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Stress and gender effects on prefrontal cortex oxygenation levels assessed during single and dual-task walking conditions

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Abstract

The ability to walk is critical for functional independence and wellbeing. The pre-frontal cortex (PFC) plays a key role in cognitive control of locomotion, notably under attention-demanding conditions. Factors that influence brain responses to cognitive demands of locomotion, however, are poorly understood. Herein we evaluated the individual and combined effects of gender and perceived stress on stride velocity and PFC Oxygenated Hemoglobin (HbO₂) assessed during single and dual-task walking conditions. The experimental paradigm included three tasks: a) Normal-Walk (NW); b) Cognitive Interference (Alpha); c) Walk-While-Talk (WWT). An instrumented walkway was used to assess stride velocity in NW and WWT conditions. Functional Near-Infrared-Spectroscopy (fNIRS) was used to quantify PFC HbO₂ levels during NW, Alpha and WWT. Perceived task-related stress was evaluated with a single 11-point scale item. Participants were community residing older adults (age=76.8±6.7ys; %female=56). Results revealed that higher perceived stress was associated with greater decline in stride velocity from single to dual-task conditions among men. Three-way interactions revealed that gender moderated the effect of perceived stress on changes in HbO₂ levels comparing WWT to NW and Alpha. Attenuation in the increase in HbO₂ levels, in high compared to low perceived stress levels, from the two single task conditions to WWT was observed only in men.

Conclusion—Older men maybe more vulnerable to the effect of perceived stress on the change in PFC oxygenation levels across walking conditions that vary in terms of cognitive demands. These findings confer important implications for assessment and treatment of individuals at risk of mobility impairments.

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Keywords

fNIRS; Executive Functions; Prefrontal Cortex; Stress; Locomotion

Introduction

Locomotion is critical for functional independence and sense of wellbeing. Poor walking has been linked to increased risk of adverse outcomes including but not limited to dementia (Verghese *et al.*, 2002; Verghese *et al.*, 2014) and mortality (Studenski *et al.*, 2011). Locomotion and cognition, specifically the executive functions and their underlying brain substrates, are interrelated (Holtzer *et al.*, 2014c). Moreover, poor performance on a well-established attention demanding dual-task walking paradigm predicted incident disability and mortality even after adjustments for single task walking speed (Verghese *et al.*, 2012). A recent review of neuroimaging studies of mobility asserted, however, that little is known about the functional brain correlates of walking because locomotion cannot be assessed in real time with conventional neuroimaging methods (Holtzer *et al.*, 2014a). Using functional Near Infrared Spectroscopy (fNIRS), a relatively limited number of studies overcame this limitation revealing that the frontal cortex and related circuits were involved in cognitive control of walking, running, and balance in healthy individuals, (Miyai *et al.*, 2001; Mihara *et al.*, 2007; Suzuki *et al.*, 2008) older adults (Harada *et al.*, 2008), and stroke patients (Mihara *et al.*, 2007). Recently, fNIRS was applied to a large cohort of older adults documenting the pivotal role of the prefrontal cortex (PFC) in cognitive control of locomotion, notably when attention demands were increased under dual-task walking conditions (Holtzer *et al.*, 2015).

Research concerning biological and psychological factors that influence the functional involvement of the brain in walking, however, is scarce. Such knowledge is essential to translating group level relations between brain and locomotion to clinical risk assessment and intervention procedures for individuals at risk of developing mobility impairments and disability. Hence, the current study was designed to determine the individual and combined effects of perceived stress and gender on brain oxygenation patterns during active locomotion assessed under single and dual-task conditions.

Perceived Stress Executive Functions Locomotion and the PFC

Stress is defined as a psychological reaction to demands that are perceived by the individual as threatening or too difficult to fulfill. Perceived stress represents appraisals of person-environment interactions and has been associated with adverse physical health outcomes in older adults (Rueggeberg *et al.*, 2012). Higher levels of perceived stress correlated with worse performance on tasks of selective and divided attention (Vedhara *et al.*, 2000) and similarly, among young adults, increased environmental stress was associated with worse performance on a divided attention task (Petrac *et al.*, 2009). Furthermore, the detrimental effect of stress on working memory was stronger at high workload levels, suggesting that more demanding tasks may serve as an additional stressor in experimental settings (Oei *et al.*, 2006; Robinson *et al.*, 2008). A robust body of empirical evidence from both animal and human studies suggests that the brain is particularly sensitive to stress during old age

