Abstract

The Impact of Perceived Pain on Neural Efficiency During Walking in Older Adults

Objective: Pain is a mechanism for attention disruption due, in part, to a shared reliance on the prefrontal cortex (PFC). Amongst older adults, the experience of pain is known to be both prevalent and functionally impactful. Dual-task walking (DTW) paradigms are not only a useful means of assessing the impact of pain on attentional control, but also known to be sensitive to changes in the cortical hemodynamic response within the PFC. To date, however, few studies have utilized such paradigms to examine the impact of self-reported pain on attentional control via assessment of cognitive and behavioral outcomes. Examining these associations would facilitate a better understanding of ways in which pain may impact cognitive and neural efficiency, thereby increasing risk of adverse functional outcomes, in healthy aging. Additionally, given evidence to suggest that males and females differ in neural responses to pain processing, exploring whether these associations differ by gender may yield useful clinical implications. **Methods:** Study participants (N= 408) were grouped into pain (n= 266) and no pain (n= 142) groups based upon their responses on the MOS-PSS and MOS-PES. These questionnaires were also used to assess self-reported levels of pain severity and interference amongst individuals with reported pain. Functional near-infrared spectroscopy was used to measure intraindividual variability (IIV) of the cortical hemodynamic response within the PFC during a DTW paradigm. PKMAS software was used to assess IIV in stride length, while rate of correct letter generation was used as a measure of cognitive accuracy. Linear mixed effects models (LMEMs) were used to examine the effects of perceived pain on neural and behavioral responses as well as on the change in these outcomes form single- to dual-task conditions. Stratified LMEMs were used to examine

whether these associations differed by gender. **Results:** LMEMs revealed that perceived pain presence was associated with reduced IIV in PFC oxygenation and reduced IIV in stride length in the DTW condition. High pain severity was associated with a greater increase in stride length IIV from STW to DTW. Stratified LMEMs revealed that the association between pain and neural IIV was significant in only males, while the associations between pain and gait IIV were significant in only females. **Potential Implications:** Study results suggest that self-reported pain over one month is associated with differential patterns of neural and behavioral responding amongst healthy, community-dwelling older adults. In this population, these patterns may reflect a tendency towards inefficient neural and behavioral modifications in response to perceived pain. These findings highlight the need for clinical use of routine pain assessments and, when appropriate, the implementation of timely and effective pain treatments in aging.

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Dedication

This dissertation is dedicated to my parents, whose love and support has been a lifelong source of inspiration. This work is also dedicated to my husband, who has patiently and lovingly stood by my side throughout the years.

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Chapter I: Introduction

Pain is prevalent in aging and is associated with decrements in affective, cognitive, and physical functioning (Geerlings et al., 2002; Hamacher et al., 2014; Leveille et al., 2009; Patel et al., 2013). Sex differences in pain processing are well documented in the literature, with women demonstrating increased pain sensitivity and a greater risk of developing clinical pain conditions as compared to men (Fillingim et al., 2009; LeResche, 2011; Monroe et al., 2015; Straube et al., 2009). In terms of cognitive impact, self-reported pain has commonly been associated with declines in frontal cortex-mediated abilities including aspects of attention/executive functions (Moore et al., 2012; Seminowicz & Moayedi, 2017). Furthermore, the impact of pain on complex motor performance (e.g., gait) is thought to be mediated, at least in part, by attention/executive functions (Coppin et al., 2006). Such associations between pain and aspects of attention/executive functions are attributable to their shared reliance on frontal brain regions, including the prefrontal cortex (PFC) (Seminowicz & Moayedi, 2017).

The PFC has also been implicated in the maintenance of behavioral consistency over time. As such, intraindividual variability (IIV) in performance outcomes is known to be associated with functional activation patterns within this brain region (De Felice & Holland, 2018; Grady et al., 2011). Age-related changes in structure and function within frontal brain regions, including the PFC, are thought to contribute to increases in behavioral IIV in older age (Garrett et al. 2011, West et al., 2002). There is a limited body of evidence to suggest that older adults also exhibit increased IIV in functional activity within frontal brain regions.

