Brain activation in high-functioning older adults and falls

Prospective cohort study

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ABSTRACT

Objective: To determine whether brain activity over the prefrontal cortex measured in real time during walking predicts falls in high-functioning older adults.

Method: We examined166 older persons (mean age 75 years, 51% women) enrolled in a prospective aging study. High-functioning status defined as the absence of dementia or disability with normal gait diagnosed by study clinicians. The magnitude of task-related changes in oxygenated hemoglobin levels over the prefrontal cortex was measured with functional near-infrared spectroscopy during motor (walking at normal pace) and cognitive (reciting alternate letters of the alphabet) single tasks and a dual-task condition (walking while reciting alternate letters of the alphabet). Incident falls were prospectively assessed over a 50-month study period.

Results: Over a mean follow-up of 33.9 ± 11.9 months, 116 falls occurred. Higher levels of prefrontal cortical activation during the dual-task walking condition predicted falls (hazard ratio adjusted for age, sex, education, medical illnesses and general mental status 1.32, 95% confidence interval 1.03–1.70). Neither behavioral outcomes (velocity or letter rate) on the dual task nor brain activation patterns on the single tasks (normal walk or talk alone) predicted falls in this high-functioning sample. The results remained robust after accounting for multiple confounders and for cognitive status, slow gait, previous falls, and frailty.

Conclusions: Prefrontal brain activity levels while performing a cognitively demanding walking condition predicted falls in high-functioning seniors. These findings implicate neurobiological processes early in the pathogenesis of falls. ***Neurology*® 2017;88:191–197**

GLOSSARY

CCMA = Central Control of Mobility in Aging; **CI** = confidence interval; **fNIRS** = functional near-infrared spectroscopy; **HbO_2** = oxygenated hemoglobin; **HR** = hazard ratio; **PFC** = prefrontal cortex; **WWT** = walking while talking.

Emerging evidence supports cognitive impairment as a major contributor to falls in aging.[1,2] Patients with dementia fall more frequently than cognitively intact peers.[1,2] Less is known about the cortical contributions to risk of falls in cognitively normal adults. Among the various cognitive processes, executive functions are strongly linked to falls[2,3] and are subserved by the prefrontal cortex (PFC) and related networks.[4] Worse performance on dual tasks that involve executive functions such as walking while talking (WWT), a mobility stress test,[5,6] predicts falls in older adults without dementia even after accounting for established fall risk factors.[6–9]

Brain activation imaging, which compares the level of brain activity while an individual performs a task to that in a control state,[10] helps reveal subtle alterations in brain function that may precede clinical dysfunction.[4,10] Functional near-infrared spectroscopy (fNIRS) is a noninvasive technology that measures changes in cortical hemodynamic response, an indirect index of neural activity, while an individual performs cognitively demanding activities.[4,11] Using fNIRS, we showed that WWT elicits a greater degree of PFC neural activity while walking.[11,12] Unlike PET and other neuroimaging methods,[4,10] fNIRS has the advantage of studying participants while they actually walk.[4] While compensatory brain activation patterns early in progressive

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neurodegenerative diseases are described,[10] whether brain activation in healthy older adults can predict a multifactorial episodic phenomenon such as falls is unknown.[13]

We selected community-dwelling older adults without dementia and disability to evaluate early brain activation changes that predict falls. Clinical gait abnormalities not only increase risk for falls and dementia but also influence PFC activation on fNIRS.[14–16] Hence, we further restricted our high-functioning cohort to individuals with clinically normal gaits without mobility limitations. We hypothesized that WWT will increase the magnitude of PFC activation on fNIRS in high-functioning older adults, which in turn would predicts falls.