(Lupien *et al.*, 2009). Stress triggers activation of the hypothalamic-pituitary-adrenal (HPA) axis, a coordinated physiological response involving autonomic, neuroendocrine, metabolic, and immune system components. While the impact of age on HPA-axis functioning is still not well understood, some studies have reported that older adults show larger cortisol release in response to stress compared to adults, adolescents, and children (Gotthardt *et al.*, 1995; Kudielka *et al.*, 2004). A review article provided converging evidence that stress has detrimental effects on the architecture and functionality of the PFC (Arnsten, 2009). Moreover, the PFC may also have an important role in coordinating physiologic and behavioral responses to stressful situations (McKlveen *et al.*, 2015). Indeed, a recent study (Gartner *et al.*, 2014) demonstrated that working memory-related frontal theta activity decreased under stress, corresponding to behavioral performance decrements during more difficult task conditions. In addition, functional neuroimaging studies have found stress-related deactivation in the dorsal and ventral prefrontal cortex and orbitofrontal cortices (Dedovic *et al.*, 2009b), though the directionality of activation patterns varied as a function of brain region and gender (for review see (Dedovic *et al.*, 2009a). The PFC, as described earlier, subserves higher order cognitive abilities that include dual-task walking performance (Holtzer, Mahoney, et al., 2015; Holtzer, Verghese, et al., 2015). However, the effect of perceived stress on locomotion and dual-task walking has not been reported to our knowledge. It is noteworthy, however, that a combination of personality traits that included high neuroticism and low extraversion was associated with greater dual-task walking costs (LeMonda *et al.*, 2015). Hence, extrapolating from the extant literature concerning the negative effect of stress on executive functions and PFC functionality would suggest that higher levels of perceived stress may be associated with worse walking and reduced PFC oxygenation under dual-task conditions. Additionally, the influence of gender on this relationship should be carefully considered as responses to both perceived and physiological stressors may differ between men and women (Geary & Flinn, 2002).

Gender Executive Functions Locomotion and the PFC

Gender differences exist in quantitative gait parameters when assessed under normal walk (Oh-Park *et al.*, 2010) and dual-task walking conditions (MacAulay *et al.*, 2014) with men demonstrating greater gait variability than women (Hollman *et al.*, 2011) suggesting they may experience more difficulty in negotiating competing cognitive demands. Furthermore, gender also influences performance (Beeri *et al.*, 2006; Munro *et al.*, 2012; Castonguay *et al.*, 2015) and decline (McCarrey *et al.*, 2016) on neuropsychological tests, an effect that maybe attributed to functional and/or structural differences in brain regions that are involved in cognitively demanding tasks. Indeed, men experience more gray matter degeneration compared to women in the PFC (Curiati *et al.*, 2009) especially in the dorsolateral region (Raz, 1993). In this context it is noteworthy that overall PFC oxygenated hemoglobin (HbO₂) levels during walking were higher in men than women (Holtzer *et al.*, 2015; Holtzer *et al.*, 2016a).

Current Study

Using an instrumented walkway and fNIRS, the current study was designed to evaluate the individual and combined effects of gender and perceived stress on the change in stride velocity and PFC HbO₂ levels from Normal-Walk (NW) to Walk-While-Talk (WWT)

conditions in a large cohort of community residing non-demented older adults. Perceived task-related stress was evaluated with a single 11-point scale item. Based on the existing literature concerning the negative effect of stress on executive functions and PFC functionality we hypothesized that higher task-related perceived stress would be associated with an attenuated increase in HbO₂ levels and with a greater decline in stride velocity from single to dual-task walking. Whereas females demonstrated overall lower oxygenation levels during walking compared to males the effect of gender on walking-task-related changes in oxygenation levels has not been reported. Furthermore, while some evidence suggests that the PFC maybe more vulnerable to the effect of aging in men associations between performance on tasks of executive functions and gender have been mixed. Hence, we examined whether gender moderated the effect of task on stride velocity and PFC oxygenation levels. Finally, we designed this investigation to, a priori, determine (via 3-way interactions of gender $\times$ perceived stress $\times$ task) whether gender moderated the effect of perceived stress on study outcomes.

Materials and Methods

Participants—Participants were community residing older adults (age 65yrs) enrolled in “Central Control of Mobility in Aging” (CCMA), a cohort study designed to determine cognitive and brain predictors of mobility. CCMA procedures were described in previous publications (Holtzer *et al.*, 2014b). Potential participants were identified from population lists of lower Westchester County, NY. Structured telephone interviews were administered to obtain verbal assent and determine initial eligibility including screens for dementia (Lipton *et al.*, 2003; Galvin *et al.*, 2006) and assessments of medical history and currently physical function. Individuals who passed the telephone interview were invited to two annual in-person study visits during which trained research assistants administered comprehensive neuropsychological, psychological, and mobility assessments. The fNIRS dual-task walking paradigm was administered during the first day of testing. The study clinician conducted structured neurological examinations. Dementia diagnoses (Association, 2000) were determined via consensus diagnostic case conferences (Holtzer *et al.*, 2008). Exclusion criteria were: current or history of severe neurological or psychiatric disorders, inability to ambulate independently, significant loss of vision and/or hearing that threatened the validity of the testing procedures, and recent or anticipated medical procedures that may affect ambulation. *The study is in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the Review Board of Albert Einstein College of Medicine. Written informed consents were obtained in-person and approved by the institutional Review Board.*

Test Procedures and Equipment

Quantitative Gait Assessment—Zenometrics. A 4 $\times$ 14 foot Zeno electronic walkway using ProtoKinetics Movement Analysis Software (PKMAS) was utilized to assess quantitative measures of gait (Zenometrics, LLC; Peekskill, NY). Gait measures were based on the location and mathematical parameters between footfalls on the instrumented walkway (i.e., geometric arrangement, spatial and temporal relationship, relative pressures). Split-half

intra-class correlations (ICC) for gait velocity in NW and WWT were greater than 0.95 revealing excellent internal consistency (Holtzer *et al.*, 2015).

