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Online Fronto-cortical Control of Simple and Attention-Demanding Locomotion in Humans

Roee Holtzer[1,2,*], **Jeannette R. Mahoney**[1], **Meltem Izzetoglu**[3], **Cuiling Wang**[4], **Sarah England**[2], and **Joe Verghese**[1,5]

[1]Department of Neurology, Albert Einstein College of Medicine of Yeshiva University Bronx, New York, USA

[2]Ferkauf Graduate School of Psychology of Yeshiva University Bronx, New York, USA

[3]Drexel University School of Biomedical Engineering Philadelphia, Pennsylvania, USA

[4]Department of Epidemiology, Albert Einstein College of Medicine of Yeshiva University Bronx, New York, USA

[5]Department of Medicine, Albert Einstein College of Medicine of Yeshiva University Bronx, New York, USA

Abstract

Knowledge of online functional brain mechanisms of locomotion is scarce due to technical limitations of traditional neuroimaging methods. Using functional Near Infrared Spectroscopy (fNIRS) we evaluated task-related changes in oxygenated hemoglobin levels (HbO_2) in real-time over the pre-frontal-cortex (PFC) regions during simple (Normal Walk; NW) and attention-demanding (Walking While Talking; WWT) locomotion tasks in a large cohort of non-demented older adults. Results revealed that the assessment of task-related changes in HbO_2 was internally consistent. Imposing greater demands on the attention system during locomotion resulted in robust bilateral PFC increases in HbO_2 levels during WWT compared to NW and the cognitive interference tasks. Elevated PFC oxygenation levels were maintained throughout the course of WWT but not during the NW condition. Increased oxygenation levels in the PFC were related to greater stride length and better cognitive performance but not to faster gait velocity in WWT. These findings elucidate online brain mechanisms of locomotion, and confer significant implications for risk assessment and intervention for major mobility outcomes.

The ability to ambulate effectively is a key determinant of functional independence in normal and disease populations. Mobility impairments are common among older adults[1] leading to increased risk of major adverse health outcomes including disability and

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[*]Corresponding Author: Roee Holtzer, Ph.D., Albert Einstein College of Medicine, Yeshiva University, 1165 Morris Park Avenue, Room 306, Bronx, New York 10461, T#: 718-430-3962, F#: 718-430-3829, roee.holtzer@einstein.yu.edu.

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mortality[2]. Converging evidence points to the key role attention, Executive Functions (EF) in particular, have in the higher order control of mobility[3–5], especially under complex locomotion tasks that further tax the attention system[6–8,59]. EF, a constellation of cognitive processes implicated in planning, organization, conflict resolution, and allocation of attention to competing task demands, are sub-served by the Pre-Frontal Cortex (PFC) and its related circuits[9,10]. Allocating attention to competing task demands, as assessed in dual-task paradigms, affords experimental control of attention resources[11], is considered a facet of EF[12], and is sensitive to aging[13]. In the context of mobility, dual-task paradigms have been used to determine the causal effect that increased demands on attention resources has on gait performance. Importantly, gait performance on a well validated and reliable Walking While Talking (WWT) paradigm has emerged as a key risk factor for incident frailty, disability and mortality in older adults[14]. Hence, delineating cognitive and brain mechanisms of locomotion, especially under attention demanding walking conditions, is critical for developing risk assessment and intervention procedures to identify and ameliorate mobility decline and disability in normal aging as well as in disease populations.

Motor control models of locomotion exist[15] as does evidence for robust associations of gray matter volume and white matter integrity in frontal and subcortical brain regions with mobility outcomes[16]. However, knowledge regarding the real time functional neural correlates of simple and attention-demanding locomotion tasks is scarce. This gap in knowledge is, in part, attributed to methodological limitations of traditional neuroimaging methods that typically require the individual to be in a supine position and remain motionless during scanning procedures. A recent targeted review of neuroimaging studies of mobility in aging emphasized the paucity of research in this area but also identified methods that could potentially circumvent some of the aforementioned challenges[17]. A few studies utilized radionuclide tracers during simple mobility tasks that were performed outside of the scanner, and subsequently using single photon emission computerized tomography (SPECT) or positron-emission-tomography (PET) examined task-related distribution patterns of the tracers in the brain[18]. However, the invasiveness of the procedure, subject selectivity and methodological limitations preclude the use of these techniques to determine online functional neural correlates of attention demanding mobility tasks including but not limited to dual-task paradigms. Mental imagery has been utilized in functional magnetic resonance imaging (fMRI) to determine functional brain correlates of imagined locomotion tasks[18–20]. A recent study found increased activation levels in PFC in imagined WWT compared to either imagined walking or silent talking tasks[21]. While promising, even with extensive training, individuals vary in their imagery proficiency, and the use of imagery tasks in fMRI does not fully capture online brain activity during actual locomotion tasks.

Functional Near-Infrared Spectroscopy (fNIRS) measures changes in cortical oxygenated hemoglobin (HbO_2) levels using light–tissue interaction properties of light within the near infrared range[22]. fNIRS has been validated against traditional neuroimaging methods[23] and is better able to handle motion artifacts[24]. A very limited number of fNIRS studies revealed differential involvement of pre-frontal, pre-motor and motor cortices in gait tasks (for review see[17]). To our knowledge, only two studies to date have reported on the cortical control of gait under single and dual-task conditions; demonstrating increased HbO_2 in PFC regions as a function of increased attention demands in the dual-task condition[25,26].