Furthermore, age-related increases in neural IIV have been found to be associated with decrements in behavioral performance (Grady et al., 2010; Garrett et al., 2011).

Dual-task walking paradigms are often used to examine the effects of divided attention on behavioral outcomes across tasks of rising cognitive demand (Hausdorff et al., 2008; Lundin-Olsson et al., 1997). In the context of such paradigms, decrements in performance from single to dual-task conditions (i.e., dual-task costs) are a means of quantifying the effects of cognitive interference on behavior (Hausdorff et al., 2008). There is evidence to suggest that dual-task costs increase with age and this effect may be partially mediated by known age-related changes in attention/executive functions (Lindenberger et al., 2000; Verhaeghen & Cerella, 2002). Furthermore, older adults with pain may exhibit greater dual-task costs as compared to individuals who are pain-free (Hamacher et al., 2014).

Neural efficiency refers to the extent of brain activation needed in order to allow an individual to appropriately meet task demands. More specifically, neural efficiency theory posits that a more efficient brain utilizes fewer resources to maintain adequate task performance (Haier et al., 1988). From this perspective, the study of neural efficiency requires examination of brain function as well as associated behavioral outcomes. To date, there is limited research regarding the impact of perceived pain on neural efficiency in healthy, community-dwelling older adults. Examining the impact of perceived pain on IIV in behavior can be useful in this regard as greater behavioral IIV has been considered to be an indication of neural inefficiency in this population (Strauss et al., 2007). Furthermore, amongst older adults, pain has been found to moderate the change in IIV in gait performances across tasks of rising cognitive load (Hamacher et al., 2014). Examining the

impact of perceived pain on IIV in the hemodynamic response within the PFC is novel and can also provide useful information regarding the impact of pain on neural efficiency in aging. More specifically, greater increases in IIV of the hemodynamic response within the PFC may be an indication of neural inefficiency in older adults (Garrett et al., 2011).

Examining the impact of perceived pain on IIV in cortical control of walking as well as on IIV in behavioral outcomes can provide important information regarding the impact of pain on neural efficiency in aging. Furthermore, given the known gender disparities in pain processing, it is important to determine whether these associations differ as a function of gender. This study aimed to investigate the moderating effect of pain, as assessed by the MOS-PSS and MOS-PES, on changes in IIV in gait performance, IIV in functional near-infrared spectroscopy (fNIRS) derived PFC oxygenation, and cognitive accuracy from single to dual-task conditions. This study also aimed to explore whether gender influences the associations between pain and gait performance, cognitive accuracy, and PFC activation levels in a sample of healthy, community-dwelling older adults.

Key Terms

- Dual-task walking (DTW): A task of divided attention which requires simultaneous engagement in walking and cognitive processing, with particular relevance for older adults given age-related changes in gait and attentional control.
- Neural Efficiency: A theoretical concept which suggests that, in the context of preserved or improved behavioral performance, reduced activation in frontal brain regions is an indicator of adaptive and well-regulated neural functioning.
- Functional near-infrared spectroscopy (fNIRS): A portable neuroimaging technique that uses light to assess changes in blood oxygenation in the cerebral cortex. Often

designed as a flexible band placed across the forehead, fNIRS is specifically sensitive to changes in the prefrontal cortex (PFC).

Background and Significance

Pain Constructs and Dimensions

Pain is a characteristic feature of a variety of disease diagnoses and is commonly defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (Henschke, Kamper, & Maher, 2015; IASP, 1994). It is known to be a multidimensional, subjective experience that is reliant on both peripheral and central nervous system processes (Melzack & Wall, 1965; Moayedi & Davis, 2013). Melzack and Casey identified three distinct dimensions of pain processing, which include: the sensory-discriminative, affective-motivational, and cognitive-evaluative dimensions (Melzack & Casey, 1968). These dimensions of pain processing are thought to occur in a sequential manner according to the level of cognitive involvement required (Wade & Hart, 2002).

