Pain Medicine, 22(2), 2021, 303–314
doi: 10.1093/pm/pnaa404
Advance Access Publication Date: 1 December 2020
Original Research Article

OXFORD

PSYCHOLOGY, PSYCHIATRY, & BRAIN NEUROSCIENCE SECTION

The Effects of Perceived Pain in the Past Month on Prefrontal Cortex Activation Patterns Assessed During Cognitive and Motor Performances in Older Adults

Hannah Pakray, MA* Elizabeth Seng, PhD*,† Meltem Izzetoglu, PhD‡ and Roee Holtzer, PhD*,†

*Ferkauf Graduate School of Psychology, Yeshiva University, Bronx, New York; †Department of Neurology, Albert Einstein College of Medicine, Bronx, New York; ‡College of Engineering, Villanova University, Villanova, Pennsylvania, USA

Correspondence to: Roee Holtzer, PhD, Ferkauf Graduate School of Yeshiva University, 1165 Morris Park Avenue, Bronx, NY 10461, USA. Tel: 718-430-3972; Fax: 718-839-7243; E-mail: roee.holtzer@yu.edu.

Funding sources: This research was supported by grants from the National Institute on Aging (R01AG036921; R01AG044007).

Disclosure and conflicts of interest: Hannah Pakray and Roee Holtzer report no conflict of interest. Meltem Izzetoglu has a minor share in the company that manufactures the fNIRS device used in this study. Elizabeth Seng receives research support from the National Institute of Neurological Disorders and Stroke (K23 NS096107; principal investigator: Seng) and has consulted for GlaxoSmithKline, Eli Lilly, and Click Therapeutics. Dr. Seng has received travel funds from the American Psychological Association, the American Academy of Neurology, the American Association of Pain Medicine Foundation, and the American Headache Society.

Abstract

Objective. Pain is prevalent and functionally impactful in older adults. The prefrontal cortex is involved in pain perception, attentional control, and cortical control of locomotion. Although pain is a known moderator of attentional capacity, its moderating effect on cortical control of locomotion has not been assessed. This study aimed to examine the effects of subjective pain on changes in functional near-infrared spectroscopy–derived measurements of oxygenated hemoglobin (HbO_2), gait velocity, and cognitive accuracy from single- to dual-task walking conditions among older adults. **Subjects**. The sample consisted of 383 healthy older adults (55% female). **Methods**. Participants completed two single tasks (Single-Task-Walk [STW] and Cognitive Interference [Alpha]) and the Dual-Task-Walk (DTW), during which participants performed the two single tasks simultaneously. The Medical Outcomes Study Pain Severity Scale and Pain Effects Scale were used to assess pain severity and interference. ProtoKinetics Movement Analysis Software was used to assess gait velocity and rate of correct letter generation to assess cognitive accuracy. Functional Near-Infrared Spectroscopy (fNIRS) was used to assess HbO_2 during active walking. **Results**. Linear mixed-effects models revealed that HbO_2 increased from single- to dual-task conditions. Perceived pain presence was associated with an attenuated increase in HbO_2 from Alpha to DTW. Among those with pain, worse pain severity was associated with an attenuated increase in HbO_2 from STW to DTW. Pain interference did not moderate the increase in HbO_2 from single to dual tasks. Pain did not have a moderating effect on behavioral outcomes. **Conclusions**. Task-related changes in the hemodynamic response in the prefrontal cortex during walking may be a sensitive marker of the effects of subjective pain on brain function in healthy older adults.

Key Words: Pain Medicine; Cognitive Function; Older Adults

Introduction

Pain is prevalent in the aging population, with an estimated 18.7 million older adults affected within the United States alone [1]. The impact of pain in this population is considerable, and older adults with pain are at an elevated risk of developing physical impairments that impact daily functionality [1]. Validated self-report measures of pain severity and interference [2, 3]

can help to predict important physical and functional outcomes in community-dwelling older adults [4].

Attentional capacity is an important pathway through which pain may impact functional outcomes [5, 6]. Dual-task walking provides conceptual and empirical frameworks to assess the relationship between attention/executive resources and observed gait performance [7, 8]. In this context, a decline in gait performance in Dual-Task-Walk (DTW) compared with Single-Task-Walk (STW) conditions is referred to as a dual-task cost, which is causally linked to the allocation of attention/executive resources, known to decline in aging, to competing task demands [9, 10].

Recent research using functional near-infrared spectroscopy (fNIRS) technology has demonstrated the key functional role of the prefrontal cortex (PFC) in cortical control of locomotion in older adults, notably under attention-demanding conditions such as dual-task walking [11–16]. Specifically, fNIRS-derived measurements of oxygenated hemoglobin (HbO_2) increased in DTW compared with STW because of greater cognitive demands that are inherent in the DTW condition.

Limited research suggests that pain moderates attentional capacity in dual-task walking [5, 6]. Lamoth and colleagues compared adults with chronic low back pain with healthy controls across three tasks of increasing cognitive load. They found that individuals with chronic low back pain demonstrated greater reductions in trunk coordination variability than their pain-free counterparts in dual-task walking conditions that required the most cognitive resources [6]. Hamacher and colleagues also examined dual-task costs associated with the experience of persistent low back pain in older adults and found that those with pain exhibited greater gait speed variability while dual-tasking as compared with pain-free controls [5]. Although the impact of perceived pain on dual-task walking performance has been examined among individuals with low back pain, its moderating effect on attention and cortical control of locomotion among relatively healthy older adults has not yet been assessed.

The associations observed between pain and attention/executive functions may be attributed in part to a shared reliance on prefrontal brain regions [17, 18]. Given that dual-task walking performance is a significant predictor of health outcomes such as frailty, disability, and death in older adults [19], examining the influence of pain on cortical control of locomotion, especially under cognitively demanding conditions such as dual-task walking, is of scientific interest and clinical utility. The present study aimed to evaluate whether pain status, severity, and interference moderated the change in fNIRS-derived HbO_2 in the PFC from single-task conditions (STW and Cognitive Interference [Alpha]) to dual-task walking conditions (DTW). Our hypothesis was that, consistent with capacity limitation theories of aging, a positive pain status, and higher pain severity and interference among people with pain, would be associated with an attenuated increase in HbO_2 from single to dual tasks [20, 21]. A secondary aim was to evaluate whether pain status, severity, and interference moderated the change in cognitive accuracy (rate of correct letter generation) and stride velocity from single- to dual-task conditions.

