a, b; Lucas et al. 2018) that deoxygenated hemoglobin complemented results that utilized HbO₂ as the primary outcome further suggesting that our findings indeed reflected task-related changes in the hemodynamic response and not systemic changes. Including deoxygenated hemoglobin in the current study would have increased the number of outcome measures without providing additional meaningful contribution to knowledge concerning the effect of FOF on cortical control of walking in older adults. Similarly, additional spatiotemporal gait measures could be examined as well. This study, however, focused on the effect of FOF on brain activation patterns during walking. Multiple behavioral measures were used to provide context and strong support to the imaging results. Including additional gait measures would have increased the probability of false discovery rate, notably for

measures that were only secondary to the primary aim of this investigation.

In summary, we provided first evidence that the presence of FOF was associated with inefficient brain activation patterns as well as with practice-related delays in improved PFC efficiency during dual-task walking in community residing older adults. These findings provide several promising avenues for mobility rehabilitation and fall prevention in older adults with FOF.

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Compliance with ethical standards The study was in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Participants signed written informed consents in the first in-person study visit. The Institutional Review Board approved this study.

Conflicts of interest Dr. Izzetoglu has a very minor share in the company that manufactures the fNIRS device used in this study. All other authors have no conflicts of interest to report in relation to the current article.

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