The sensory-discriminative dimension, which requires minimal cognitive involvement, refers to an individual's processing of sensory, spatial, and temporal aspects of pain stimulation. For example, individual differences in sensory-discriminative aspects of pain processing can be measured via self-reported pain quality, intensity, location, and duration. The affective-motivational dimension, which requires limited cognitive involvement, refers to an individual's affective response to pain stimulation. For example, individual differences in affective-motivational aspects of pain processing can be measured

via self-reported pain unpleasantness ratings. And finally, the cognitive-evaluative dimension refers to an individual's cognitive appraisal of pain and can be measured via self-reported pain catastrophization and pain coping beliefs (Melzack & Casey, 1968; Moayedi & Davis, 2013; Wade & Hart, 2002). Interactions between the various dimensions of pain processing are thought to contribute to individual differences in the subjective experience of pain (Melzack & Casey, 1968; Moayedi & Davis, 2013).

Self-report questionnaires are commonly used in clinical pain research and are known to be reliable and valid methods of assessment in older adults (Gagliese, 2009; Sherbourne, 1992). Pain questionnaires can assess a wide variety of constructs including, but not limited to, pain severity and pain-related functional interference (Sherbourne, 1992; Von Korff et al., 2000). Pain severity refers to the intensity of pain experienced, while interference refers to the extent of pain-related disability experienced. While these constructs were originally proposed to be theoretically independent, there is evidence to suggest that this may not always be the case (Kratz et al., 2017; Sherbourne, 1992; Von Korff et al., 2000). In their review of pain assessments used in recent clinical research, Von Korff and colleagues propose that severity and interference may either represent a single construct or distinct constructs depending on the chosen method of assessment as well as the extent of variation in pain severity scores within the study sample (Von Korff et al., 2000).

Pain and Attention

Attention is considered to be one aspect of a broad set of cognitive processes referred to as executive functions. Executive functions are comprised of cognitive abilities that regulate an individual's ability to engage in purposeful, task-oriented behaviors (Lezak, 1995; Stuss, 2011). Since the development of early theoretical models, attention has been

conceptualized as a mechanism for the selection of action (Broadbent, 1958; James, 1980). More specifically, attention has been postulated to function as a filter for information processing and can be directed either internally or externally (Eccleston & Crombez, 1999; Rueda, Posner, & Rothbart, 2005). When directed internally, attention allows for the processing of memories, thoughts, and emotions. When attention is directed externally, however, it allows for the processing of environmental stimuli and relevant task demands. Furthermore, the focus of attention can be shifted according to external factors (i.e., bottom-up processing) as well as internal, motivational factors (i.e., top-down processing) (Rueda, Posner, & Rothbart, 2005).

Pain is theorized to be a mechanism for attention disruption. From an evolutionary perspective, the purpose of pain is to shift attention away from the task at hand and to divert cognitive resources towards behaviors that are intended to promote survival (Eccleston & Crombez, 1999). Pain is known to affect aspects of attention as a result of shared neural substrates, which include frontal brain regions such as the prefrontal cortex (PFC) (Lorenz et al., 2003; Moore et al., 2012; Seminowicz & Moayedi, 2017; Sevel et al., 2016). More specifically, the PFC has been found to play a role in sensory processing activities (e.g., pain processing) as well as in attention processes (Seminowicz & Moayedi, 2017). As a result, it has been theorized that pain impacts attention as a result of the competition for resources inherent within a limited-capacity cognitive system (Kahneman, 1973; Logan, 1985).

The impact of pain on attention may vary as a function of the level of cognitive demand inherent in a particular task. For example, Moore and colleagues examined the effects of experimentally induced pain on cognitive performances in healthy adults across various tasks of attention. While pain did not affect performances on simple tasks of basic

and divided attention, it did impact performance accuracy on more difficult tasks of attention span and divided attention (Moore et al., 2012). As such, it may be that the effects of pain on aspects of attention are apparent only when task demands are high.