METHODS

Participants. We studied community-residing adults ≥65 years of age participating in the Central Control of Mobility in Aging (CCMA) study.[11,12,17,18] The objective of CCMA is to determine cognitive processes and brain substrates controlling mobility.[11,12,17,18] CCMA procedures were previously described.[11,15,19] Research assistants interviewed potential participants by telephone to assess eligibility and to rule out dementia using cognitive screeners.[11,12,17,18] Individuals who passed the interview were invited to in-person visits at our center.[11,12,17,18] Dementia diagnoses were assigned at consensus case conferences.[20] Exclusion criteria for CCMA were the presence of dementia, inability to walk, active neurologic or psychiatric disorders severe enough to interfere with study assessments, presence of major visual or hearing loss, and recent or planned surgical procedures restricting walking. High-functioning status was defined as the absence of dementia or disability and presence of normal clinical gait. Hence, additional exclusion criteria for this analysis included disability, the need for assistance or assistive devices to walk, and presence of clinical gait abnormalities (see below).[14] As previously described, disability was defined as the need for assistance or inability to perform any of 7 activities of daily living: bathing, walking, rising from a chair, dressing, feeding, toileting, and grooming.[5]

Between June 2011 and December 2013, 349 CCMA participants without dementia or disability underwent baseline fNIRS assessments. After the exclusion of 157 participants with abnormal gaits (66 neurologic and 91 nonneurologic) and 26 without follow-up data, 166 high-functioning adults (mean age 75.0 ± 6.1 years, 51% women) were eligible for this analysis. Falls were prospectively ascertained over a 50-month period until August 2015.

Standard protocol approvals, registrations, and patient consents. All participants provided written informed consent. The Albert Einstein College of Medicine institutional review board approved the study protocol.

Walking paradigm. Gait was assessed with a 4 × 14-ft electronic walkway (Zenometrics LLC, Peekskill, NY).[17] ProtoKinetics Movement Analysis Software was used to derive stride velocity (meters per second) from footfall data.[17] Two single tasks and one dual task were presented in random order to minimize task order and practice effects.[11] In the cognitive single task (Alpha), participants recited alternate letters of the alphabet for 30 seconds while standing. In the motor single task, participants were asked to walk on the walkway at their normal pace for 3 continuous loops consisting of 6 straight segments and 5 turns, starting with the straight segment.[17] For the dual task, WWT,[5,6,21] participants were instructed to walk 3 continuous loops while reciting alternate letters of the alphabet.[19,22] They were instructed to pay equal attention to both tasks to minimize task prioritization.[21] WWT has high reliability and excellent validity for predicting falls.[5,11,21,23] Gait (stride) velocity during normal-pace walking and WWT (both straight segments), as well as correct letter rate per minute during Alpha and WWT, were recorded as previously described.[11,17]

fNIRS assessment. Details regarding fNIRS are provided in our recent publications.[11,15] In brief, fNIRS measures changes in cortical hemodynamic response by monitoring changes in light intensity within near-infrared range.[11] fNIRS can assess brain activity during walking[4,11,15] and can handle motion artifacts.[24,25] fNIRS Imager 1000 (fNIRS Devices LLC, Potomac, MD; sampling rate 2 Hz) was used to assess PFC hemodynamic activity.[11] The fNIRS sensor, consisting of 4 light-emitting diode light sources and 10 photodetectors (16 voxels), was placed using a standard placement over the participants' foreheads.[24]

Preprocessing and signal extraction. To eliminate artifacts due to 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 with a cutoff frequency of 0.14 Hz.[25] The modified Beer-Lambert law was used to calculate oxygenated hemoglobin (HbO_2), deoxygenated hemoglobin, and oxygenation index signals.[25] Only HbO_2 is reported because it is more reliable and sensitive to walking-related cerebral oxygenation changes than the other measures.[11] We used a standing 10-second baseline condition recorded immediately before each of the 3 tasks to determine relative task-related changes in PFC HbO_2 concentrations.[11,12] Participants were asked to stand still and count silently to minimize distractions and to standardize the procedure for the baseline measurement.[11] Levels for the 10-second baseline period for each of the 3 tasks were adjusted to a mean HbO_2 value of zero so that activation levels were normalized to the same level of the individualized baseline condition.[11]