Walking Paradigm—There were two single task conditions: 1) Normal Pace Walk (NW) and 2) Cognitive (Alpha). In NW participants were asked to walk around the electronic walkway at their “normal pace” for three consecutive loops. In Alpha, participants were required to stand still while reciting alternate letters of the alphabet starting with the letter B for 30-sec out loud. In Walk-While-Talk (WWT) participants were instructed to walk around the walkway for three consecutive loops at their normal pace while reciting alternate letters of the alphabet starting with the letter ‘B’. Participants were instructed to pay equal attention to both tasks (Holtzer *et al.*, 2015; Holtzer *et al.*, 2016a; Holtzer *et al.*, 2016b). WWT is a more ecologically valid mobility assessment that approximates real world tasks. Specifically, poor WWT performance was associated with increased risk of incident falls (Ayers *et al.*, 2014) as well as frailty, disability and mortality in older adults (Verghese *et al.*, 2012). The three test conditions were presented in a counterbalanced order using a Latin-square design.

fNIRS system—Validation studies with this fNIRS system have been reported (Izzetoglu, 2004a; Izzetoglu *et al.*, 2004b; Izzetoglu *et al.*, 2005a; Platek *et al.*, 2005b). fNIRS measures changes in cortical oxygenated hemoglobin (HbO₂) levels using light–tissue interaction properties of light within the near infrared range. fNIRS has been validated against traditional neuroimaging methods and is better able to handle motion artifacts (Izzetoglu *et al.*, 2005a; Cooper *et al.*, 2012). Changes in hemodynamic activity in the PFC were assessed using fNIRS Imager 1000 (fNIRS Devices, LLC, Potomac, MD). The system collects data at a sampling rate of 2Hz. The fNIRS sensor consists of 4 LED light sources and 10 photodetectors, which cover the forehead using 16 voxels, with a source-detector separation of 2.5 cm. The light sources on the sensor (Epitex Inc. type L4X730/4X805/4X850-40Q96-I) contain three built-in LEDs having peak wavelengths at 730, 805, and 850 nm, with an overall outer diameter of 9.2 ± 0.2 mm. The photodetectors (Bur Brown, type OPT101) are monolithic photodiodes with a single supply transimpedance amplifier. We implemented a standard sensor placement procedure (Ayaz *et al.*, 2006). Given the sensitivity of the fNIRS recording device, the lighting in the test room was reduced such that the mean illumination on the forehead was approximately 150 lux, which is about one-third of typical office lighting. Figure 1 provides a visual depiction of the apparatus and environment in which fNIRS and PKMAS devices are used to conduct concurrent brain imaging and gait assessments, respectively.

Preprocessing and Hemodynamic Signal Extraction—Raw data at 730 and 850nm 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 850nm were low-pass filtered with a finite impulse response filter of cut-off frequency at 0.14Hz (Izzetoglu *et al.*, 2005a; Izzetoglu *et al.*, 2010).

Motion artefacts: While fNIRS methodology offers important advantages, motion artefacts remain an issue that should be acknowledged. Several algorithms were developed by different groups to remove motion artefacts from fNIRS measurements; most of them

designed to suppress the sensor movement noise (Izzetoglu *et al.*, 2005a; Izzetoglu *et al.*, 2010; Scholkmann *et al.*, 2010; Cooper *et al.*, 2012; Sweeney *et al.*, 2012; Brigadoi *et al.*, 2014). In the current study we were able to identify saturated and dark current measurements from the signal levels using the methodology described in previous publications (Izzetoglu *et al.*, 2011; Leon-Dominguez *et al.*, 2014; McKendrick *et al.*, 2014). We were also able to identify some of the high frequency noise that may be coming from the cable movement or from the sensor movement by using a unique feature in the current fNIRS system that provides dark current measurements (Izzetoglu *et al.*, 2011; Rodrigo *et al.*, 2014). In addition, motion artefacts can result from head movement. Distinguishing noise from real brain signal in data that contain motion artefacts remains, however, a challenge. Therefore, instead of making assumptions and suppressing this type of noise we eliminated these data (4% of the entire data collected) by visual inspection of an expert fNIRS data analyst (M. Izzetoglu). Oxygenated hemoglobin (HbO₂), deoxygenated hemoglobin (Hb), oxygenation or oxygen index (HbO₂-Hb) and total hemoglobin (HbO₂+Hb) signals can be calculated **from the low-pass filtered raw intensity measurements** at 730 and 850 nm using modified Beer-Lambert law (Izzetoglu *et al.*, 2005a; Izzetoglu *et al.*, 2010). In addition to restricting the number of dependent measures, HbO₂ is more reliable and sensitive to locomotion-related changes in cerebral oxygenation (Hoshi *et al.*, 2001; Miyai *et al.*, 2001; Strangman *et al.*, 2003; Harada *et al.*, 2009) and was thus used in the current study. Proximal baseline conditions ranging from 5-15 seconds have been previously reported in fNIRS studies (Izzetoglu *et al.*, 2007). Consistent with our prior studies (Holtzer *et al.*, 2015; Mahoney *et al.*, 2015; Holtzer *et al.*, 2016a; Holtzer *et al.*, 2016b) separate proximal 10-second baselines, administered prior to each experimental condition, were used to determine relative changes HbO₂ concentrations in NW, Alpha and WWT.