Methods

Participants

The present experimental study is a secondary analysis nested within a longitudinal, cohort study of community-dwelling older adults, titled "Central Control of Mobility in Aging" (CCMA) [7, 8]. The present study uses data collected during the baseline assessment. The aims of the parent study include the identification of cognitive and neurological predictors of mobility performance, decline, and disability in aging. Participants were recruited from the population of individuals 65 years of age or older who live within Westchester County, New York. Potential participants were contacted first by letter and later by telephone to determine their interest in and eligibility for participation. Inclusion criteria required that participants be at least 65 years of age, have the capacity to ambulate independently, and be free of neurodegenerative disease. Exclusion criteria included an inability to speak English, a diagnosis of dementia, the presence of significant functional disability, and extensive audiovisual loss. Further exclusion criteria included a prior history of neurological or psychiatric disorders, ongoing treatment with hemodialysis, and any recent or scheduled future medical procedures that could compromise mobility. Initial eligibility requirements were determined by a structured telephone interview consisting of verbal consent, a brief medical history questionnaire, mobility questions, and validated cognitive screens to exclude dementia [22–24]. Cognitive status was determined by formal case conference diagnostic procedures, as previously described [25]. Participants included in the present study were older adults who had complete cognitive, gait, and oxygenation data collected within their first year of participation (i.e., baseline). Dates of enrollment for the full study sample spanned from June of 2011 to March of 2015.

Procedures

After the telephone interview, eligible individuals were scheduled for two in-person visits in the study clinic, located on the Albert Einstein College of Medicine campus in the Bronx, New York. Written informed consent was obtained from each participant on site according to the study protocol, which had been approved by Albert Einstein College of Medicine's institutional review board. CCMA study protocols have been further described in detail in previous literature [7, 8]. During each visit, participants completed neuropsychological, cognitive, psychological, and mobility assessments.

Measures

Dual-Task Walking Protocol

The reliability and validity of the dual-task procedure used in this study have been well established and described [7, 8]. In the Single-Task-Walk (i.e., STW) conditions, individuals were asked to walk at their "normal pace" on an oblong pressure sensor mat for three consecutive loops. In the Cognitive Interference (i.e., Alpha) condition, participants were instructed to stand still on the mat and recite "alternate letters of the alphabet" beginning with the letter 'B' for 30 seconds. The rate of correct letter generation served as the measure of cognitive performance during Alpha and DTW. In the Dual-Task-Walk (i.e., DTW) condition, participants were instructed to walk along the mat at their normal pace while reciting alternate letters of the alphabet for three consecutive loops. Participants were instructed to pay equal attention to both portions of the task (cognitive and motor). Test conditions were presented in a counterbalanced manner via the use of a Latin-square design. Participants completed all walking tasks in a quiet room and were instructed to wear comfortable footwear for ease of task completion.

Quantitative Gait Assessment

A 4×20-ft Zeno electronic walkway was used to assess stride velocity (centimeters per second) from the location and mathematical parameters between footfalls under the STW and DTW conditions (Zenometrics, LLC, Peekskill, New York) [26]. ProtoKinetics Movement Analysis Software technology (PKMAS) was used to assess quantitative measures of gait and determine, algorithmically, entry and end points under the STW and DTW conditions [27]. Split-half intraclass correlations for stride velocity in STW and DTW are indicative of excellent (i.e., >0.95) internal consistency [12].

fNIRS System

The fNIRS sensor is designed to measure changes in oxygenation within the PFC. The device allows for the detection of hemodynamic changes in response to cognitive and motor demands [28]. For the purposes of the present study, the fNIRS Imager 1100 (fNIR Devices, LLC, Potomac, Maryland) was used to measure changes in PFC hemodynamic activity during tasks of cognition and locomotion within the dual-task paradigm. Prior publications have addressed a number of relevant methodological issues, including artifact removal algorithms and optimization of baseline procedures [12,13,28,29]. The system sampling rate was set at 2 Hz. The fNIRS sensor consists of 10 photodetectors and four light sources, with a source–detector separation of 2.5 cm. The sensor contains 16 voxels and covers the forehead. Sensor light sources (Epitex Inc., Kyoto, Japan, type L4X730/4X805/4X850-40Q96-I) contain three light-emitting diodes with peak wavelengths at 830, 805, and 850 nm and an overall outer diameter of 9.2 ± 0.2 mm. Sensor photodetectors (BurrBrown, Tuscon, Arizona, type OPT101) are monolithic photodiodes featuring a single-supply transimpedance amplifier. A standard sensor placement procedure, based on landmarks from the international 10–20 system, was implemented [30].

Preprocessing and Hemodynamic Signal Extraction

Raw data from each of the 16 fNIRS channels under all experimental conditions were inspected to identify and remove raw intensity measurements that met saturation or dark current conditions. Saturation or dark current conditions were identified in 4% of the data, which were consequently excluded from analysis. To minimize the effects of respiration and heart rate signals, as well as high-frequency noise, the remaining 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 [28]. This filtering process allowed for accurate identification and reduction of artifacts. An expert in fNIRS data processing (M. Izzetoglu) also identified high-frequency noise by visual inspection. The modified Beer-Lambert law was used to calculate HbO_2 for each channel [31]. HbO_2 has previously been demonstrated to be a reliable and sensitive measure of cerebral oxygenation change during locomotion [32].

Relative changes in HbO_2 were obtained by comparison with the 10-second baseline task within each experimental condition [12, 13, 29]. During this baseline task, participants were instructed to stand still and keep their eyes fixed on the wall in front of them while counting silently at the rate of one number per second. A 10-second baseline task was administered immediately before the start of each experimental condition (i.e., STW, Alpha, DTW). The baseline levels for each of the 10-second periods were adjusted to a zero mean HbO_2 value. As such, the changes in HbO_2 levels in each task condition were normalized to the same level of the individualized baseline condition by subtracting the mean of the baseline from the task epoch. HbO_2 levels were extracted separately for each channel on the basis of the entire experimental condition. Mean HbO_2 values were calculated for the STW, Alpha, and DTW conditions. Split-half intraclass correlations within each task were indicative of excellent internal consistency in the HbO_2 measurements. These coefficients were 0.830 for STW, 0.864 for Alpha, and 0.849 for DTW [29]. Gait and fNIRS data acquisition were synchronized, as previously described, by using a main "hub" computer with E-Prime 2.0 software (Psychology Software Tools Inc., Pittsburgh, Pennsylvania) [12, 13, 29].