Gender Disparities in Pain Processing

There is recent evidence to suggest the presence of sex differences in neural mechanisms of pain processing. To date, however, the literature appears to be mixed with regards to the directionality of gender differences in pain-related activation patterns within the PFC. Monroe and colleagues utilized a thermal stimulation paradigm to conduct an fMRI study examining gender differences in the neural response to pain. They found that women exhibited attenuated reductions in activation within brain regions associated with pain processing, including the dorsolateral PFC (Monroe et al., 2015). In contrast, results of another fMRI study conducted by Straube and colleagues indicate that, during select pain stimulation conditions (i.e., pain anticipation condition, intense pain condition), women displayed stronger neural activation in a select region of the PFC (i.e. pregenual medial PFC) (Straube et al., 2009).

Such discrepancies in pain processing are thought to contribute to known gender disparities in pain prevalence. More specifically, there is a wide body of literature to suggest that pain is more prevalent in women than in men (Fillingim et al., 2009; LeResche, 2011). Furthermore, women are known to demonstrated increased pain sensitivity and an increased risk of developing multi-site pain as compared to their male counterparts (Bartley & Palit, 2016; Monroe et al., 2015; Straube et al., 2009). Such findings draw attention to the need for further examination of gender differences in the neural response to pain, particularly in the context of aging.

Pain in Older Adults

Pain is known to be prevalent in aging (Leveille et al., 2009; Patel et al., 2013). Based upon data from the 2011 National Health and Aging Trends Study it has been estimated that approximately 18.7 million older adults in the United States experience recent, bothersome pain (Patel et al., 2013). Furthermore, there is evidence to suggest a high prevalence of multi-site pain amongst those older adults who endorse recent, bothersome pain (Patel et al., 2013). Pain has known associations with a variety of cognitive, affective, and behavioral outcomes in aging (Geerlings et al., 2002; Hamacher et al., 2014; Leveille et al., 2009; Patel et al., 2013).

Studies that have examined the relationship between self-reported pain and mobility outcomes in older adults have consistently found pain to be associated with decrements in physical functioning (Leveille et al., 2009; Patel et al., 2013; Weiner et al., 2004). Patel and colleagues examined the prevalence and impact of pain in a nationally-representative sample of older adults and found that individuals with reported pain as well as those with multiple sites of bodily pain demonstrated decrements in grip strength, gait speed, and lower-extremity function when compared to their pain-free counterparts (Patel et al., 2013). Leveille and colleagues examined the association between pain and risk of falls in aging and found that self-reported pain at baseline was associated with a 77% increased likelihood of falling in the subsequent month (Leveille et al., 2009).

Pain is a known predictor of health service usage and individuals with pain utilize a greater number of healthcare resources as compared to the general population (Henschke et al., 2015; McBeth & Jones, 2007). The continued growth of the older adult population within the United States is expected to place an increasing economic burden on the healthcare

system (Gagliese, 2009; Henschke et al., 2015). Given the high prevalence of pain in aging as well as its known association with healthcare utilization, there has been an increased demand for research examining predictors and effects of geriatric pain. In a review of recent literature related to geriatric pain, Gagliese found that the number of publications about pain and aging has increased by approximately six-fold over two decades (Gagliese, 2009).

Gait in Aging

Gait disturbances are common in aging and it has been estimated that 32% of community-dwelling older adults over the age of 60 demonstrate signs of impaired gait (Mahlknecht et al., 2013). Older adults are known to be susceptible to age-related declines in gait automaticity. These declines in automaticity, in turn, necessitate a compensatory reliance on executive functions as a means of regulating gait (Lindenberger, Mariske, & Baltes, 2000; Pugh & Lipsitz, 2002).