Epoch and feature extraction. All eligible participants completed fNIRS protocols successfully. Individual mean HbO_2 data were extracted separately for each channel for each condition.[12] fNIRS and gait events were synchronized to optimize HbO_2 acquisition and extraction during the tasks.[4,11,15] Average oxygenation level based on 16 channels in each participant over the entire talking (Alpha 30 seconds), normal-pace walking, and WWT tasks was used for analyses.[11,15] We reported excellent internal consistency for HbO_2 measurements in all 3 conditions.[12]

Falls. Falls were defined as unintentionally coming down on the floor or to a lower level not as a result of a major intrinsic or extrinsic event.[26] Research assistants interviewed participants at yearly in-person visits and every 2 to 3 months between annual visits by telephone regarding occurrence of any new falls since the last interview. A standardized questionnaire was used to ensure consistency between interviewers and over the follow-up. If participants reported a fall, interviewers ascertained whether there were any associated injuries (such as fractures). We reported excellent test-retest reliability for fall self-reports using this protocol.[27]

Table 1 Summary of cohort characteristics at baseline

Participants, n	166
Age, mean (SD), y	74.95 (6.07)
Women, n (%)	85 (51.20)
Education, mean (SD), y	14.15 (3.13)
Handedness,[a] n (%)	
Right	146 (87.95)
Left	16 (9.63)
Ambidextrous	4 (2.40)
Comorbidity count (range 0–9), mean (SD)	1.40 (1.1)
Diabetes mellitus, n (%)	25 (15.1)
Hypertension, n (%)	96 (57.8)
Previous myocardial infarction, n (%)	9 (5.4)
Angina, n (%)	6 (3.6)
Congestive heart failure, n (%)	2 (1.2)
Stroke, n (%)	6 (3.6)
Chronic obstructive pulmonary disease, n (%)	12 (7.2)
Arthritis, n (%)	64 (38.6)
Depression, n (%)	13 (7.8)
RBANS total index score, mean (SD)	91.56 (12.00)
Digit Symbol Substitution score, mean (SD)	52.76 (14.25)
Task conditions: clinical outcomes, mean (SD)	
Gait velocity normal-pace walk condition, m/s	1.07 (0.21)
Gait velocity WWT condition, m/s	0.70 (0.18)
Alpha condition, correct letter count/min	33.34 (6.12)
WWT condition, correct letter count/min	34.12 (15.35)
fNIRS prefrontal HbO_2 levels, mean (SD)	
Normal-pace walk condition, SD units	0.08 (0.62)
Alpha condition, SD units	0.68 (0.52)
WWT condition, SD units	0.74 (0.85)

Abbreviations: Alpha: reciting alternate letters while standing for 30 seconds; fNIRS = functional near-infrared spectroscopy; HbO_2 = oxygenated hemoglobin; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; WWT = walking while talking.
[a] Assessed with the Edinburgh Handedness Inventory.

Other covariates. Study clinicians determined whether gaits were normal or abnormal after visual inspection of walking patterns.[14,16] Abnormal gaits were subtyped as nonneurologic (due to causes such as arthritis) or neurologic (unsteady, ataxic, frontal, parkinsonian, neuropathic, hemiparetic, and spastic).[14,16] More details and video web links of abnormal gaits are available.[14,16] This gait assessment has excellent test-retest and interrater reliability.[16] Normal gait was defined as the absence of neurologic or nonneurologic gait abnormalities.

The following covariates were assessed at baseline. General mental status was assessed with the Repeatable Battery for the Assessment of Neuropsychological Status total score.[28] We also included the Digit Symbol Substitution test, a timed test assessing executive functions, attention, and processing speed, to assess cognitive domains linked to falls and WWT.[3,29] A comorbidity count (range 0–9) was obtained by the study clinician from the presence or absence of diabetes mellitus, arthritis, hypertension, depression, chronic lung disease, stroke, chronic heart failure, angina, and myocardial infarction.[8,20]

Statistical analysis. Descriptive statistics were used to examine baseline characteristics. The effect of the magnitude of HbO_2 levels during WWT on recurrent falls during follow-up was studied with the Andersen-Gil extension of the Cox model,[30] which is recommended by experts as appropriate to analyze recurrent fall events[31,32] and makes no assumptions about distribution of the outcome. Robust sandwich covariance estimates accounted for correlations among multiple events within the same participant. Associations were reported as hazard ratios (HRs) with 95% confidence intervals (CI). Model 1 was adjusted for age, sex, education, comorbidity count, and Repeatable Battery for the Assessment of Neuropsychological Status score. We also examined laterality effects (right vs left channels) on falls.