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However, critical methodological limitations and small sample sizes in those studies present significant limitations to both the interpretation of the findings and the scope of contribution to basic knowledge concerning higher order cortical control of attention demanding locomotion tasks. It is noteworthy that in contrast to traditional neuroimaging methods fNIRS has never been used in population-based studies to obtain reproducible estimates of changes in the PFC in response to cognitive demands, notably during actual locomotion.

Using fNIRS, the current study was designed to determine the role that the PFC has in allocating attention resources to gait under single and dual-task conditions in a large cohort of non-demented community residing older adults. We hypothesized that bilateral increase in PFC oxygenation levels (HbO_2) would be evident in WWT compared to Normal Pace Walk (NW) and the cognitive interference (Alpha) task. Consistent with the hemodynamic response and principles of neurovascular coupling[27], we expected initial elevations in HbO_2 levels across all tasks relative to baseline. However, we hypothesized opposite task-related trajectories wherein high oxygenation levels would be maintained throughout the course of WWT but decline in NW due to the greater and sustained cognitive demands that are inherent in the former task. Finally, we aimed to determine whether oxygenation levels within task were related to walking performance. Whereas compensatory reallocation predicts that higher bilateral task-related activation levels in the PFC would be associated with better performance[28], neural compensation argues that task-related activation levels are necessary to support behavior but might not be related to performance[29].

METHODS

Participants

Participants were community residing non-demented individuals, age 65 years and older, enrolled in a longitudinal cohort study entitled “Central Control of Mobility in Aging” (CCMA). The primary aims of the study are to determine cognitive and brain predictors of mobility in aging. CCMA study recruitment and procedures were previously described[59,6]. In brief, using population lists of lower Westchester county, NY, potential participants were identified, contacted by mail and then by telephone. A structured telephone interview was administered to potential participants to obtain verbal assent, assess medical history and mobility function[30] and rule out dementia[31]. Exclusion criteria were: significant loss of vision and/or hearing, inability to ambulate independently, current or history of neurological or psychiatric disorders, and recent or anticipated medical procedures that may affect mobility. Individuals who passed the telephone interview and agreed to participate in the study were invited to two in-person study visits at our research center, each lasting approximately three hours. During the visits participants received comprehensive neuropsychological, cognitive, psychological, and mobility assessments as well as a structured neurological examination. Diagnoses of dementia were assigned according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV TR, 2000[32]) at consensus diagnostic case conferences as previously described[33]. CCMA participants are followed longitudinally at yearly intervals. Written informed consents were obtained at clinic visits according to study protocols and approved by the institutional review board.

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Test Procedures and Equipment

Quantitative Gait Assessment

Zenometrics system: A 4 × 14 foot Zeno electronic walkway using ProtoKinetics Movement Analysis Software (PKMAS) was utilized to assess quantitative measures of gait that included stride velocity and stride length (Zenometrics, LLC; Peekskill, NY). Quantitative 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).

Walking protocol—Reliability and validity for our walking paradigms including practice procedures have been established[4,14]. Participants were presented with two single task conditions: 1) Normal Pace Walk (NW) and 2) Cognitive (Alpha – requiring participants to generate alternate letters of the Alphabet). In the dual-task condition participants were required to perform the two single tasks concurrently (Walk While Talk; WWT). In the NW condition participants were asked to walk around the electronic walkway (see Zenometrics system above) at their "normal pace" for three consecutive loops. In the Alpha condition participants were asked to stand still on the electronic walkway while reciting alternate letters of the alphabet out loud, starting with the letter B for 30 seconds. In the WWT condition participants were instructed to walk around the walkway at their normal pace while reciting alternate letters of the alphabet starting with the letter 'B'. Participants were specifically reminded to pay equal attention to both the walking and cognitive interference tasks (i.e. equal priority) as previously described.[6,39] The three test conditions were presented in a counterbalanced order using a Latin-square design.

Testing was conducted in a quiet room. Participants wore comfortable footwear with the fNIRS sensor attached to their forehead. Start and end points for each trial were clearly demarcated. The two walking conditions required participants to walk in three continuous loops around the walkway which consisted of six straight walks and five left-sided turns. The duration of each task condition varied depending on the individual's walking speed. The participants did not use assistive devices during the walking protocol.

fNIRS System

In the current study, fNIRS Imager 1000 (fNIRS Devices, LLC, Potomac, MD) was used to monitor changes in hemodynamic activity in the PFC of participants during actual locomotion in NW and WWT conditions and while performing the cognitive interference task (Alpha condition) in a standing position. The fNIRS system consists of a flexible circuit board (102gr) that was placed on the participants' forehead using standard procedures, a control box for data acquisition and a computer for data collection and storage. There was excellent correlation of gait velocity while walking with and without the fNIRS sensor in 15 non-demented participants ($r=0.881$, $p<0.001$) indicating that quantitative gait patterns in the two conditions were highly related. The system can collect 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 L4×730/4×805/4×850-40Q96-I) contain three built-in LEDs having peak wavelengths at 730, 805, and 850 nm, with an overall outer diameter of 9.2 ±

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0.2 mm. The photodetectors (Bur Brown, type OPT101) are monolithic photodiodes with a single supply transimpedance amplifier. Light sources and detectors are built on a flexible printed circuit board which is covered by silicone for sealing, durability, comfort and hygiene. Since the fNIRS sensor is flexible, the components can move and adapt to the various contours of the participants' foreheads, allowing the sensor elements to maintain an orthogonal orientation to the skin surface, improving light coupling efficiency and signal strength. There is a standard sensor placement procedure followed in all of our studies. The fNIRS is placed on the forehead so that the horizontal symmetry axis central (y-axis) coincides with symmetry axis of the head, (i.e. in between the eyes). On the vertical axis, the sensor is positioned right above the eyebrows in relation to the international 10–20 system so that FP1 and FP2 marker locations are approximately positioned on the bottom channel row level[34]. Given the sensitivity of the fNIRS recording device, the lighting in the test room was reduced such that the mean illumination of the forehead was approximately 150 lux, which is about one-third of typical office lighting.