Epoch and Feature extraction—Individual mean HbO₂ data were extracted separately in NW and WWT. For Alpha, mean HbO₂ values, which were based on the entire 30 sec task duration, were used for feature extraction and comparison. We implemented additional steps that were designed to optimize the acquisition of task related HbO₂ in NW and WWT by synchronizing fNIRS and gait events. A central “hub” computer with E-Prime 2.0 software sent synchronized triggers to both the fNIRS system and PKMAS. The fNIRS acquisition software received numerical triggers from E-prime that are each indicative of a unique condition and represented the beginning or end of either a baseline or test condition. A second level post-processing time synchronization method was implemented using the first recorded foot contact with the walkway as a time stamp. The recording of fNIRS was terminated at the end of the 6th and final straight walk. This end point was determined algorithmically by PKMAS as previously described (England *et al.*, 2015). HbO₂ data in NW and WWT within this range are extracted and used for comparisons between task conditions.

Reliability of fNIRS measurements—Internal consistency of HbO₂ measurements, determined by split-half intra-class correlations within each task, was excellent for NW (0.830), Alpha (0.864) and WWT (0.849) (Holtzer *et al.*, 2015).

Level of stress—Level of task-related stress was assessed using a single 11-point scale item. Specifically, participants were asked to quantify how stressful was the experience of the walking paradigm with zero indicating no stress at all and 10 being the highest level of stress.

Other Covariates

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was used to assess overall level of cognitive function (Duff *et al.*, 2008). A disease comorbidity summary score (range 0–10) was used to characterize overall levels of health (Holtzer *et al.*, 2006; Holtzer *et al.*, 2008). The Beck Anxiety Inventory (Beck *et al.*, 1988) (BAI) a 21-item self-report scale (range 0–63) was used to assess the severity of anxiety symptoms. The BAI has adequate psychometric properties in older adults (Therrien & Hunsley, 2012) allowing for assessment of both cognitive and somatic anxiety (Schoen & Holtzer, 2016).

Statistical Analysis

Linear mixed effects and Generalized Estimating Equations (GEE) Poisson models were used to assess the moderating effects of stress and gender on the change in gait velocity and rate of letter generation in WWT compared to NW and Alpha, respectively. The normality assumption for gait velocity was tested and adequately met. A linear mixed effect model using robust empirical variance estimates was used to assess the moderating effects of stress and gender on HbO₂ levels in WWT compared to NW and Alpha, allowing different variations in HbO₂ levels among fNIRS channels. Variations between different stress levels as well as between women and men were examined and found to be similar. A linear mixed effect model was used to assess the moderating effects of stress and gender on HbO₂ levels in WWT compared to NW and Alpha. Task was the three-level repeated measure variable comparing WWT to both NW and Alpha. Moderation effects were determined by 2 and 3-way interactions. Two-way interactions were stress $\times$ task and gender $\times$ task as well as stress $\times$ gender. The influence of gender on the moderating effects of stress on behavioral outcomes and HbO₂ levels were examined via three-way interactions of gender $\times$ stress $\times$ task. In addition to gender and stress, analyses controlled for age, education, disease comorbidity, total BAI score, and RBANS total index score. Two sided tests were used and statistical significance was set at 0.05. Statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, N.C.).

Results

A total of 318 non-demented participants (mean age in years= 76.66 $\pm$ 6.7; mean education in years=14.46 $\pm$ 3.04; %female=56) were included in the current study. Descriptive statistics of demographic, behavioral and fNIRS data were further stratified by high versus low levels of task-related stress (see table 1). The mean RBANS Index score (91.38 $\pm$ 12.07) was indicative of average overall cognitive function based on age and education corrected normative data. The Mean BAI score for the entire sample (5.06 $\pm$ 5.97) was indicative of minimal levels of anxiety. Mean disease comorbidity score (1.08 $\pm$ 1.73) confirmed the relatively healthy nature of the sample indicating that, on average, participants had one chronic health condition. As expected, stride velocity was faster in NW (80.06 $\pm$ 17.36) compared to WWT (65.28 $\pm$ 18.52).