We conducted secondary analyses to account for potential confounders. To examine whether brain activation levels during WWT provided incremental value for predicting falls over brain activation levels in single tasks, we adjusted model 1 for HbO_2 levels during normal walking and Alpha conditions (model 2). Although we accounted for general mental status in this sample without dementia, we also adjusted for Digit Symbol Substitution test scores (model 3).[3,29] To test whether WWT PFC activation levels were an early marker of falls compared to behavioral markers, we reran model 1 adjusting for WWT velocity (model 4) and correct letter rate.

To account for the possibility that participants who walk slowest explained our findings, we reran model 1 excluding 15 with slow gait defined with a widely used normal-pace velocity cut score of 0.80 m/s.[33] The sample size precluded examination of higher cut scores. In addition, our continuous loop protocol includes slower turns, and the corresponding velocity walking straight will be higher.[17] We repeated model 1 excluding 6 participants with instrumental activity limitations (taking medications 1, writing checks 2, and planning and organizing activities 3). Finally, because falls may influence baseline brain activity (reverse causation), we redid analyses excluding 21 participants who fell in the 12 months before baseline. Proportional hazards assumptions of models were examined by testing interactions between time and predictors in models and were adequately met. Statistical analyses were done with SAS 9.4 (SAS Institute Inc, Cary, NC).

RESULTS Our high-functioning cohort had low comorbidity (1.4 illnesses). While 38.6% had arthritis, it was not associated with abnormal gait. Two participants reported head injuries unrelated to falls. Study clinicians did not find neurologic signs of stroke (although 6 self-reported strokes) or other neurologic diseases that may limit mobility. Velocity was lower in WWT than normal walking (table 1), demonstrating a dual-task effect. Letter rate was not different between the WWT and Alpha conditions.

Over a mean follow-up of 33.9 ± 11.9 months, 71 participants reported 116 falls (76% occurred outdoors and 24% indoors). The incidence rate of falls was 25 per 100 person-years. Median time to the first fall was 19.5 months. Thirty-four participants fell more than once. In this high-functioning cohort,

most falls were mild, with only 6 (5.2%) resulting in fractures. Higher PFC activation levels on fNIRS during WWT (HR corresponding to a 1-unit increase in oxygenation level 1.32, 95% CI 1.03–1.70) predicted falls (table 2).

Older age and female sex among the covariates included in model 1 predicted falls. However, there was no interaction between WWT activation levels and sex in model 1 ($p = 0.60$).

Left-sided (HR 1.60, 95% CI 1.15–2.24) but not right-sided (HR 0.78, 95% CI 0.54–1.14) fNIRS channels predicted falls. Associations of individual fNIRS channels were not reported to avoid multiple comparisons in the absence of specific predictions.

Association of HbO_2 levels during WWT with falls in model 1 was unchanged by the exclusion of persons with slow gait (HR 1.45, 95% CI 1.13–1.84), instrumental activity limitations (HR 1.32, 95% CI 1.03–1.69), or prior falls (HR 1.32, 95% CI 1.01–1.74).

WWT (0.74 SD units) and Alpha (0.68) conditions elicited higher PFC activation than normal walking (0.04), corroborating their greater cognitive demands (table 1). However, when fNIRS activation levels in all 3 conditions were entered together, PFC activation during WWT but not Alpha predicted falls (model 2, table 2). The association of PFC activation during WWT with falls was unchanged when adjusted for Digit Symbol Substitution test scores (model 3). The association of WWT activation with falls remained in model 4, but WWT velocity was not significant. When adjusted for WWT letter rate in model 4, the association of WWT activation with falls was unchanged (HR 1.34, 95% CI 1.05–1.71), but WWT letter rate was not significant (HR 0.99, 95% CI 0.98–1.01).