Pain

All participants completed the Medical Outcomes Study Pain Effects Scale (MOS-PES) and Pain Severity Scale (MOS-PSS). The MOS-PSS was administered to

determine pain status and pain severity. The MOS-PSS includes five items that assess frequency, duration, and intensity of pain. Response options are provided on a Likert scale, with values ranging from 1 to 6 for the first three items and 0 to 20 for the last two items. Pain status was determined by the responses given to the first item, which queries about the presence and severity of pain experienced in the past month. Participants were dichotomized into pain status groups on the basis of their responses to this first item, with individuals who denied having experienced pain (i.e., "none") categorized within the no-pain group. Individuals who endorsed having experienced pain in the past month were categorized within the pain group. Pain severity and interference scores were calculated for individuals in the positive pain status group (i.e., yes pain). For individuals who endorsed pain, as determined by their response to item 1, a pain severity score was calculated by transforming each individual score onto a 0–100 scale and then calculating the mean of these transformed items. The pain severity score was then dichotomized by tertile, such that individuals within the highest tertile (i.e., 55.00–96.67) were categorized as having "high pain severity," and individuals within the lower two tertiles (i.e., 14.67–55.00) were categorized as having "low pain severity." The MOS-PSS has a Cronbach's alpha of 0.93 and has been shown to also have robust convergent validity [33]. In the present study, the MOS-PSS had an adequate level of internal consistency, as determined by a Cronbach's alpha of 0.70.

The MOS-PES includes six items that query about pain interference in mood, mobility, sleep, work, recreation, and enjoyment of life. Response options are provided on a Likert scale and range from 1 (i.e., "not at all") to 5 (i.e., "extremely"). For individuals with a positive pain status, as determined by item 1 of the MOS-PSS, a pain interference score was calculated by averaging responses across the six items and transforming the final value onto a 0–100 scale, with higher scores indicating higher levels of pain interference. The pain interference score was then dichotomized by tertile, such that individuals within the highest tertile (i.e., 33.33–90.00) were categorized within the "high pain interference" group, and those within the lower two tertiles (i.e., 20.00–33.33) were categorized within the "low pain interference" group. There is literature to suggest that the MOS-PES has a Cronbach's alpha coefficient of 0.93 and demonstrates good convergent validity (i.e., correlation of 0.79) when compared with the MOS-PSS [33]. In the present study, the MOS-PES had a high level of internal consistency, as determined by a Cronbach's alpha of 0.86.

Patient Characteristics

Demographic data, such as participant age, gender, ethnicity, and years of education, were collected via self-report at baseline and included as covariates in adjusted models. Severity of depressive symptomology, as assessed by the Geriatric Depression Scale, and cognitive functioning, as assessed by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total score, were also assessed [34, 35]. The Global Health Score (GHS) is a disease comorbidity score calculated from participants' dichotomous ratings (i.e., presence vs. absence) of a number of diseases, including arthritis, angina, hypertension, chronic heart failure, stroke, chronic obstructive disease, myocardial infarction, depression, and Parkinson's disease (range 0–10) [25]. Patient self-report of disease has been demonstrated to be a valid and reliable measure of disease history in adults [36]. The GHS score was also included as a covariate in adjusted models.

Statistical Analysis

Distributions of all study variables were visually inspected and described (mean/standard deviation, n and %). Bivariate analyses evaluated whether participant characteristics differed by pain status. Statistical tests used for bivariate analyses included *t* tests for independent samples, Pearson chi-squared tests for independence, chi-squared tests for trend, and a Mann-Whitney *U* test. The original sample consisted of 407 individuals who had completed all baseline procedures (i.e., two clinic visits during baseline). A total of 24 individuals were excluded from the study sample as a result of missing pain data. Cases with missing data for any of the study's outcome variables were retained in our analyses, as linear mixed-effects models (LMEMs) are robust in the face of missing data. The final study sample included a total of 383 individuals with and without reported pain.

All analyses were first conducted on the full study sample (N = 383) to determine the effect of pain status on study outcomes. Analyses evaluating the associations between pain severity and interference on study outcomes were conducted in the individuals who reported pain (n = 246). Three separate LMEMs assessed the fixed effects of task (DTW vs. STW; DTW vs. Alpha) and pain (Model 1: pain vs. no pain [n = 383]; Model 2: high pain severity vs. low–medium pain severity [n = 246]; Model 3: high pain interference vs. low–medium pain interference [n = 246]) and their interaction on HbO_2. With regard to HbO_2, there was a three-level task effect (DTW vs. STW; DTW vs. Alpha), and models allowed for individual channel data (optodes 1–16) to vary (i.e., channels were treated as random effects repeated measures). Notably, however, model estimates and means presented for each experimental condition in the figures represent the average oxygenation levels based on all available data from all channels.

Three separate LMEMs evaluated the fixed effects of task (DTW vs. STW), pain (Model 1: pain vs. no pain;

Model 2: high pain severity vs. low–medium pain severity; Model 3: high pain interference vs. low–medium pain interference), and their interaction on gait (gait velocity). Three additional models were used to evaluate the effect of task (DTW vs. Alpha), pain (Model 1: pain vs. no pain; Model 2: high pain severity vs. low–medium pain severity; Model 3: high pain interference vs. low–medium pain interference), and their interaction on cognitive performance (rate of correct letter generation). There were two-level task effects with respect to gait (STW vs. DTW) and cognitive performance (Alpha vs. DTW). Analyses were adjusted for age, gender, ethnicity, education, comorbidity status (i.e., GHS score), depression (i.e., GDS score), and overall level of cognitive functioning (i.e., RBANS total index score). Alpha was set at 0.05 for all analyses. SPSS Premium GradPack 26 was used to conduct all analyses.

Results

Study participants (n = 383; mean age= 76 ± 6.7 years; mean education= 14 ± 2.9 years; % female= 54.6) were individuals who had completed the dual-task paradigm and self-report pain questionnaires at baseline. Of the 383 participants included in the study, approximately 83% of the sample self-identified as Caucasian, 13% identified as Black, and the remaining 3% identified as belonging to another ethnicity. Participants were generally well educated, with an average of 14 years of education. The mean RBANS Index score (91.5 ± 11.8) indicated average overall cognition among the study participants. The mean GHS score (1.6 ± 1.1) suggested that the sample was relatively healthy. A positive pain status was reported by 64.2% (n = 246) of the sample. Bivariate analyses revealed that pain severity, pain interference, education, ethnicity, gender, GHS, and RBANS Index Score differed significantly by pain status (Table 1). On average, participants with pain reported higher levels of pain severity (47.2 ± 19.3 vs. 3.3 ± 0.0, $P < 0.001$) and pain interference (31.8 ± 12.8 vs. 20.0 ± 0.0, $P < 0.001$) than the no-pain group. Participants with pain were more likely to be female (61.0% vs. 43.1%, $P = 0.001$) and reported a higher level of education (14.5 ± 2.9 vs. 13.9 ± 2.8, $P = 0.046$). They were also more likely to have a moderate global health score (38.6% vs. 25.5%, $P = 0.001$) and a higher RBANS Index Score (92.5 ± 11.3 vs. 89.4 ± 12.6, $P = 0.040$).