Also, error rate in the letter generation task (Alpha) was lower in the single task condition (3.64 ± 5.54) compared to WWT (6.80 ± 7.34). Mean reported task-related stress (range 0-10) was 4.43 ± 2.95 .

Effects of Stress and Gender on Gait Velocity

For visual depiction and interpretation of the data, stress was dichotomized based on median split. Analyses using stress as a continuous variable were not materially different. As expected, gait velocity was significantly reduced in WWT compared to NW (estimate=-12.401; $p < 0.001$; 95% CI=-14.925 to -9.876) among men reporting low stress levels. The interaction of stress and task was significant revealing greater decline in gait velocity in WWT compared to NW in high versus low stress groups among men (estimate=-4.586; $p < 0.019$; 95% CI=-8.412 to -0.760) but not among women (estimate=-2.495; $p < 0.152$; 95% CI=-5.919 to 0.928). The three-way interaction of gender $\times$ stress $\times$ task, however, was not significant ($p = 0.423$). Summary of the linear mixed effect model examining the effects of task and covariates on gait velocity is presented in Table 2; the interactions of stress $\times$ task stratified by gender are presented in Figure 2.

Because the main and moderating effects of gender were not significant the effect of stress on the change in gait velocity due to dual-task interference was also examined in the entire sample. Overall gait velocity declined in WWT compared to NW by 12.92 cm/sec (CI: 11.086-14.756, $P < 0.0001$) among participants reporting low stress, while the decline was 3.43cm/sec (CI: 0.927-5.938, $P = 0.0074$) higher among those who reported high stress. The effects of stress on gait velocity within each task condition stratified by gender, which were deduced directly from the linear mixed effects model, are presented below.

Stress effects in men (NW: estimate=1.77; $p < 0.525$; 95% CI=-3.595 to 7.029; WWT: estimate=-2.869; $p < 0.289$; 95% CI=-8.195 to 2.456). Stress effects in women (NW: estimate=-2.464; $p < 0.311$; 95% CI=-7.250 to 2.322; WWT: estimate=-4.960; $p < 0.042$; 95% CI=-9.756 to -0.174).

Effects of gender and stress on Alpha (Cognitive Interference Task)

GEE analysis revealed that the rate of errors (estimate of log of rate ratio =0.511; $p < 0.001$; 95% CI=0.262 to 0.759) was significantly increased in WWT compared to Alpha but the rate of correct letter generation did not differ between the two task conditions (estimate=0.006; $p = 0.818$; 95% CI=-0.052 to 0.066). Stress and gender as well as their interaction were not significantly associated with performance or task-related changes in letter generation performance (data not shown).

Effects of gender and stress on task-related changes in HbO₂ levels

Gender moderated the effect of stress on task-related changes in HbO₂ levels. Specifically, three-way interactions revealed that, in men relative to women, high stress was associated with attenuated increases in HbO₂ levels from NW to WWT (estimate=-0.415; $p = 0.019$; 95% CI=-0.764 to -0.065) and from Alpha to WWT (estimate=0.445; $p = 0.024$; 95% CI=-0.834 to -0.056; see Table 3 for a summary of the findings and Figure 3 for visual depiction of the three way interactions).

Stress effects in men (NW: estimate=-0.075; $p<0.490$; 95%CI=-0.291 to 0.139; Alpha: estimate=0.043; $p<0.625$; 95%CI=-0.131 to 0.218; WWT: estimate=-0.353; $p<0.0021$; 95%CI=-0.651 to -0.055). Stress effects in women (NW: estimate=0.067; $p<0.377$; 95%CI=-0.082 to 0.217; Alpha: estimate=0.156; $p<0.020$; 95%CI=0.023 to 0.289; WWT: estimate=0.204; $p<0.034$; 95%CI=0.015 to 0.394).

Discussion

The present study was designed to determine the individual and combined effects of gender and perceived stress on gait velocity and PFC HbO₂ levels during locomotion. We found that higher levels of stress were associated with more difficulties in negotiating the demands of dual-task walking as well as attenuation of brain oxygenation patterns under attention-demanding walking in older men. These findings and their implications are discussed below.

Higher task-related stress was associated with a greater decrement in stride velocity in dual-task compared to single task walking in older men. Specifically, the average decline in gait velocity due to dual-task interference was 4.586 cm/sec greater among men in the high compared to the low stress group. The difference in the average dual-task cost in gait velocity in women in the high versus low stress group was 2.496 cm/sec (see Figure 2 for visual depiction of these results). Greater dual-task costs in aging have been attributed to diminished attention and executive control resources (Holtzer *et al.*, 2004). Hence, the findings reported herein suggest that higher level of task-related stress further diminished cognitive resources necessary to support walking under attention demanding conditions, particularly in older men. While previous research suggested that older men may experience more difficulties in negotiating the demands of dual-task walking (Hollman *et al.*, 2011), the interaction of gender $\times$ task was not significant in this study. It appears, however, that older men were more vulnerable to the negative effect of stress on dual-task performance than older women. While reasons for this finding maybe multifaceted, research has demonstrated that sex hormones were implicated in general cognitive status (Janicki & Schupf, 2010) and specifically in executive functions (Janowsky *et al.*, 2000; Genazzani *et al.*, 2007). Sex hormones also influence the brain's differentiation process from development and throughout adulthood (Cosgrove *et al.*, 2007; Gong *et al.*, 2009). The frontal cortex is susceptible to the aging process (Raz *et al.*, 2004; Fjell & Walhovd, 2010), and neurobiological alterations in the prefrontal cortex have been associated with age-related decline in executive functions (West, 1996). It has also been reported that men experience more gray matter degeneration compared to women in the PFC (Curiati *et al.*, 2009), especially in the dorsolateral region (Raz *et al.*, 1993). Hence, it is possible that the behavioral findings reported above are attributed, at least in part, to greater degeneration in the PFC in older men. This issue is further discussed below.