The association of WWT activation with falls in model 1 was similar after the exclusion of 6 cases with mild cognitive impairment syndrome[34] (HR 1.33, 95% CI 1.03–1.72) or 7 with frailty[5,35] (HR 1.36, 95% CI 1.06–1.74). There was a low rate of other adverse events over the 50-month study period; 5 participants developed dementia, 2 became disabled, and 2 died. Excluding individuals with these incident events from model 1 did not change the findings (HR 1.38, 95% CI 1.06–1.80).

DISCUSSION Our study shows that brain activity level during a cognitively demanding walking task predicts falls in high-functioning community-dwelling older adults; each 1-SD increase in the intensity of prefrontal activation during WWT measured by fNIRS was associated with a 32% increased risk of falls. The association remained even after accounting for well-established fall risk factors. Our finding builds on our behavioral studies that showed that WWT velocity predicted falls in older adults without dementia and disability.[6,7] However, these studies did not exclude individuals with gait abnormalities or slow gait.[6,7] While we used cognitive, functional, and gait performance to define high-functioning status, these criteria did not result in a sample free of diseases or clinical impairments. Nonetheless, accounting for

Table 2 Hazard ratio (HR) for risk of falls

	HR (95% CI)			
Variables	**Model 1**	**Model 2**	**Model 3**	**Model 4**
WWT: HbO_2 levels, SD units	1.32 (1.01–1.70)	1.31 (1.00–1.45)	1.32 (1.02–1.69)	1.37 (1.05–1.79)
Age	1.04 (1.01–1.08)	1.05 (1.01–1.08)	1.05 (1.01–1.08)	1.06 (1.02–1.11)
Female	2.05 (1.26–3.27)	2.05 (1.28–3.39)	1.99 (1.23–3.20)	2.24 (1.33–3.77)
Education	0.98 (0.92–1.04)	0.98 (0.92–1.04)	0.98 (0.92–1.05)	0.99 (0.93–1.05)
Global Health Scale score	1.07 (0.89–1.28)	1.07 (0.89–1.28)	1.08 (0.90–1.30)	1.02 (0.85–1.23)
RBANS score	1.00 (0.99–1.02)	1.00 (0.99–1.02)	1.00 (0.98–1.02)	1.00 (0.98–1.02)
Normal-pace walking: HbO_2 levels, SD units		1.06 (0.78–1.45)		
Alpha: HbO_2 levels, SD units		0.99 (0.71–1.39)		
Digit Symbol Substitution test score			1.00 (0.98–1.02)	
WWT velocity				1.01 (0.99–1.03)

Abbreviations: Alpha = Reciting alternate alphabets while standing for 30 seconds; CI = confidence interval; HbO_2 = oxygenated hemoglobin; RBANS = total scaled index score on the Repeatable Battery for the Assessment of Neuropsychological Status; WWT = walking while talking.
Model 1: adjusted for age, sex, education, comorbidity count, and RBANS.
Model 2: adjusted for all covariates in model 1 and HbO_2 levels on normal-pace walking and Alpha conditions.
Model 3: adjusted for all covariates in model 1 and Digit Symbol Substitution test scores.
Model 4: adjusted for all covariates in model 1 and WWT velocity.

cognitive and physical frailty and diseases did not change results.

Our findings are in line with studies that have reported increased brain activity in older adults while performing cognitively demanding activities.[4,10,36] Higher brain activation was reported in persons at risk for Alzheimer disease, which has a long preclinical phase.[10] However, very little is known about the neural substrates of multifactorial episodic phenomenon such as falls in healthy adults.[13] Our findings suggest that changes in brain activity may precede behavioral abnormalities on mobility tasks and implicate neurobiological processes early in the pathogenesis of falls. The underlying biological mechanisms and the influence of pathologic processes such as cerebrovascular or neurodegenerative diseases on brain activity associated with falls need to be examined.