Preprocessing and Hemodynamic Signal Extraction

First, data from each of the 16 fNIRS channels under the three experimental conditions were carefully inspected and removed from analysis if saturation or dark current conditions were identified. Saturation and dark current conditions were identified in 4% of the data, typically due to sensor placement. The raw intensity measurements at 730 and 850nm that were not saturated or at dark current levels were then low-pass filtered with a finite impulse response filter of cutoff frequency at 0.14Hz to eliminate possible respiration and heart rate signals and unwanted high frequency noise[35]. Oxygenated hemoglobin (HbO_2), deoxygenated hemoglobin (Hb), oxygenation or oxygen index (HbO_2-Hb) and total hemoglobin (HbO_2+Hb) signals can be calculated from the artifact-removed raw intensity measurements at 730 and 850 nm using modified Beer-Lambert law as previously described[36] for each of the 16 channels. In the current experiment, HbO_2 values were used to characterize changes in the PFC during the NW, Alpha and WWT conditions since they were more reliable and sensitive to locomotion-related changes in cerebral blood flow[37]. Also, using one index for task-related hemodynamic changes in the PFC reduced the number of comparisons and thus the probability of increased Type I error.

Proximal baseline conditions ranging from 5–15 seconds have been previously reported in fNIRS studies[38]. Relative changes in the concentrations of HbO_2 in each experimental condition were obtained using the most proximal standing 10-second baseline where participants were asked to remain still, fixate on the wall directly in front of them, and count silently in their head at a rate of about one number per second. A separate baseline was administered immediately prior to the start of each of the three experimental conditions. For each condition, the baseline levels for the 10-sec period were adjusted to a zero mean value in HbO_2 values. Hence, the changes in HbO_2 values in NW, Alpha and WWT were normalized to the same level of the individualized baseline condition.

Epoch and Feature extraction for NW, Alpha and WWT

Individual mean HbO_2 data were extracted separately for each of the 16 channels in each of the three experimental conditions. For the Alpha condition, mean HbO_2 values per channel,

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which were based on the entire 30 sec task duration, were used for feature extraction and comparison.

In the NW and WWT conditions, we implemented additional steps that were designed to optimize the acquisition of task related HbO_2 by synchronizing fNIRS and gait events. Specifically, concurrent assessments were controlled via a central "hub" computer with E-Prime 2.0 software. The hub computer was used to send synchronized triggers to both the fNIRS system (via serial port) and the Zenometrics quantitative gait system (via parallel port). The fNIRS acquisition software (COBI Studio) accepted numerical triggers from E-prime that ranged in value from 1–12. Each numerical trigger was indicative of a unique condition and represented the beginning or end of either a baseline or test condition. The gait acquisition software (PKMAS) accepted TTL (transistor-transistor-logic; 5 volts) pulses (square waves) that varied in duration based on each test condition. Specifically, 15ms pulses were indicative of the beginning and end of the NW condition, 30ms pulses were used for WWT, and 45ms pulses were used for the Alpha condition. Figure 1 provides a graphic illustration of the fNIRS and PKMAS systems as well as their synchronized communication via E-Prime.

We then employed a second level post-processing time synchronization method. Here, a time stamp of the first foot contact with the walkway was recorded. We started the fNIRS recording at 800 ms before the first foot contact time. The recording of fNIRS was terminated at the end of the 6^{th} and final straight walk just prior to entering the last turn. This end point was determined algorithmically by PKMAS. HbO_2 data in NW and WWT within this range were extracted and used as the trial epoch for comparisons between task conditions. In addition, HbO_2 data for each of the six straight walks were extracted to delineate changes in task-related brain activation trajectories during NW and WWT.

Covariates—Structured clinical interviews were used to identify self-reported medical diagnoses. Consistent with our previous studies[33,39] dichotomous rating (presence or absence) of physician diagnosed diabetes, chronic heart failure, arthritis, hypertension, depression, stroke, Parkinson's disease, chronic obstructive lung disease, angina, and myocardial infarction was used to calculate a disease comorbidity summary score (range 0–10).

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was used to assess overall cognitive function. The RBANS is a brief cognitive test with several alternate forms that measures attention, language, visuospatial skills and, immediate and delayed memory.

It also provides a total index score for global cognitive function and is useful for the detection and characterization of dementia in older adults[40]. Additional covariates included age, education and gender.