The Effects of Task, Pain, and Their Interaction on HbO_2

The first LMEM was designed to replicate previous findings concerning the effect of walking tasks on PFC oxygenation. Results revealed the expected significant task effect, whereby HbO_2 increased from STW (estimate = -0.536, 95% confidence interval [CI]: -0.566 to -0.507, $P < 0.001$) and from Alpha (estimate = -0.043, 95% CI: -0.073 to -0.014, $P = 0.004$) to DTW.

A separate LMEM then evaluated the main and moderation effects of pain on HbO_2. As above, HbO_2 increased from STW (estimate = -0.575, $P < 0.001$) and Alpha (estimate = -0.099, $P < 0.001$) to DTW. However, the increase in HbO_2 from Alpha to DTW was attenuated among participants who reported pain compared with those who did not report pain (estimate = 0.085, $P = 0.007$). The moderating effect of pain on the increase in HbO_2 from STW to DTW did not meet the threshold for significance but followed a similar trend (estimate = 0.060, $P = 0.058$). The main effect of pain was not significant (estimate = -0.028, $P = 0.590$) (Table 2).

The LMEM that examined the main effect of task within individuals with reported pain revealed a significant task effect, such that HbO_2 increased from STW to DTW (estimate = -0.515, 95% CI: -0.550 to -0.480,

Table 1. Demographics stratified by pain status

Variable	Total N = 383	No Pain n = 137	Pain n = 246	Significance
Age, years	76 ± 6.7	76 ± 6.6	75 ± 6.7	0.177
Education, years	14 ± 2.9	13 ± 2.8	14 ± 2.9	0.046
Ethnicity				0.020
Caucasian	319 (83.3%)	114 (83.2%)	205 (83.3%)	
Black	51 (13.3%)	14 (10.2%)	37 (15.0%)	
Other	13 (3.4%)	9 (6.6%)	4 (1.6%)	
Gender				0.001
Male	174 (45.4%)	78 (56.9%)	96 (39.0%)	
Female	209 (54.6%)	59 (43.1%)	150 (61.0%)	
GHS				0.001
0	62 (16.2%)	30 (21.9%)	32 (13.0%)	
1	115 (30.0%)	50 (36.5%)	65 (26.4%)	
2	130 (33.9%)	35 (25.5%)	95 (38.6%)	
3	60 (15.7%)	20 (14.6%)	40 (16.3%)	
4	16 (4.2%)	2 (1.5%)	14 (5.7%)	
RBANS total scaled score	91 (11.8)	89 (12.6)	92 (11.3)	0.040

Values given as mean±standard deviation, median (interquartile range), or number (percentage).

Table 2. LMEM evaluating the effect of task and pain status on HbO_2

Variable	Estimate	*t*	95% CI	*P*
Task				
STW vs. DTW	−0.575	−22.553	−0.625 to -0.525	< 0.001
Alpha vs. DTW	−0.099	−3.871	−0.149 to -0.049	<0.001
Pain status				
Pain yes vs. no	−0.028	−0.539	−0.128 to 0.073	0.590
Task × pain				
STW vs. DTW × pain yes vs. no	0.060	1.896	−0.002 to 0.122	0.058
Alpha vs. DTW × pain yes vs. no	0.085	2.698	0.023 to 0.147	0.007
Covariates				
Age	0.001	0.260	−0.006 to 0.007	0.795
Channel	−0.002	−1.234	−0.004 to 0.001	0.217
Education	−0.016	−2.015	−0.031 to -0.000	0.045
GDS	0.002	0.288	−0.010 to 0.013	0.774
Gender	−0.290	−6.472	−0.378 to -0.202	<0.001
GHS	−0.018	−0.871	−0.060 to 0.023	0.384
RBANS	0.002	0.856	−0.002 to 0.005	0.393

Results of model adjusted for age, fNIRS channel, gender, education, depression (i.e., GDS), comorbidity status (i.e., GHS), and RBANS total index score.

$P < 0.001$). The increase in HbO_2 from Alpha to DTW, however, did not meet the threshold for significance (estimate = -0.013, 95% CI: -0.048 to 0.022, $P = 0.458$).

The LMEM examining the effects of task, pain severity, and their interaction on prefrontal oxygenation (Table 3) revealed a significant task effect, whereby HbO_2 increased from STW to DTW (estimate = -0.588, $P < 0.001$). Although HbO_2 also increased from Alpha to DTW, this effect did not meet the threshold for significance (estimate = -0.030, $P = 0.195$). However, participants who reported high pain severity (e.g., those in the highest tertile on the MOS-PSS) demonstrated an attenuated increase in HbO_2 from STW to DTW when compared with those with low pain severity (estimate = 0.171, $P < 0.001$). The main effect of pain severity was not significant (estimate = -0.106, $P = 0.103$).

The main and moderation effects of pain interference on HbO_2 were not significant (Table 3).

The Effects of Task, Pain, and Their Interaction on Gait Velocity

The LMEM that examined the main effect of task on gait velocity in the total sample revealed a significant task effect, such that gait velocity decreased from STW to DTW (estimate = 15.005, 95% CI: 13.721 to 16.289, $P < 0.001$). Pain status did not moderate the association between task and gait velocity (estimate = -1.475, $P = 0.278$) (Table 4).

The LMEM that examined the main effect of task on gait velocity among people with pain revealed a significant decrease in gait velocity from STW to DTW (estimate = 14.561, 95% CI: 12.962 to 16.160, $P < 0.001$). Neither pain severity (estimate = -1.454, $P = 0.392$) nor pain interference (estimate = -0.925, $P = 0.575$) moderated the relationship between task and gait velocity among people with pain (Table 5). The main effect of pain severity was not significant (estimate = -1.936, $P = 0.462$). The main effect of pain interference, however, was significant, such that participants who reported highest interference demonstrated reduced gait velocity across walking tasks (estimate = -6.947, $P = 0.007$).

The Effects of Task, Pain, and Their Interaction on Rate of Correct Letter Generation

The LMEM that examined the main effect of task on the rate of correct letter generation in the total sample did not reveal a significant relationship between task and correct letter generation (estimate = -0.019, 95% CI: -0.040 to 0.003, $P = 0.088$). Pain status did not moderate this relationship (estimate = -0.007, $P = 0.768$) (Table 6).