The PFC has been identified as a key brain region implicated in executive control processes (Koechlin *et al.*, 2003; Koechlin & Summerfield, 2007) including dual-task walking (Holtzer *et al.*, 2011; Mirelman *et al.*, 2014; Holtzer *et al.*, 2015; Hernandez *et al.*, 2016; Holtzer *et al.*, 2016a; Holtzer *et al.*, 2016b). The PFC may also have an important role in coordinating physiologic and behavioral responses to stressful situations (McKlveen *et al.*, 2015). It has been well-established that neurochemical changes that occur during acute stress significantly

disrupt performance on neuropsychological tasks of working memory and executive functions (Lupien *et al.*, 1999; Young *et al.*, 1999; Lupien *et al.*, 2007), as well as PFC network connections and functionality (Arnsten, 2009; McEwen & Morrison, 2013). Furthermore, research has consistently shown that administration of cortisol reduces working memory performance (Petra *et al.*, 2009) and behavioral flexibility (Cerqueira *et al.*, 2007), both of which rely heavily on prefrontal circuits. These stress-induced cognitive impairments have also been associated with synaptic and/or dendritic reorganization in the hippocampus and medial prefrontal cortex (Dias-Ferreira *et al.*, 2009). In electrophysiological studies, increases in frontal theta activity during working memory have been observed across different tasks (Gevins *et al.*, 1997; Jensen & Tesche, 2002). Gartner and colleagues (Gartner *et al.*, 2014) demonstrated that working memory-related frontal theta activity decreased under stress, corresponding to behavioral performance decrements during more difficult task conditions. In addition, functional neuroimaging studies have found stress-related deactivation in the dorsal and ventral prefrontal cortex and orbitofrontal cortices (Dedovic *et al.*, 2009b). Hence, the effect of higher task-related stress on the attenuation in PFC activation patterns during dual-task walking is consistent with the extant literature; it is noteworthy, however, that the effect of stress on cortical control of human locomotion has not been previously reported.

The individual and combined effects of task-related stress and gender on the change in HbO₂ levels across task conditions complemented and extended the behavioral findings described earlier (see figures 2 and 3 for visual depiction of the effect of perceived stress on stride velocity and PFC oxygenation levels across task conditions, respectively, in older women and men). Whereas the decline in stride velocity from NW to WWT was greater in high compared to low perceived stress groups in older men the trend was similar but less pronounced in older women, though differences in the latter group as a function of perceived stress status were significant in WWT. Higher levels of perceived stress, however, attenuated the increase in oxygenation levels from single task conditions to dual-task walking only in men, which was evident by the significant 3-way interaction of gender $\times$ stress $\times$ task. In fact, higher perceived stress was associated with higher oxygenation levels in Alpha and WWT but not in the change across task condition in women. It can be speculated that greater age-related atrophy in the PFC in men (as discussed earlier) underlies the decoupling of behavioral and neuroimaging findings. PFC oxygenation levels are more proximate measures to the structural integrity of the PFC compared to stride velocity that is influenced by multiple causes within and outside the central nervous system. Furthermore, it appears that brain resources, defined herein as task-related HbO₂ levels, among older men who reported higher stress levels were limited, which in turn resulted in greater dual-task costs in gait velocity. Several and possibly competing cognitive aging models may account for these findings. Overall, task-related HbO₂ levels were higher in men compared to women. It could be argued that greater involvement of the PFC has a compensatory function for aging men. The Compensatory Reallocation hypothesis (Cabeza, 2002; Cabeza *et al.*, 2002) suggests that increased activation in the PFC in older adults is designed to compensate for reduced efficiency of brain networks that underlie task performance in younger individuals. The corollary, according to the Compensatory Reallocation hypothesis, is that increased brain activation is associated with better performance (walking speed in this case). Neural