Statistical Analysis

The effect of dual-tasking on velocity, stride length and the rate of correct and incorrect letter generation were determined. Split-half intra-class correlations (ICC) within NW,

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Alpha and WWT were used to assess the internal consistency of HbO_2 and gait measurements. Linear mixed effect models were used to assess the effect of dual-tasking on HbO_2 levels in WWT compared to NW and Alpha. In those models task served as the three-level within person repeated measures variable representing the change in HbO_2 levels in WWT compared to NW and Alpha overall and in each of the 16 fNIRS channels. Two separate linear mixed effect models were used to examine the effect of time on HbO_2 levels in NW and WWT. Time served as the 6-level within person repeated measures variable representing the change in the average HbO_2 levels comparing the first straight walk (used as a reference) to the subsequent five straight walks. Extraction of the 6 walking segments was accomplished using an established and validated algorithm[41]. Two separate linear regressions were used to determine association between total average HbO_2 levels (predictor) and stride length in NW and WWT serving as the outcome variable. Separate Poisson models assessed the association between total average HbO_2 levels and the rate of correct and incorrect letter generation in Alpha and WWT. Data were inspected descriptively and graphically and model assumptions were formally tested. All analyses reported controlled for gender, age, education, disease comorbidity, and total index RBANS score. Statistical analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, N.C.).

RESULTS

A total of 348 non-demented CCMA participants (mean age in years=76.8; %female=59) were included in the current study. The low mean disease comorbidity score (1.6) confirmed the relatively healthy nature of the sample. The mean RBANS Total Scale Index score (91.4) was indicative of average cognitive function level (see Table 1 for sample characteristics and mean HbO_2 levels in NW, Alpha and WWT).

Stride length in WWT (mean=92.37±19.97) compared to NW (mean=99.48±17.54) was significantly reduced (estimate=−7.04; 95%CI=−7.941 to −6.144; p<0.0001). Mean gait velocity in WWT (mean=64.91±17.63cm/sec) compared to NW (mean=79.81±18.98cm/sec) was significantly reduced as well (estimate=−14.876; 95%CI=−16.081 to −13.672; p<0.0001). Split-half intra-class correlations (ICC) for gait velocity and stride length in NW and WWT were all greater than 0.95 revealing excellent internal consistency of gait measurements within each task. Whereas the time for Alpha was fixed at 30 seconds, the time for WWT varied depending on the individual's gait speed and was not fixed. Thus, Poisson repeated measure models were used to assess the effect of dual-tasking on the rate of correct and incorrect letter generation. The rate of correct letter generation was not significantly reduced in WWT compared to Alpha (estimate of log of rate ratio=-0.014, 95%CI=-0.059 to 0.030; p=0.521). However, the error rate was significantly increased in WWT compared to Alpha (estimate of log of rate ratio=0.562; 95%CI=0.447 to 0.677; p<0.001).

Split-half intra-class correlations (ICC) for NW (0.830), Alpha (0.864) and WWT (0.849) revealed excellent internal consistency of HbO_2 measurements within each task. The results of the linear mixed effect models comparing HbO_2 levels in WWT to NW and Alpha are summarized in Tables 2 and 3.

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As shown in Table 2, overall HbO_2 levels were significantly higher in WWT compared to NW and approached significance in the comparison to Alpha. The effect of gender was significant with men showing higher HbO_2 levels then women. As shown in Table 3, HbO_2 levels in all 16 channels were significantly higher in WWT compared to NW. Higher HbO_2 levels in WWT compared to Alpha were also observed bilaterally in channels 2, 3 and 13. Significantly higher HbO_2 levels in Alpha compared to WWT were noted in channels 9 and 10. The effects of time on HbO_2 levels during the course of NW and WWT were depicted graphically (Figure 2) and tested using linear mixed effects models (Table 4).

As shown in Figure 2 and Table 3, initial task-related elevations in HbO_2 during NW subsided quickly and were reduced during the final straight walk of the task to levels that were below the first straight walk, which served as the reference point. In contrast, significant elevations in HbO_2 levels during WWT were consistently maintained throughout the duration of the task.

Median split in HbO_2 levels within NW and WWT were used as predictors in separate linear regression models with gait velocity and stride length serving as the outcome measures. Analyses revealed that HbO_2 levels during NW (estimate=−0.554; SE=2.045; p=0.786) and WWT (estimate=−0.818; SE=2.197; p=0.709) were not related to gait velocity. HbO_2 levels were not related to stride length in NW (estimate=3.544; SE=2.014; p=0.079). However, during WWT, higher HbO_2 levels were related to increased stride length (estimate=5.394; SE=2.285; p=0.018). Poisson models revealed that higher (median split) HbO_2 levels during Alpha (estimate=0.061; 95CI%= 0.006 to 0.116; p=0.027) and during WWT (estimate=0.076; 95CI%= 0.029 to 0.124; p=0.001) were related to increased rate of correct letter generation.

Discussion

The present study determined PFC involvement in simple and attention-demanding locomotion tasks in non-demented older adults. The application of optical imaging, fNIRS, during active locomotion tasks is novel and promising but has been extremely scarce, plagued with methodological limitations and notably absent in large cohorts. Hence, the current study addressed a major gap in knowledge regarding the online involvement of PFC regions in human locomotion while providing first evidence for the feasibility and utility of fNIRS in assessing higher order control of gait in population-based studies. Noteworthy is the internal consistency of the measurement of task-related changes in HbO_2 levels as evidenced by the high intra-class correlations in NW, Alpha and WWT.