The LMEM that examined the main effect of task on the rate of correct letter generation among individuals with reported pain did not reveal a significant relationship between task and correct letter generation (estimate = -0.021, 95% CI: -0.049 to 0.007, $P = 0.148$). Neither pain severity (estimate = -0.008, $P = 0.795$) nor pain interference (estimate = 0.013, $P = 0.664$) moderated this relationship. Furthermore, the main effects of pain severity (estimate = -0.000, $P = 0.997$) and pain interference (estimate = -0.007, $P = 0.820$) on rate of correct letter generation were not significant (Table 7).

Discussion

The present study evaluated how subjective perceptions of the presence, severity, and interference of pain in the past month influenced cortical control of active walking, gait velocity, and cognitive performance during walking in community-residing older adults. The key findings revealed that pain status and pain severity moderated changes in cortical control of walking (operationalized through fNIRS-derived measurements of HbO_2 in the PFC) across tasks that experimentally manipulated cognitive demands. We discuss the specific findings below.

Table 3. LMEMs evaluating the effect of task, pain severity, and pain interference on HbO_2

Variable	Estimate	*t*	95% CI	*P*
Model 1				
Task				
STW vs. DTW	−0.588	−24.997	−0.634 to -0.542	< 0.001
Alpha vs. DTW	−0.030	−1.297	−0.076 to 0.016	0.195
Pain severity				
High vs. low–medium	−0.106	−1.635	−0.234 to 0.022	0.103
Task × severity				
STW vs. DTW × severity high vs. low–medium	0.171	4.245	0.092 to 0.251	< 0.001
Alpha vs. DTW × severity high vs. low–medium	0.030	0.755	−0.049 to 0.110	0.450
Covariates				
Age	−0.002	−0.542	−0.010 to 0.006	0.588
Channel	−0.003	−1.532	−0.006 to 0.001	0.126
Education	−0.022	−2.312	−0.040 to -0.003	0.022
GDS	0.009	1.366	−0.004 to 0.023	0.174
Gender	−0.258	−4.632	−0.368 to -0.148	<0.001
GHS	−0.057	−1.770	−0.120 to 0.006	0.078
RBANS	−0.000	−0.111	−0.005 to 0.005	0.912
Model 2				
Task				
STW vs. DTW	−0.535	−21.089	−0.585 to -0.486	<0.001
Alpha vs. DTW	−0.040	−1.593	−0.090 to 0.009	0.111
Pain interference				
High vs. low–medium	−0.006	−0.104	−0.127 to 0.114	0.917
Task × interference				
STW vs. DTW × interference high vs. low–medium	0.013	0.333	−0.063 to 0.089	0.739
Alpha vs. DTW × interference high vs. low–medium	0.047	1.219	−0.029 to 0.123	0.223
Covariates				
Age	−0.002	−0.555	−0.010 to 0.006	0.579
Channel	−0.003	−1.528	−0.006 to 0.001	0.126
Education	−0.021	−2.273	−0.040 to -0.003	0.024
GDS	0.008	1.169	−0.006 to 0.022	0.244
Gender	−0.262	−4.704	−0.371 to -0.152	<0.001
GHS	−0.063	−2.011	−0.124 to -0.001	0.046
RBANS	−0.000	−0.37	−0.005 to 0.005	0.971

Results of model adjusted for age, fNIRS channel, gender, education, depression (i.e., GDS), comorbidity status (i.e., GHS), and RBANS total index score.

As expected, irrespective of pain status, fNIRS-derived measurements of HbO_2 in the PFC increased from the single tasks (STW and Alpha) to DTW. Consistent with the study hypothesis, positive pain status was associated with an attenuated increase in PFC oxygenation from Alpha to DTW. Moreover, among participants with a positive pain status, those who reported the highest level of pain severity showed attenuated increases in HbO_2 from STW to DTW but not from Alpha to DTW. Pain interference, however, was not associated with any moderating effects on cortical control of walking.

Table 4. LMEM evaluating the effect of task and pain status on gait velocity

Variable	Estimate	*t*	95% CI	*P*
Task				
STW vs. DTW	15.782	14.569	13.651 to 17.914	<0.001
Pain status				
Pain yes vs. no	0.154	0.077	−3.755 to 4.062	0.938
Task × pain				
STW vs. DTW × pain yes vs. no	−1.475	−1.086	−4.147 to 1.197	0.278
Covariates				
Age	−1.043	−8.069	−1.297 to -0.788	<0.001
Education	−0.117	−0.381	−0.724 to 0.489	0.704
GDS	−0.491	−2.177	−0.934 to -0.047	0.030
Gender	−0.233	−0.132	−3.705 to 3.240	0.895
GHS	−2.814	−3.445	−4.422 to -1.207	0.001
RBANS	0.361	4.766	0.212 to 0.510	<0.001

Results of model adjusted for age, gender, education, depression (i.e., GDS), comorbidity (i.e., GHS), and RBANS total index score.

Table 5. LMEMs evaluating the effect of task, pain severity, and pain interference on gait velocity

Variable	Estimate	*t*	95% CI	*P*
Model 1				
Task				
STW vs. DTW	14.827	14.638	12.829 to 16.825	<0.001
Pain severity				
High vs. low–medium	−1.936	−0.737		0.462
Task × severity				
STW vs. DTW × severity high vs. low–medium	−1.454	−0.858	−4.795 to 1.888	0.392
Covariates				
Age	−1.136	−6.792	−1.466 to -0.806	<0.001
Education	−0.402	−1.014	−1.185 to 0.381	0.312
GDS	−0.506	−1.668	−1.105 to 0.092	0.097
Gender	−1.831	−0.775	−6.496 to 2.833	0.439
GHS	−2.927	−2.718	−5.051 to -0.802	0.007
RBANS	0.360	3.512	0.158 to 0.563	0.001
Model 2				
Task				
STW vs. DTW	14.696	13.773	12.591 to 16.800	<0.001
Pain interference				
High vs. low–medium	−6.947	−2.729	−11.963 to -1.931	0.007
Task × interference				
STW vs. DTW × interference high vs. low–medium	−0.925	−0.561	−4.173 to 2.324	0.575
Covariates				
Age	−1.137	−6.951	−1.459 to -0.814	<0.001
Education	−0.269	−0.692	−1.037 to 0.499	0.490
GDS	−0.276	−0.901	−0.880 to 0.328	0.369
Gender	−1.618	−0.699	−6.183 to 2.947	0.485
GHS	−2.652	−2.539	−4.712 to -0.591	0.012
RBANS	0.348	3.464	0.150 to 0.546	0.001

Model 1 evaluated effects of task and pain severity; Model 2 evaluated effects of task and pain interference. Results of models adjusted for age, gender, education, depression (i.e., GDS), comorbidity status (i.e., GHS), and RBANS total index score.