Declines in complex gait performance are thought to be mediated, at least in part, by age-related changes in executive functions (Coppin et al., 2006; Holtzer et al., 2006; Hausdorff et al., 2008). More specifically, there is evidence to suggest that age-related decrements in gait automaticity are attributable to declines in aspects of executive functions (Coppin et al., 2006; Lindenberger, Marsiske, & Baltes, 2000). Indeed, these age-related declines in gait performance and focal aspects of cognition are thought to be attributable to the shared neural substrates underlying these processes (Paraskevoudi, Balci, & Vatakis, 2018). Coppin and colleagues examined the relationship between executive functions, as assessed by performance on the Trail Making Test, and complex gait performances in a sample of community-dwelling older adults. They found that individuals who performed poorly on the Trail Making Test demonstrated reduced gait velocity across task conditions

(Coppin et al., 2006). As such, examining complex gait outcomes in older adults may serve as a proxy measure of the integrity of executive functions in aging.

Dual-Task Walking in Aging. Studies that have utilized dual-task walking paradigms, which require individuals to walk while performing a simultaneous task, provide further evidence for the occurrence of age-related declines in complex gait functions. For example, Lindenberger and colleagues examined the impact of age on dual-task walking in a sample comprised of younger and older adults. They found that, in the dual-task walking condition, older adults showed greater reductions in gait velocity as well as an increased number of missteps as compared to their younger counterparts (Lindenberger et al., 2000).

Dual-task paradigms also present a useful means for examining the impact of age on executive control (Medeiros-Ward et al., 2015). Considered to be an aspect of a broader set of executive functions, the executive control of attention (i.e., executive control) refers to an individual's ability to allocate attentional resources to meet environmental demands. Executive control has been found to be associated with functional activity within specific frontal brain areas such as the lateral prefrontal cortex (Norman & Shallice, 1986; Posner & Fan, 2008; Rueda et al., 2005). It is often assessed via the administration of tasks of divided attention, which require the splitting of cognitive resources between simultaneous tasks (Baddeley & Hitch, 1974; Botvinick et al., 2001; MacDonald et al., 2012).

The dual-task walking paradigm, which is comprised of both single and dual-task walking conditions, can be utilized to examine the impact of age on executive control processes as well as on simple and complex gait performance. There are recent review and meta-analysis studies which demonstrate the utility and reliability of such a paradigm, which is commonly used to assess gait outcomes in aging (Smith et al., 2016; Smith et al., 2017).

Within this paradigm, the dual-task condition demands a greater level of executive control as well as differential involvement of the PFC relative to the single-task condition (Holtzer et al., 2011; Lovden et al., 2008). As such, it is perhaps unsurprising that neuropsychological performance on tasks of attention and executive functions have been shown to predict dual-task walking performance (Holtzer et al., 2005; Holtzer et al., 2006). When attention is concurrently divided between two cognitively demanding tasks, decrements in performance are expected to occur. These decrements in performance, known as dual-task costs, are a means of quantifying the effects of divided attention on behavior (Hausdorff et al., 2008; Lundin-Olsson et al., 1997; Tombu & Jolicoeur, 2003). Dual-task costs in walking are known to increase with age, providing further evidence that the prevalence of gait disturbances in aging may be associated with age-related decrements in executive control (Lindenberger et al., 2000).

Neural Efficiency

First introduced by Haier and colleagues (1988), neural efficiency theory posits that brain efficiency can be assessed as a function of the magnitude of brain activations necessary in order to enable an individual to meet specific task demands. More specifically, this theory suggests that, in the context of preserved behavioral performance, greater neural efficiency is associated with reduced brain activity (Haier et al., 1988; Neubaeur & Fink, 2009). As such, it has been suggested that the ideal methods for the assessment of neural efficiency in a clinical research setting should involve consideration of both neural and behavioral outcomes (Neubauer & Fink, 2009; Krauker et al., 2017). Neural efficiency is commonly examined in the context of brain activation patterns in frontal brain regions (e.g., PFC) as these areas are

known to be involved in the recruitment and allocation of cognitive resources during goal-directed behavior (Medeiros-Ward et al., 2015; Neubaeur & Fink, 2009).