Consistent with the first study hypothesis imposing greater demands on the attention system during locomotion resulted in robust bilateral increases in HbO_2 levels in WWT compared to NW. This finding is consistent with our initial report demonstrating greater bilateral activation in the PFC in WWT compared to NW in a small group of young and old participants[25]. Whereas, increased oxygenation levels in WWT relative to NW were evident in all 16 fNIRS channels, the differences between WWT and Alpha were more selective albeit bilateral and notably in channels 2, 3 and 13 that may be more sensitive to changes in activation in lateral portions of the PFC[42]. Moreover, the left lateral PFC has been identified

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in several independent fMRI studies as a key functional region that subserves dual-tasking [43–45]. In a recent resting-state fMRI study we have shown that increased functional connectivity in a left lateralized fronto-parietal network, especially in the PFC and supplementary motor areas, was uniquely related WWT performance[46]. Hence, the relatively greater changes observed in channel 2 and 3 in WWT compared to both NW and Alpha are consistent with the above referenced literature extending the unique role of the left lateral PFC to attention demanding locomotion. It is noteworthy that additional regions in the PFC have been linked to dual-tasking including areas in the right PFC[47–49], possibly due to task specific demands. The increased HbO_2 levels in medial channels (9 and 10) in Alpha compared to WWT points to the functional diversity of the PFC,[9,10] and may be attributed to the increased sensitivity of these channels to activations in underlying primary speech areas.

Consistent with the second hypothesis of the study, the effect of time trajectories on HbO_2 levels varied as a function of task. Initial elevations in HbO_2 in NW subsided and were lower relative to the reference point at the end of the task. This finding suggests that after a relatively brief adjustment period, gait becomes more automatic and likely controlled by lower brain mechanisms[15]. In contrast, elevated HbO_2 levels in WWT remained consistent throughout the task suggesting that sustained cognitive effort was required to support performance on this attention-demanding locomotion task. It is noteworthy that performance on neuropsychological measures of executive functions predicts falls risk[50] and variability on WWT walking performance[39]. In turn, performance on WWT also predicts falls risk[51]. The consistently elevated HbO_2 levels during WWT help explain the aforementioned associations between EF and WWT, and their utility in predicting falls, pointing to the key functional role the PFC plays in all three measures. Walking conditions in natural settings, where most falls occur, involves sensory and cognitive distractions as approximated by the WWT paradigm in the laboratory. Hence, this finding also confers significant implications for fall risk assessment and mobility rehabilitative efforts. Indeed, cognitive remediation that focused on attention and executive functions enhanced WWT performance[52] as did practice on walking paradigms that involved cognitive interference tasks[53].

Beyond the hypotheses concerning the effect of task and time trajectories on PFC oxygenation levels during NW, Alpha and WWT we also aimed to determine whether activation levels within task predicted performance. The results were mixed. Higher HbO_2 levels were not related to faster gait velocity in either NW or WWT. These findings can be interpreted in the context of neural compensation, a model that has received support in other investigations (see[29] for review). Neural compensation proposes that increased levels of brain activations in response to greater task demands are necessary for the individual to perform the task. The levels of activation within a task, however, do not have to correlate with performance. In the current study, older adults demonstrated a significant increase in HbO_2 levels in WWT compared to NW. This finding point to the key role the PFC has in monitoring and allocation cognitive resources to support WWT performance. The correlation between activation levels and gait velocity, however, was not significant. In contrast, consistent with compensatory reallocation models[28] our findings confirmed that higher HbO_2 levels were related to increased stride length during WWT and to better cognitive performance during both alpha and WWT. While dual-task strategies have been

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discussed elsewhere[54] these findings along with the observable behavioral effects of dual-tasking on cognitive and gait performance during WWT lend support to the notion that non-demented older participants were able to allocate cognitive resources to both tasks at the same time as instructed.

Limitations and Future Directions

It is noteworthy that opposing theoretical models were proposed to account for the mixed findings observed in the plethora of neuroimaging studies that aimed to determine associations between the magnitude task-related brain activations and performance (see[55] for a brief overview and empirical findings). The lack of association between HbO_2 levels and gait velocity within tasks may be attributed to individual differences inherent in negotiating the cognitive demands of locomotion. Indeed, descriptively, we observed that increased task-related HbO_2 levels were associated with both faster and lower velocity values suggesting that both compensatory reallocation and neural inefficiency models might explain contrasting brain behavior associations in subsamples that may be distinguished by important characteristics. Noteworthy, is the findings that overall oxygenation levels during locomotion were higher in men than women in this sample. Gender differences in mobility, cognitive functions and their underlying biological mechanisms, although mixed, have been documented[56]. In addition, self-report of fatigue[57] and cognitive fatigue[58,59] are common in aging and have been associated with mobility performance. Future studies should aim to identify potential moderating and mediating factors including but not limited to gender and fatigue that predispose individuals to exhibit differential brain behavior relationship vis-à-vis higher order control of locomotion. The mean velocity under the normal walk condition was relatively low. We note that significant variability in gait speed has been documented in community residing older adults (see[60] for normative data). Two factors, however, might have accounted the lower gait speed observed in this study. The participants were required to turn for a total of five times to complete the required three walking loops of each experimental condition on a relatively short (14-foot) instrumented walkway; and turning often results in reduced gait speed. Second, attaching the fNIRS device and wires, although very light, to the participants' forehead might have slowed them as well. Nonetheless, behaviorally, the differences in gait velocity between the single and dual-task conditions reported herein were comparable to those found in our previous studies[6,39,59]. The letter B was used as the starting point for the letter generation task in the single and dual-task conditions. While different letters for this task can be used as the starting point[61] research has shown that psychometric properties of alternate forms of the same test are not the same (for review see[62]); and using the same form has specific advantages, especially in quantifying learning and fatigue effects[63]. Moreover, because test order was randomized leaning did not systematically affect one task condition more than the other.

fNIRS has better temporal but worse spatial resolution compared to traditional neuroimaging methods such as fMRI. The fNIRS array in this study focused on PFC based on theoretical and previous clinical observations, but other brain areas (both related and independent of PFC) have a role in locomotion. Hence, using fNIRS in concert with other neuroimaging methods in future studies can further elucidate brain mechanisms of locomotion, and provide a broader and more accurate context for the findings reported herein. For instance, white

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matter lesions have been linked to both mobility outcomes and executive functions; and EF mediated the relationship between white matter hyperintensities and mobility outcomes[64]. It remains to be evaluated whether white matter integrity in normal and pathological populations, especially in tracts that sub-serve EF, influence online PFC activation levels during simple and attention-demanding locomotion tasks.