Table 6. LMEM evaluating the effect of task and pain status on rate of letter generation

Variable	Estimate	*t*	95% CI	*P*
Task				
Alpha vs. DTW	−0.016	−0.859	−0.052 to 0.020	0.391
Pain status				
Pain yes vs. no	0.024	1.009	−0.023 to 0.072	0.313
Task × pain				
Alpha vs. DTW × pain yes vs. no	−0.007	−0.296	−0.052 to 0.038	0.768
Covariates				
Age	−0.000	−0.226	−0.003 to 0.003	0.822
Education	0.020	5.775	0.013 to 0.027	<0.001
GDS	0.004	1.411	−0.001 to 0.009	0.159
Gender	0.048	2.375	0.008 to 0.087	0.018
GHS	−0.025	−2.708	−0.044 to -0.007	0.007
RBANS	0.006	7.167	0.004 to 0.008	<0.001

Results of model adjusted for age, gender, education, depression (i.e., GDS), comorbidity status (i.e., GHS), and RBANS total index score.

The results of this study are consistent with known theories of cognitive aging that attempt to explain neural patterns of under-activation across tasks of increasing cognitive demand. Our findings indicate that both the presence and severity of pain are associated with PFC under-activation in the change from single- to dual-task walking. These outcomes may be consistent with capacity limitation models in aging, which suggest that because of diminished brain resources, older adults tend to exhibit reduced increases in brain activations in response to cognitively challenging tasks [20, 21]. The presence of pain, and certainly severe pain, can pull cognitive resources away from the task at hand. As such, we may interpret these results to suggest that the presence of pain, particularly when severe, contributes to these known, age-related reductions in brain activation vis-à-vis cognitively demanding tasks.

Our findings are consistent with the interpretation that it is the cognitive demand of pain, rather than the impact of pain on a person's life, that is contributing to

Table 7. LMEMs evaluating the effect of task, pain severity, and pain interference on rate of letter generation

Variable	Estimate	*t*	95% CI	*P*
Model 1				
Task				
Alpha vs. DTW	−0.020	−1.113	−0.055 to 0.015	0.267
Pain severity				
High vs. low–medium	−0.000	−0.004	−0.060 to 0.060	0.997
Task × severity				
Alpha vs. DTW × severity high vs. low–medium	−0.008	−0.260	−0.068 to 0.052	0.795
Covariates				
Age	0.000	0.226	−0.003 to 0.004	0.821
Education	0.021	5.158	0.004 to 0.008	<0.001
GDS	0.003	0.963	−0.003 to 0.009	0.337
Gender	0.034	1.370	−0.015 to 0.083	0.172
GHS	−0.018	−1.600	−0.041 to 0.004	0.111
RBANS	0.006	5.480	0.004 to 0.008	<0.001
Model 2				
Task				
Alpha vs. DTW	−0.028	−1.478	−0.065 to 0.009	0.141
Pain interference				
High vs. low–medium	−0.007	−0.228	−0.065 to 0.052	0.820
Task × interference				
Alpha vs. DTW × pain yes vs. no	0.013	0.435	−0.045 to 0.070	0.664
Covariates				
Age	0.000	0.225	−0.003 to 0.004	0.822
Education	0.021	5.161	0.013 to 0.293	<0.001
GDS	0.003	0.909	−0.003 to 0.009	0.365
Gender	0.034	1.376	−0.015 to 0.083	0.170
GHS	−0.019	−1.644	−0.041 to 0.004	0.102
RBANS	0.006	5.498	0.004 to 0.008	<0.001

Model 1 evaluated effects of task and pain severity; Model 2 evaluated effects of task and pain interference. Results of models adjusted for age, gender, education, depression (i.e., GDS), comorbidity status (i.e., GHS), and RBANS total index score.

PFC under-activation across tasks of increasing cognitive demand. In this study, high pain severity, but not pain interference, moderated the change in prefrontal oxygenation across tasks of increasing cognitive load. This differential association suggests that task-related differences in brain activation patterns may be more sensitive to the effects of self-perceived pain severity than interference. Pain severity and pain interference are theoretically independent constructs [2]. For example, a national sample of adults with chronic pain found that, although pain severity accounted for a significant portion of pain interference, other factors, such as pain catastrophizing, fear of pain, guarding, and control beliefs, also contributed significantly to pain interference [37]. Thus, our findings suggest that it is the severity of pain, not the interference of pain in one's daily life, that further stresses the attention system, which in turn results in an attenuated brain response to tasks that increase in complexity and difficulty.

Our results did not support the expected moderating effects of perceived pain on performance-based outcomes such as gait velocity and letter generation. A possible explanation for the discrepancy in the results comparing fNIRS-derived measurements of HbO_2 with performance-based outcomes is that the former may be more sensitive to the effects of perceived pain in our study sample. Our findings are inconsistent with prior studies that have found pain to be a moderator of physical performance outcomes, such as trunk coordination and gait speed variability, in adults with chronic low back pain [5, 6]. This inconsistency may be attributable to differences in our study measures and sample population, which consisted of older adults who were relatively healthy and who did not report chronic back pain.

Results of this study also indicated that general cognition (i.e., RBANS) was associated with better performance on behavioral tasks. General cognition and education were positively associated with cognitive performance during the Cognitive Interference (i.e., Alpha) task. Education was also significantly associated with prefrontal oxygenation levels during study tasks. Given that education is often used as a proxy measure of cognitive reserve, these results suggest that, among older adults, cognitive factors play an important role in brain and behavior outcomes during walking. These results provide further justification for the inclusion of education and general cognition as covariates in this study.

Clinical Implications

The present study sheds light on the importance of the clinical use of routine pain assessments for community-dwelling older adults. The present findings revealed that

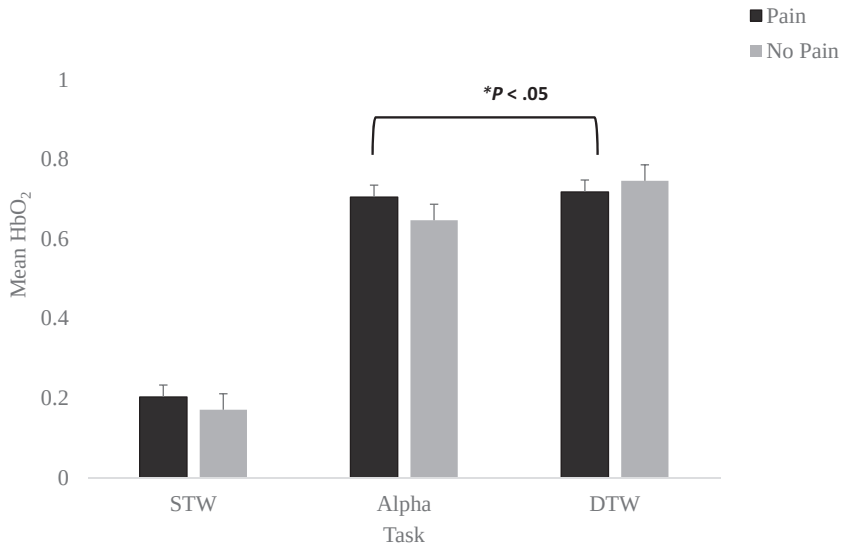

Figure 1. Moderation effect of pain status on prefrontal oxygenation in single vs. dual tasks.