Gait performance in normal and WWT conditions predicts falls in the general elderly population.[6,7,9,27] However, when restricted to high-functioning seniors, neither WWT behavioral outcomes (velocity or letter rate) nor brain activation during single tasks (normal walk and talk alone) predicted falls. Furthermore, excluding individuals with slow gait strengthened the association of brain activity with falls. These observations support the hypothesis that brain activity predictive of falls may precede clinical dysfunction on complex walking conditions (such as WWT behavioral measures) and may not be elicited by less cognitively demanding conditions such as normal-pace walking.

The additional processing required for cognitively demanding tasks such as WWT may be achieved by altering the magnitude (increasing or sustaining neural activation levels) or pattern (recruiting more neural tissue) of brain activity.[10,15] Our findings are consistent with compensatory reallocation models suggesting that in at-risk older individuals increased PFC activation brings task performance to near-normal levels.[37] Furthermore, we reported that high PFC activation was sustained the whole duration of the WWT task in our participants but not during the more automatic normal walking condition.[11] While our primary focus was on the magnitude of PFC activity, our exploratory analysis also indicates a laterality effect (pattern); left but not right fNIRS channels were associated with falls. Reallocation of resource to areas involved in cognitive processing during WWT may compromise gait and increase fall risk. Activation of left-sided PFC fNIRS channels on other dual tasks has been reported.[36] Although left-sided fNIRS channels overlie speech areas, PFC activation during talking alone was not associated with falls. Excluding 16 left-handed persons did not change results (data not shown).

The rigorous phenotyping to identify high-functioning persons, prospective fall ascertainment, and reliable clinical and statistical procedures are strengths.[11,15,16,27,31,32] The psychometrics,[8,21] reliability,[23] clinical validity,[5–7] and neurobiological correlates[11,12,18,38] of our WWT task are well established. Support for the validity of our high-functioning definition is provided by the low comorbidity count, low rate of incident adverse events, and low prevalence of mild cognitive impairment (3.6%)[34] and frailty (4.2%)[5,35] in the sample who qualified for this analysis. Moreover, mean gait velocity on normal walk was higher in this sample (1.07 m/s) compared to that reported in the overall CCMA cohort (0.79 m/s) using the same walking protocol and equipment.[11] High reliability of falls recall over short intervals in our previous study and over longer intervals in other cohorts was reported.[27,39] Potential limitations are noted. We focused on the PFC on the basis of the relationships of this brain area established with mobility in previous studies.[22] In the same cohort, we reported that PFC was associated with WWT in an fMRI study of imagined walking[38] and in a resting-state fMRI study of the correlates of actual walking.[18] We also reported that a cognitive remediation intervention targeting PFC-based cognitive processes improved WWT performance.[40] We acknowledge that other brain areas not examined in our study are implicated in gait control and may have a role in increasing fall risk[4] and should be studied. While our clinical gait assessment is reliable, very mild clinical signs may be missed. Neurologic gaits are a marker of brain disease[14,16] and can influence PFC activation patterns on fNIRS.[15] It is possible that the compensatory brain activity may not be seen in later clinical stages when gait abnormalities occur.[2,4,15,16,38] While we reported high correlation between gait velocity during straight and loop protocols,[11] negotiating turns might be more cognitively demanding. However, this hypothesis is not supported by lower PFC activation during the normal walking condition that also had loops. Given the observational design, our findings do not establish causality but indicate that WWT brain activity changes precede falls.

High-functioning older persons at risk for falls have alterations in brain activity patterns without obvious behavioral manifestations, which can be used to assess fall risk and to implicate neural processes early in the pathogenesis of falls. Further studies are needed to establish the underlying biological and physiologic processes and to identify interventions that may influence brain activity during complex walking conditions as a prelude to preventing falls.