Clinical Implications

The definitive role the PFC has in allocating and monitoring cognitive resources to support walking, especially under attention-demanding conditions, may have significant implications for fall risk assessment and mobility rehabilitative efforts. Cognitive remediation that focused on attention and executive functions enhanced WWT performance[52], which in turn is an important risk factor for several adverse outcomes[14] including falls[65]. These findings support the inclusion of measures of attention and executive functions as well as WWT in risk assessment for falls and mobility decline and disability. It remains to be evaluated whether using fNIRS to assess brain control of locomotion provides incremental prediction of individuals at risk of falls or mobility decline and disability. At present, however, the clinical utility of fNIRS in this context has not been established. Finally, it would be of interest to determine whether the functional PFC signature of locomotion differs as a function of diseases, syndromes and transition states that affect cognitive and motoric functions in aging.

In summary, using fNIRS we have provided internally consistent online measurements of task-related changes in oxygenation levels in ecologically valid locomotion tasks in a large cohort of non-demented and ambulatory older adults. Our findings provide definitive evidence for the functional role the PFC plays in monitoring and allocating cognitive resources during locomotion, especially when cognitive demands are increased. Levels of activation in the PFC were increased in response to greater cognitive demands and were related to both cognitive and gait performance during walking while talking. These findings elucidate online brain mechanisms of human locomotion, and confer significant implications for risk assessment and intervention for major mobility outcomes in aging.

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Highlights

1. fNIRS was used to determine online cortical control of locomotion in humans
2. Assessment of cortical control of locomotion, using FNIRS, was highly reproducible
3. fNIRS methodology was successfully applied to a population-based study
4. $HB0_2$ levels were increased and maintained in attention-demanding locomotion
5. Definitive role for the pre-frontal-cortex in higher-order control of locomotion

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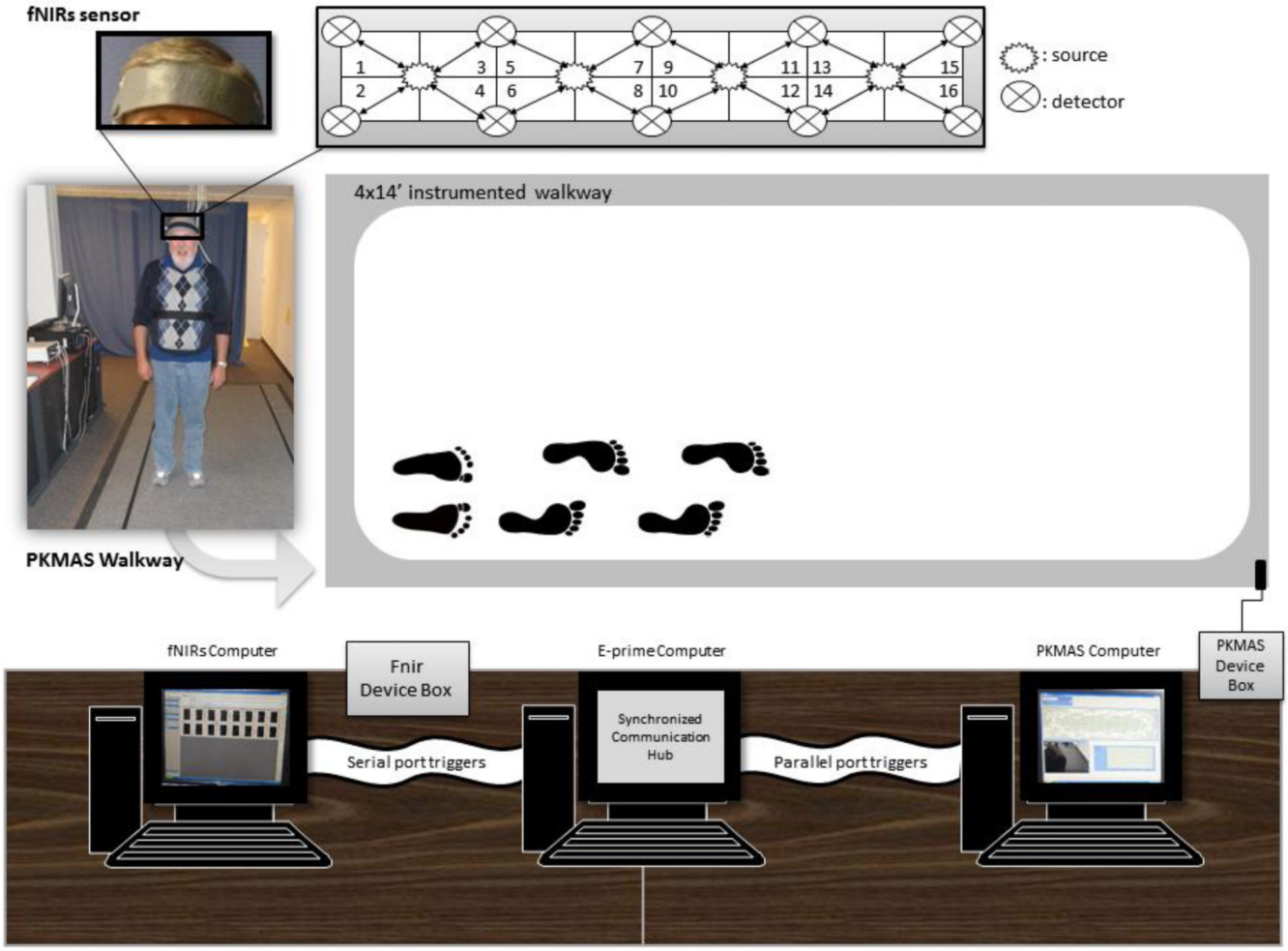

Figure 1.