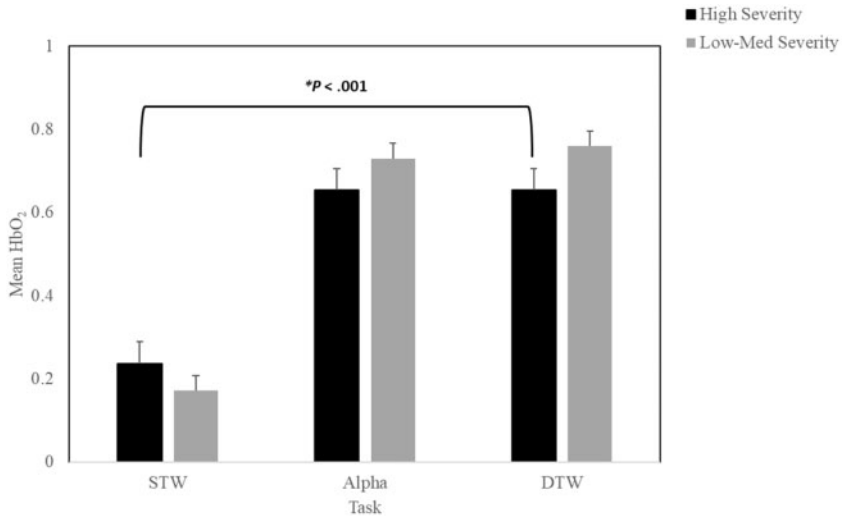

Figure 2. Moderation effect of pain severity on prefrontal oxygenation in single vs. dual tasks.

the presence and severity of pain over 1 month were associated with attenuated patterns of PFC activation during dual-task walking. These pain-related patterns of neural under-activation may be clinically relevant in that they appear to precede the effect of perceived pain on performance and functional outcomes. Furthermore, our findings are consistent with existing literature that indicates that perceived pain severity and interference are theoretically independent constructs [2]. These results suggest that clinical assessments that inquire about pain presence and severity may be useful in identifying older adults at risk of experiencing patterns of neural under-recruitment during dual-task walking.

Strengths, Limitations, and Future Directions

Strengths of the present investigation include the use of novel experimental procedures, as well as the use of a community-dwelling sample. Although prior studies have examined the impact of pain on physical performance in pain populations, the present investigation extends the generalizability of these findings to community-dwelling older adults [5, 6]. To our knowledge, the present study is the first to consider the impact of pain on the cortical control of locomotion in healthy older adults. The fNIRS system we used provides a number of advantages, which include enhanced portability and a means of assessing cortical activation during active walking. Although the system is somewhat limited in terms of depth of penetration and spatial resolution, the results of our recent MRI fNIRS co-registration study provide further validation for the use of this system among older adults [38].

This study has several limitations to consider. First, this study did not consider the impact of differences in participants' clinical pain status. Thus, future studies

may consider further dichotomizing their sample to determine the effects of clinical pain status (e.g., low back pain, fibromyalgia, etc.) on neurological outcomes. Furthermore, this study did not consider the impact of self-reported pain location and level of pain during walking on study outcomes. Therefore, the effects of various pain locations and pain types (e.g., nociceptive inflammatory pain vs. neuropathic pain; somatic pain vs. visceral pain) on brain and behavior outcomes were not assessed. Additionally, this study used a pain measure that required participants to aggregate their pain experiences over the course of 1 month. As such, the impact of current pain was not assessed.

Methodological issues associated with the use of fNIRS measurements must also be noted. More specifically, this technology is susceptible to spontaneous fluctuation or physiology-based systemic interferences in the signal due to cardiac pulsation, respiration, and other spontaneous low-frequency oscillations [39]. However, the method used in this study to process the fNIRS signal has been recently validated against automated algorithms designed to remove such interference effects [40]. Moreover, such limitations were not likely to influence the moderating effects of perceived pain 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. The use of mean performance outcomes may also be considered a limitation of the present study, as measures of performance variability (i.e., stride and swing time variability) have been shown to be more sensitive predictors of long-term physical function in community-dwelling older adults [41]. Furthermore, there is prior literature to suggest that measures of intra-individual variability may be more sensitive to the effects of pain [42]. Future studies may consider the use of measures of performance variability in order to further explore the impact of pain on neural and behavioral outcomes.

Conclusion

The present findings revealed that the presence and severity of pain over 1 month were associated with attenuated patterns of PFC activation during dual-task walking.

Acknowledgments

We thank all members of the Neuropsychology Cognition and Mobility Lab for their contributions toward data collection and the management of study-related activities.