Compensation models (Stern, 2009), on the other hand, postulates that increased or distinct task related activation patterns are necessary to support the task but will not necessarily result in better performance. It is reasonable to suggest that the greater HbO₂ levels observed in men have a compensatory function, especially if they find the cognitive demands of locomotion both arduous and stressful. It can be further argued that the Capacity Limitations (Grady *et al.*, 1995; Madden *et al.*, 1996; Reuter-Lorenz *et al.*, 2000; Cabeza *et al.*, 2004) hypothesis of working memory explains stress-related differences in PFC HbO₂ levels during locomotion in men. Evidence for Capacity Limitations exists among groups with known brain pathology wherein individuals show attenuated brain activations in response to cognitive challenges. Accordingly, due to compromised structural and/or functional networks, the brain's response to tasks, particularly when cognitive demands are increased is attenuated (Holtzer *et al.*, 2009; Holtzer *et al.*, 2016a). Hence, we propose that due to the detrimental effects of stress on PFC architecture and functionality, older men who reported higher perceived stress levels were unable to recruit and increase the involvement of this brain region to support the cognitive demands of locomotion, notably under attention-demanding dual-task conditions.

Clinical implications

Dual-task walking is a robust predictor of falls (Ayers *et al.*, 2014) and disability and mortality (Verghese *et al.*, 2012). Behavioral stress reduction techniques have established effectiveness in various populations (Gotink *et al.*, 2015). It is also noteworthy that computerized cognitive remediation (Verghese *et al.*, 2010) and training in dual-task walking (Schwenk *et al.*, 2010) resulted in improved WWT walking performance. Whether or not stress reduction techniques and/or cognitive training can reduce task-related stress levels and modify brain HbO₂ levels during active locomotion remains to be evaluated. It appears, however, that inclusion of a brief stress instrument in risk assessment of individuals prone to developing mobility impairments and disability could be beneficial.

Limitations and future directions—The sample in the current study, although variable, consisted of relatively healthy and independent older adults whose overall anxiety levels were low. The generalizability of these findings to patient populations, especially those with neurological diseases or conditions associated with a high prevalence of anxiety and stress symptoms that are not task-dependent, has to be determined in future studies. While the participants were community dwelling, ambulatory and dementia free, our study design did not include traditional imaging in all participants that would enable further insights into underlying brain substrates. The stress question was specific to the task examined, and we do not discount the effect that other context dependent stress or predisposition may have on other mobility functions. It is noteworthy, however, that analyses controlled for a number of confounders including anxiety, which was assessed using a well validated scale for older adults (Therrien & Hunsley, 2012; Schoen & Holtzer, 2016). Stress is a multifaceted construct and while the operational definition used herein was based on self-report further examination of objective physiological stress indicators such as cortisol levels and inflammatory markers is of interest. While the fNIRS system used in the current study offers significant advantages in terms of portability and capability to assess PFC oxygenation levels during walking its spatial limitations should be acknowledged. The limited depth of

penetration and brain regions surveyed by this system provide a critical, though limited, window into brain control of locomotion. Future studies should utilize multi-imaging modalities to provide whole brain structural and functional context to fNIRS findings. HbO₂ is more reliable and sensitive to locomotion-related changes in cerebral oxygenation compared to deoxygenated hemoglobin (Hoshi *et al.*, 2001; Miyai *et al.*, 2001; Strangman *et al.*, 2003; Harada *et al.*, 2009) and was thus used in the current study. Furthermore, using one outcome measure reduces the probability of false discovery rate. Future studies, however, should evaluate whether other chromophores, such as deoxygenated hemoglobin, provide different patterns in the data that can complement and add to the HbO₂ findings reported herein. In addition, the limitations of the current fNIRS device preclude direct assessment of factors including but not limited to skull thickness or skin response that might influence cortical changes in oxygenation patterns during locomotion. These important issues have been previously discussed (Kirilina *et al.*, 2012; Erdogan *et al.*, 2014). We emphasize, however, that these factors as well as the effect of motion artefacts, while important, were not likely to influence the moderating effects of gender and perceived stress on task related changes in PFC oxygenation levels given that experimental conditions were administered in a random order and had the same walking environment and physical requirements.

Conclusion

Perceived stress influenced both the dual-task cost in gait velocity and locomotion-related differences in HbO₂ levels, particularly among older men. The implications of these findings on risk assessment and treatment of individuals at risk of incident mobility impairments and falls should be further evaluated. Whether improving subjective or objective indicators of stress may improve locomotion in healthy and impaired older adults requires additional investigation.

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Figure 1.

Visual depiction of the apparatus, synchronization of fNIRS and PKMAS and walking environment. fNIRS - Functional Near Infrared Spectroscopy; PKMAS -ProtoKinetics Movement Analysis Software. 1a) a participant standing on PKMAS with the fNIRS sensor already attached to his forehead. 1b) visual depiction of the sensor that is placed on the participant's forehead using standard procedures; 1c) synchronized communication between fNIRS and PKMAS is implemented via a dedicated computer with E-Prime computer.

Figure 2. Changes in stride velocity (Y axis – units expressed in cm/sec) from Normal-Walk (NW) to Walk-While-Talk (WWT) as a function of group status determined by task-related perceived stress level in female (panel A) and males (panel B).