Apparatus and synchronized communication center: fNIRS device and sensor, PKMAS device and instrumented walkway, and E-prime computer. fNIRS=functional Near Infrared Spectroscopy; PKMAS= ProtoKinetics Movement Analysis Software

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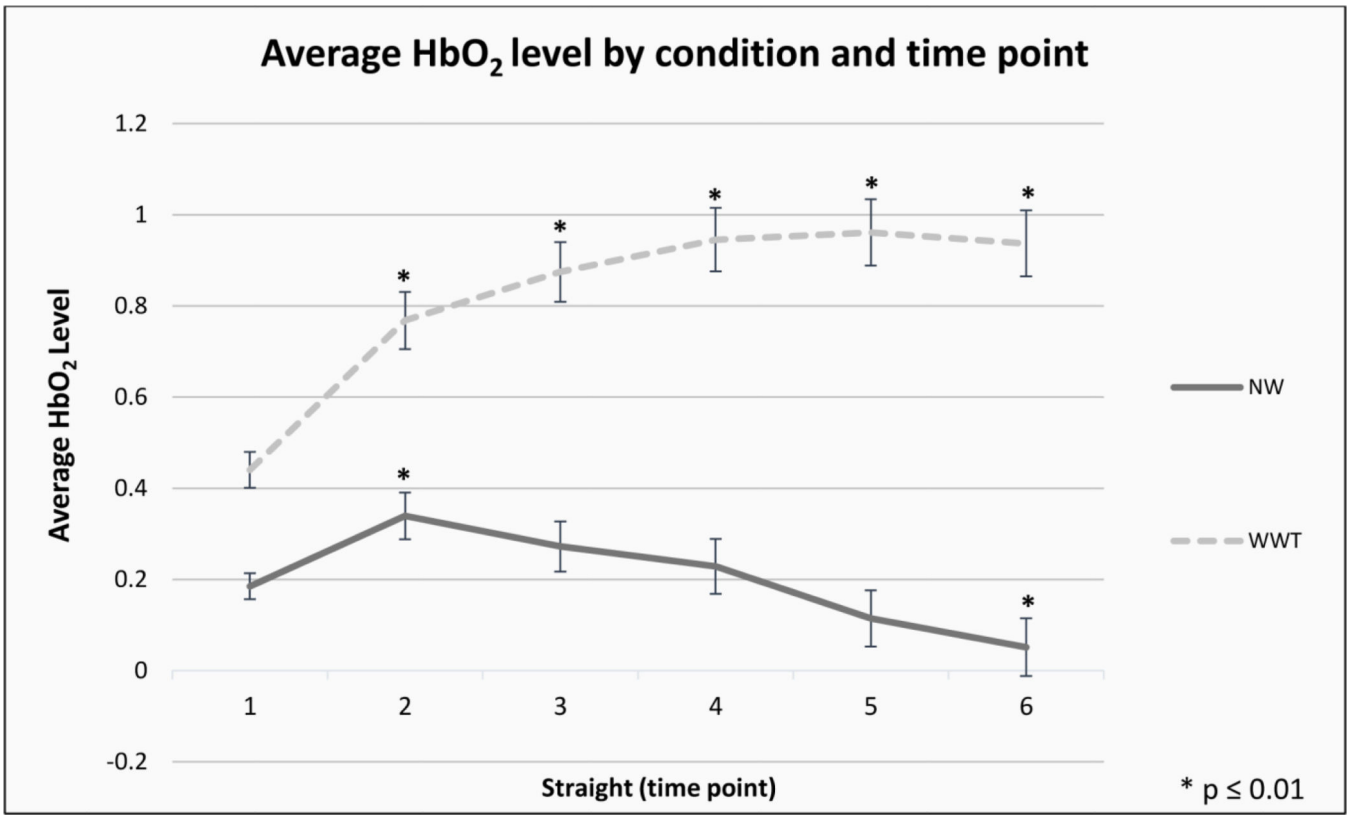

Figure 2.