AUTHOR CONTRIBUTIONS

Verghese was responsible for study concept, acquisition of data, initial draft, and analysis of data. Holtzer and Verghese obtained funding for the study. Izzetoglu was responsible for processing the fNIRS data. Wang was responsible for content analysis of data. Ayers, Izzetoglu, and Holtzer were responsible for interpretation of data and revising draft for content.

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DISCLOSURE

J. Verghese, C. Wang, and E. Ayers report no disclosures relevant to the manuscript. M. Izzetoglu has a very minor share in the company that manufactures the fNIRS device used in this study. R. Holtzer reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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REFERENCES

1. Montero-Odasso M, Verghese J, Beauchet O, Hausdorff JM. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. J Am Geriatr Soc 2012;60:2127–2136.
2. Sheridan PL, Hausdorff JM. The role of higher-level cognitive function in gait: executive dysfunction contributes to fall risk in Alzheimer's disease. Dement Geriatr Cogn Disord 2007;24:125–137.
3. Kearney FC, Harwood RH, Gladman JR, Lincoln N, Masud T. The relationship between executive function and falls and gait abnormalities in older adults: a systematic review. Dement Geriatr Cogn Disord 2013;36:20–35.
4. Holtzer R, Epstein N, Mahoney JR, Izzetoglu M, Blumen HM. Neuroimaging of mobility in aging: a targeted review. J Gerontol A Biol Sci Med Sci 2014;69:1375–1388.
5. Verghese J, Holtzer R, Lipton RB, Wang C. Mobility stress test approach to predicting frailty, disability, and mortality in high-functioning older adults. J Am Geriatr Soc 2012;60:1901–1905.
6. Verghese J, Buschke H, Viola L, et al. Validity of divided attention tasks in predicting falls in older individuals: a preliminary study. J Am Geriatr Soc 2002;50:1572–1576.
7. Ayers EI, Tow AC, Holtzer R, Verghese J. Walking while talking and falls in aging. Gerontology 2014;60:108–113.
8. Holtzer R, Verghese J, Xue X, Lipton RB. Cognitive processes related to gait velocity: results from the Einstein Aging Study. Neuropsychology 2006;20:215–223.
9. Beauchet O, Annweiler C, Dubost V, et al. Stops walking when talking: a predictor of falls in older adults? Eur J Neurol 2009;16:786–795.
10. Bookheimer SY, Strojwas MH, Cohen MS, et al. Patterns of brain activation in people at risk for Alzheimer's disease. N Engl J Med 2000;343:450–456.
11. Holtzer R, Mahoney JR, Izzetoglu M, Wang C, England S, Verghese J. Online fronto-cortical control of simple and attention-demanding locomotion in humans. Neuroimage 2015;112:152–159.
12. Holtzer R, Mahoney JR, Izzetoglu M, Izzetoglu K, Onaral B, Verghese J. fNIRS study of walking and walking while talking in young and old individuals. J Gerontol A Biol Sci Med Sci 2011;66:879–887.
13. Sorond FA, Cruz-Almeida Y, Clark DJ, et al. Aging, the central nervous system, and mobility in older adults: neural mechanisms of mobility impairment. J Gerontol A Biol Sci Med Sci 2015;70:1526–1532.
14. Verghese J, Ambrose AF, Lipton RB, Wang C. Neurological gait abnormalities and risk of falls in older adults. J Neurol 2010;257:392–398.
15. Holtzer R, Verghese J, Allali G, Izzetoglu M, Wang C, Mahoney JR. Neurological gait abnormalities moderate the functional brain signature of the posture first hypothesis. Brain Topogr 2016;29:334–343.
16. Verghese J, Lipton RB, Hall CB, Kuslansky G, Katz MJ, Buschke H. Abnormality of gait as a predictor of non-Alzheimer's dementia. N Engl J Med 2002;347:1761–1768.
17. England SE, Verghese J, Mahoney JR, Trantzas C, Holtzer R. Three-level rating of turns while walking. Gait Posture 2015;41:300–303.
18. Yuan J, Blumen HM, Verghese J, Holtzer R. Functional connectivity associated with gait velocity during walking and walking-while-talking in aging: a resting-state fMRI study. Hum Brain Mapp 2015;36:1484–1493.
19. Holtzer R, Wang C, Verghese J. Performance variance on walking while talking tasks: theory, findings, and clinical implications. Age 2014;36:373–381.
20. Holtzer R, Verghese J, Wang C, Hall CB, Lipton RB. Within-person across-neuropsychological test variability and incident dementia. JAMA 2008;300:823–830.
21. Verghese J, Kuslansky G, Holtzer R, et al. Walking while talking: effect of task prioritization in the elderly. Arch Phys Med Rehabil 2007;88:50–53.
22. Holtzer R, Wang C, Verghese J. The relationship between attention and gait in aging: facts and fallacies. Motor Control 2012;16:64–80.
23. Brandler TC, Oh-Park M, Wang C, Holtzer R, Verghese J. Walking while talking: investigation of alternate forms. Gait Posture 2012;35:164–166.
24. Ayaz H, Izzetoglu M, Platek SM, et al. Registering fNIR data to brain surface image using MRI templates. Conf Proc IEEE Eng Med Biol Soc 2006;1:2671–2674.
25. Izzetoglu M, Chitrapu P, Bunce S, Onaral B. Motion artifact cancellation in NIR spectroscopy using discrete Kalman filtering. Biomed Eng Online 2010;9:16.
26. Gibson MJ, Andres RO, Isaacs B, Radebaugh T, Wormpetersen J. The prevention of falls in later life: a report of the Kellogg-International-Work-Group on the prevention of falls by the Elderly. Dan Med Bull 1987;34:1–24.
27. Verghese J, Holtzer R, Lipton RB, Wang C. Quantitative gait markers and incident fall risk in older adults. J Gerontol A Biol Sci Med Sci 2009;64:896–901.
28. Randolph C, Tierney MC, Mohr E, Chase TN. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. J Clin Exp Neuropsychol 1998;20:310–319.
29. Muir SW, Gopaul K, Montero Odasso MM. The role of cognitive impairment in fall risk among older adults: a systematic review and meta-analysis. Age Ageing 2012;41:299–308.
30. Andersen P, Gil R. Cox's regression model for counting processes: a large sample study. Ann Stat 1982;10:1100–1120.