Figure 3. Changes in HbO₂ levels, (Y-axis - expressed in micromolar units), from Normal Walk (NW) and Alpha to Walk-While-Talk (WWT) as a function of group status determined by task-related perceived stress level in female (panel A) and males (panel B).

Table 1
Summary of sample characteristics stratified by levels of perceived stress

	Total sample	Low perceived Stress	High perceived Stress
Participants (n)	318	147	171
Women: Number, (%)	179(56.3)	69(46.9)	110(64.3)
	Mean(SD)	Mean(SD)	Mean(SD)
Age, years:	76.65(6.59)	76.72(6.87)	76.58(6.37)
Education, years:	14.46(3.04)	14.86(3.10)	14.11(2.95)
Disease Comorbidity Index:	1.73(1.08)	1.57(1.09)	1.67(1.08)
RBANS (total Index score):	91.38(12.07)	93.20(11.98)	89.81(11.97)
Stride Velocity NW (cm/sec):	80.06(17.36)	81.15(17.83)	79.13(16.94)
Stride Velocity WWT (cm/sec):	65.28(18.52)	68.22(18.20)	62.73(18.48)
Alpha: rate of letter generation (correct)	33.74(11.86)	34.57(11.51)	33.06(12.14)
WWT: rate of letter generation (correct)	34.63(14.90)	35.82(13.58)	33.65(15.88)
Alpha: rate of letter generation (errors)	3.64(5.54)	3.61(6.96)	3.67(4.03)
WWT: rate of letter generation (errors)	6.80(7.34)	5.74(8.16)	7.69(6.48)
NW: HbO ₂ levels	0.11(0.65)	0.13(0.65)	0.09(0.65)
Alpha: HbO ₂ levels	0.68(0.53)	0.62(0.51)	0.73(0.54)
WWT: HbO ₂ levels	0.66(0.86)	0.72(0.91)	0.61(0.81)
BAI total score	5.06(5.97)	4.52(5.81)	5.53(6.07)
Perceived Stress	4.43(2.95)	1.68(1.47)	6.79(1.51)

Note: RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; NW=normal walk; WWT=walk while talk; BAI=Beck Anxiety Inventory

Table 2
linear mixed effects models: effects of gender and perceived stress on stride velocity

Variables	Estimate	t	95% CI	P
NW vs. WWT	-12.401	-9.67	-14.925 to -9.876	<0.0001
Stress × NW vs. WWT (men)	-4.586	-2.36	-8.412 to -0.760	0.0190
Stress × NW vs. WWT (women)	-2.4957	-1.43	-5.919 to 0.928	0.152
Gender	2.88	1.09	-2.302 to 8.066	0.274
Gender × NW vs. WWT	-1.108	-0.59	-4.792 to 0.2576	0.544
Gender × Stress	-4.181	-1.15	-11.312 to 2.949	0.249
Gender × Stress × NW vs. WWT	2.090	0.80	-3.043 to 7.225	0.423
Age	-0.991	-7.87	-1.239 to -0.743	<0.0001
Education	0.025	0.09	-0.525 to 0.576	0.928
Disease comorbidity index	-2.832	-3.66	-3.354 to -1.310	0.0003
RBANS Total Index Score	0.323	4.63	0.185 to 0.460	<0.0001
BAI total Score	-0.277	-1.91	-0.562 to 0.007	0.056

Note: RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; NW=normal walk; WWT=walk while talk; BAI=Beck Anxiety Inventory

Table 3
linear mixed effects models: effects of gender and perceived stress on oxygenation levels during locomotion

Variables	Estimate	t	95% CI	P
NW vs. WWT	-0.792	-7.90	-0.989 to -0.595	<0.0001
Alpha vs. WWT	-0.372	-3.39	-0.587 to -0.157	0.0007
Gender	-0.732	-5.93	-0.974 to -0.490	<0.0001
Gender × NW vs. WWT	0.411	3.32	0.168 to 0.653	0.0009
Gender × Alpha vs. WWT	0.473	3.47	0.205 to 0.741	0.0005
Stress	-0.353	-2.32	-0.651 to -0.055	0.0201
Stress × NW vs. WWT	0.277	1.88	-0.012 to 0.567	0.060
Stress × Alpha vs. WWT	0.397	2.43	0.077 to 0.717	0.015
Gender × Stress	0.558	3.09	0.204 to 0.912	0.002
Gender × Stress × NW vs. WWT	-0.415	-2.33	-0.764 to -0.065	0.019
Gender × Stress × Alpha vs. WWT	-0.445	-2.25	-0.834 to -0.056	0.024
Age	0.0001	0.04	-0.007 to 0.007	0.964
Education	-0.006	-0.71	-0.022 to 0.010	0.0478
Disease comorbidity index	-0.006	-0.30	-0.052 to 0.038	0.767
RBANS Total Index Score	-0.0005	-0.21	-0.005 to 0.004	0.832
BAI total Score	0.004	1.14	-0.002 to 0.010	0.255

Note: RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; NW=normal walk; WWT=walk while talk; BAI=Beck Anxiety Inventory