Mean HbO_2 levels in NW and WWT are depicted as a function of six consecutive straight walks that were extracted from each walking condition. There is no parallel time course for Alpha. Overall mean HbO_2 level in Alpha (.68±.54) is provided herein as a reference. NW=Normal Walk; WWT=Walk While Talk

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Table 1

Sample characteristics and Mean (SD) HbO_2 levels in NW, Alpha and WWT

Sample Characteristics		
Variables		
Total Sample (n)	348	
Women: number (%)	205 (59%)	
	Mean (SD)	*Range*
Age (years)	76.8 (6.8)	65 – 95
Education (years)	14.4 (3.0)	3 – 28
Disease comorbidity index	1.6 (1.2)	0 – 5
RBANS (standard total Index score)	91.4 (12.2)	62 – 137

Mean(SD) of HbO_2 levels Per Experimental Condition and fNIRS Channel			
fNIRS Channels	Normal Walk	Alpha	Walk While Talk
1	0.11 (0.73)	0.64 (0.89)	0.67 (1.00)
2	0.27 (1.40)	0.53 (0.73)	0.74 (1.42)
3	0.22 (0.77)	0.66 (0.68)	0.85 (1.02)
4	0.31 (1.12)	0.70 (0.92)	0.83 (1.35)
5	0.17 (0.83)	0.70 (0.72)	0.80 (1.02)
6	0.11 (1.03)	0.81 (0.88)	0.76 (1.45)
7	0.07 (1.06)	0.69 (0.95)	0.64 (1.18)
8	−0.26 (1.88)	0.78 (1.26)	0.70 (1.94)
9	−0.02 (1.16)	0.65 (0.93)	0.47 (1.38)
10	−0.31 (1.98)	0.85 (1.37)	0.52 (1.72)
11	0.13 (0.62)	0.53 (0.53)	0.55 (0.87)
12	0.12 (1.14)	0.79 (0.73)	0.76 (1.32)
13	0.25 (0.75)	0.68 (0.61)	0.85 (0.98)
14	0.24 (1.15)	0.77 (0.76)	0.81 (1.24
15	0.15 (0.71)	0.53 (0.61)	0.63 (0.92)
16	0.19 (1.09)	0.61 (0.68)	0.68 (1.17)

NW=Normal Walk; Alpha=letter generation task; WWT=Walk While Talk

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Table 2

Linear mixed effect model with task as the three-level within person repeated measure (NW, Alpha, WWT) and HB02 levels as the dependent measure

	Model parameters		
Experimental Condition	**β**	**95%CI**	**p**
WWT vs. NW	−.613	−.681 to −.546	<0.001
WWT vs. Alpha	−.055	−.120 to .009	0.092
Covariates			
Age	.0008	−.003 to .005	.700
RBANS total Index Score	.002	−.004 to 0002	.086
Education	−.002	−.012 to .006	.540
GHS	.017	−.008 to .043	.178
Gender	.262	.204 to .320	<0.001

NW=Normal Walk; Alpha=letter generation task; WWT=Walk While Talk

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Table 3

Linear mixed effects models with task as the three-level within person repeated measure (NW, Alpha, WWT) and HB02 levels as the dependent measure in each of the 16 fNIRS channels

Channels	WWT vs. NW			WWT vs. Alpha		
	β	95%CI	p	β	95%CI	p
1	−0.561	−0.658 to −0.465	<0.001	−0.561	−0.658 to 0.465	0.677
2	−0.473	−0.643 to −0.303	<0.001	−0.213	−0.394 to −0.032	0.020
3	−0.630	−0.737 to −0.523	<0.001	−0.188	−0.304 to −0.071	0.001
4	−0.527	−0.657 to −0.397	<0.001	−0.135	−0.287 to 0.016	0.080
5	−0.633	−0.744 to −0.522	<0.001	−0.099	−0.221 to 0.021	0.105
6	−0.651	−0.777 to −0.525	<0.001	0.046	−0.111 to 0.205	0.561
7	−0.568	−0.704 to −0.432	<0.001	0.048	−0.109 to 0.205	0.548
8	−0.958	−1.172 to −0.744	<0.001	0.093	−0.147 to 0.334	0.448
9	−0.492	−0.636 to −0.347	<0.001	0.177	0.019 to 0.336	0.028
10	−0.831	−1.037 to −0.625	<0.001	0.322	0.116 to 0.528	0.002
11	−0.423	−0.515 to −0.331	<0.001	−0.019	−0.115 to 0.076	0.690
12	−0.640	−0.768 to −0.513	<0.001	0.033	−0.109 to 0.175	0.648
13	−0.598	−0.669 to −0.498	<0.001	−0.175	−0.287 to −0.063	0.002
14	−0.574	−0.714 to −0.435	<0.001	−0.047	−0.189 to 0.095	0.516
15	−0.484	−0.577 to −0.390	<0.001	−0.104	−0.223 to 0.014	0.085
16	−0.486	−0.630 to −0.343	<0.001	−0.071	−0.207 to 0.063	0.298

NW=Normal Walk; Alpha=letter generation task; WWT=Walk While Talk

Linear mixed effect models controlled for age, education, gender, disease comorbidity summary score, and mean RBANS total Scale Index score.

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Table 4

Linear mixed effects models examining the effect of time on average HB02 levels separately in NW and WWT

Time effects	NW			WWT		
	β	95%CI	p	β	95%CI	p
1 vs. 2	0.154	0.081 to 0.227	<0.001	0.327	0.242 to 0.413	<0.001
1 vs. 3	0.087	−0.002 to 0.177	0.057	0.434	0.337 to 0.531	<0.001
1 vs. 4	0.043	−0.054 to 0.140	0.383	0.505	0.396 to 0.613	<0.001
1 vs. 5	−0.070	−0.171 to 0.030	0.172	0.521	0.402 to 0.639	<0.001
1 vs. 6	−0.133	−0.240 to −0.027	0.013	0.496	0.376 to 0.617	<0.001

NW=Normal Walk; WWT=Walk While Talk; 1=first straight walk; 2=second straight walk; 3=third straight walk; 4=fourth straight walk; 5=fifth straight walk; 6-sixth straight walk.

Linear mixed effect models controlled for age, education, gender, disease comorbidity summary score, and mean RBANS total Scale Index score.