References

1. Patel KV, Guralnik JM, Dansie EJ, Turk DC. Prevalence and impact of pain among older adults in the United States: Findings from the 2011 National Health and Aging Trends study. Pain 2013;154(12):2649–57.
2. Sherbourne CD. Pain measures. In: Stewart AL, Ware JE, eds. Measuring Functioning and Well-Being: The Medical Outcomes Study Approach. Durham: Duke University Press; 1994:220–34.
3. Von Korff M, Jensen MP, Karoly P. Assessing global pain severity by self-report in clinical and health services research. Spine 2000;25(24):3140–51.
4. Weiner DK, Rudy RE, Kim YS, Golla S. Do medical factors predict disability in older adults with persistent low back pain? Pain 2004;112(1–2):214–20.
5. Hamacher D, Hamacher D, Schega L. A cognitive dual task affects gait variability in patients suffering from chronic low back pain. Exp Brain Res 2014;232(11):3509–13.
6. Lamoth CJC, Stins JF, Pont M, Kerckhoff F, Beek PJ. Effects of attention on the control of locomotion in individuals with chronic low back pain. J Neuroeng Rehabil 2008;5(1):13.
7. Holtzer R, Mahoney J, Verghese J. Intraindividual variability in executive functions but not speed of processing or conflict resolution predicts performance differences in gait speed in older adults. J Gerontol A Biol Sci Med Sci 2014;69(8):980–6.
8. Holtzer R, Wang C, Verghese J. Performance variance on walking while talking tasks: Theory, findings, and clinical implications. Age (Dordr) 2014;36(1):373–81.
9. Holtzer R, Stern Y, Rakitin BC. Age-related differences in executive control of working memory. Mem Cognit 2004;32 (8):1333–45.
10. Holtzer R, Stern Y, Rakitin BC. Predicting age-related dual-task effects with individual differences on neuropsychological tests. Neuropsychology 2005;19(1):18–27.
11. Holtzer R, Mahoney JR, Izzetoglu M, et al. fNIRS study of walking and walking while talking in young and old individuals. J Gerontol A Biol Sci Med Sci 2011;66A(8):879–87.
12. Holtzer R, Mahoney JR, Izzetoglu M, et al. Online fronto-cortical control of simple and attention-demanding locomotion in humans. Neuroimage 2015;112(15):152–9.
13. Holtzer R, Verghese J, Allali G, et al. Neurological gait abnormalities moderate the functional brain signature of the posture first hypothesis. Brain Topogr 2016;29(2):334–43.
14. Holtzer R, Kraut R, Izzetoglu M, Ye K. The effect of fear of falling on prefrontal cortex activation and efficiency during walking in older adults. Geroscience 2019;41(1):89–100.
15. Lucas M, Wagshul ME, Izzetoglu M, Holtzer R. Moderating effect of white matter integrity on brain activation during dual-task walking in older adults. J Gerontol A Biol Sci Med Sci 2019; 74(4):435–41.
16. Wagshul ME, Lucas M, Ye K, Izzetoglu M, Holtzer R. Multimodal neuroimaging of dual-task walking: Structural MRI and fNIRS analysis reveals prefrontal grey matter volume moderation of brain activation in older adults. Neuroimage 2019;189 (1):745–54.
17. Seminowicz DA, Mikuli DJ, Davis KD. Cognitive modulation of pain-related brain responses depends on behavioral strategy. Pain 2004;112(1–2):48–58.
18. Moore DJ, Keogh E, Eccleston C. The interruptive effect of pain on attention. Q J Exp Psychol (Hove) 2012;65(3):565–86.
19. 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(10):1901–5.
20. Logan JM, Sanders AL, Snyder AZ, Morris JC, Buckner RL. Under-recruitment and nonselective recruitment: Dissociable neural mechanisms associated with aging. Neuron 2002;33 (5):827–40.
21. Zacks RT, Hasher L. Capacity theory and the processing of inferences. In: Light LL, Burke DM, eds. Language, Memory,

and Aging. New York: Cambridge University Press; 1988:154–70.
22. Baker PS, Bodner EV, Allman RM. Measuring life-space mobility in community-dwelling older adults. J Am Geriatr Soc 2003; 51(11):1610–4.
23. Galvin JE, Roe CM, Powlishta KK, et al. A brief informant interview to detect dementia. Neurology 2005;65(4):559–64.
24. Lipton RB, Katz MJ, Kuslansky G, et al. Screening for dementia by telephone using the memory impairment screen. J Am Geriatr Soc 2003;51(10):1382–90.
25. Holtzer R, Verghese J, Wang C, Hall CB, Lipton RB. Within-person across-neuropsychological test variability and incident dementia. JAMA 2008;300(7):823–30.
26. Lynall RC, Zukowski LA, Plummer P, Mihalik JP. Reliability and validity of the Protokinetics Movement Analysis Software in measuring center of pressure during walking. Gait Posture 2017;52:308–11.
27. England SE, Verghese J, Mahoney JR, Trantzas C, Holtzer R. Three-level rating of turns while walking. Gait Posture 2015;41 (1):300–3.
28. Izzetoglu M, Devaraj A, Bunce S, Onaral B. Motion artifact cancellation in NIR Spectroscopy using wiener filtering. IEEE Trans Biomed Eng 2005;52(5):934–8.
29. Holtzer R, Schoen C, Demetriou E, et al. Stress and gender effects on prefrontal cortex oxygenation levels assessed during single and dual-task walking conditions. Cogn Neurosci 2017; 45(5):660–75.
30. Ayaz H, Izzetoglu M, Platek SM, et al. Registering fNIR data to brain surface image using MRI templates. IEEE J Biomed Health Inform 2006;2671–4.
31. Izzetoglu M, Chitrapu P, Bunce S, Onaral B. Motion artifact cancellation in NIR Spectroscopy using discrete Kalman filtering. Biomed Eng Online 2010;9(1):16.
32. Harada T, Miyai I, Suzuki M, Kubota K. Gait capacity affects cortical activation patterns related to speed control in the elderly. Exp Brain Res 2009;193(3):445–54.
33. Hays RD, Sherbourne CD, Mazel RM. User's Manual for the Medical Outcomes Study (MOS) Core Measures of Health-Related Quality of Life. Santa Monica: Rand Corporation. 1995.
34. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: A preliminary report. J Psychiat Res1982;17(1):37–49.
35. Duff K, Humphreysclark J, Obryant S, et al. Utility of the RBANS in detecting cognitive impairment associated with Alzheimer's disease: Sensitivity, specificity, and positive and negative predictive powers. Arch Clin Neuropsychol 2008;23(5):603–12.
36. Okura Y, Urban LH, Mahoney DW, Jacobsen SJ, Rodeheffer RJ. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. J Clin Epidemiol 2004;57(10):1096–103.
37. Karoly P, Ruehlman LS. Psychosocial aspects of pain-related task interference: An exploratory analysis in a general population sample. Pain Med 2007;8(7):563–72.
38. Chen M, Pillemer S, England S, et al. Neural correlates of obstacle negotiation in older adults: An fNIRS study. Gait Posture 2017;58:130–5.
39. Erdogan SB, Yucel MA, Akin A. Analysis of task-evoked systemic interference in fNIRS measurements: Insights from fMRI. NeuroImage 2014;87(15):490–504.
40. Izzetoglu M, Holtzer R. Effects of processing methods on fNIRS signal assessed during active walking task in older adults. IEEE Trans Neural Syst Rehabil Eng 2020;28(3):699–709.
41. Hausdorff JM, Rios DA, Edelberg HK. Gait variability and fall risk in community-living older adults. Arch Phys Med Rehabil 2001;82(8):1050–6.
42. Fuentes K, Hunter MA, Strauss E, Hultsch DF. Intraindividual variability in cognitive performance in persons with chronic fatigue syndrome. Clin Neuropsychol 2001;15(2):210–27.