31. Donaldson MG, Sobolev B, Cook WL, Janssen PA, Khan KM. Analysis of recurrent events: a systematic review of randomised controlled trials of interventions to prevent falls. Age Ageing 2009;38:151–155.
32. Therneau TM, Hamilton SA. rhDNase as an example of recurrent event analysis. Stat Med 1997;16:2029–2047.
33. Cesari M, Kritchevsky SB, Penninx BWHJ, et al. Prognostic value of usual gait speed in well-functioning older people: results from the Health, Aging and Body Composition Study. J Am Geriatr Soc 2005;53:1675–1680.
34. Petersen RC, Roberts RO, Knopman DS, et al. Mild cognitive impairment: ten years later. Arch Neurol 2009;66:1447–1455.
35. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–M156.
36. Lague-Beauvais M, Fraser SA, Desjardins-Crepeau L, et al. Shedding light on the effect of priority instructions during dual-task performance in younger and older adults: a fNIRS study. Brain Cogn 2015;98:1–14.
37. Stern Y. Cognitive reserve. Neuropsychologia 2009;47:2015–2028.
38. Blumen HM, Holtzer R, Brown LL, Gazes Y, Verghese J. Behavioral and neural correlates of imagined walking and walking-while-talking in the elderly. Hum Brain Mapp 2014;35:4090–4104.
39. Cigolle CT, Ha J, Min LC, et al. The epidemiologic data on falls, 1998-2010: more older Americans report falling. J JAMA Intern Med 2015;175:443–445.
40. Verghese J, Mahoney J, Ambrose AF, Wang C, Holtzer R. Effect of cognitive remediation on gait in sedentary seniors. J Gerontol A Biol Sci Med Sci 2010;65:1338–1343.