Pain and Dual-Task Walking in Older Adults

There is currently a limited number of studies that have utilized dual-task walking paradigms to examine the impact of pain on physical performance outcomes in aging. Based upon the literature to date, there is mixed evidence with regards to the direct impact of pain on gait performance. Asai and colleagues examined the effect of perceived pain on gait performances in a sample of community-dwelling adults ages 65 and older. They found that perceived pain, as assessed by the number of reported musculoskeletal pain sites, was not associated with stride time variability in single and dual-task walking conditions (Asai et al., 2015). In another study, Lamoth and colleagues utilized a dual-task paradigm to examine the effects of chronic pain on a number of gait outcomes amongst a sample of adults with and without chronic low back pain. Their results indicated that individuals with chronic low back pain demonstrated reduced stride velocity, stride length, and stride length variability in the dual-task walking condition as compared to healthy controls (Lamoth et al., 2008).

There is evidence to suggest that pain may have a moderating effect on gait outcomes in aging (Hamacher et al., 2014). Hamacher and colleagues used a dual-task paradigm to examine the main and moderating effects of pain on gait performances in a sample of middle and older-age adults with and without low back pain. Similar to the study conducted by Asai and colleagues, Hamacher and colleagues' results also suggest no direct association between pain and gait performance across walking tasks. Results of the study did indicate, however, that pain status moderated the change in gait performance across tasks of rising complexity (i.e., executive demands). More specifically, individuals with low back pain exhibited a

significant increase in stride variability of trunk movements from single to dual-task walking as compared to healthy controls (Hamacher et al., 2014).

A recent study conducted in this lab also utilized a dual-task paradigm to examine the moderating effect of pain on gait performances in a sample of community-dwelling older adults. Results of the study indicated that perceived pain did not moderate the change in average gait velocity from single to dual-task walking conditions (Pakray et al., 2021). When considering the moderating effects of pain on gait performance, the discrepancy in findings between the aforementioned studies may be attributable to differences in the metrics used to evaluate gait performances. More specifically, it may be that measures of performance variability are more sensitive to the effects of pain on physical performance as compared to mean performance measures.

Pain and Cognitive Control of Gait in Older Adults. To date, there are very few studies that have examined the impact of pain on the cognitive control of gait in aging. A recent study conducted in this lab examined the effects of perceived pain on changes in fNIRS-derived oxygenated hemoglobin (HbO_2) in the PFC as well as in behavioral performances from single to dual-task walking conditions in a sample of community-dwelling older adults. Study findings revealed that perceived pain moderated task-related changes in PFC HbO_2 levels. More specifically, individuals with perceived pain as well as those with self-reported high pain severity demonstrated attenuated increases in PFC HbO_2 from single to dual-task conditions. Although perceived pain was found to have a moderating effect on the cognitive control of locomotion, it was not found to be a moderator of behavioral outcomes such as average gait velocity and rate of correct letter generation

(Pakray et al., 2021). As such, the authors were limited in their scope of conclusions with regards to the effects of perceived pain on neural efficiency in this population.

Defining Intraindividual Variability

Variability is a measure of the level of consistency inherent within a distribution. It is heterogeneous in that it can be considered at various levels of analysis and over various periods of time. More specifically, variability can either refer to differences in the consistency of biological or behavioral outcomes between individuals (i.e., inter-individual variability) or within individuals (i.e., intra-individual variability). Furthermore, it can be assessed within different temporal periods (e.g., moment-to-moment variability vs. day-to-day variability).

Much of the focus of cognitive and behavioral research has been placed upon the measurement of central group tendency (e.g., mean) as opposed to the measurement of variability (Cronbach, 1957; Stuss & Binns, 2008). However, there is evidence to suggest that examining measures of performance variability can provide unique information with regards to cognitive and behavioral functioning as compared to measures of central tendency. In terms of clinical utility, examining the variability inherent in performances can provide useful information regarding an individual's ability to sustain behaviors in a consistent manner over time (Stuss & Binns, 2008).

Intra-individual variability (IIV) in behavior refers to the level of consistency within an individual's performance over time (Stuss & Binns, 2008). It is commonly measured through the use of either an individual standard deviation (ISD) or coefficient of variation (COV). The ISD refers to the standard deviation of standardized scores across different tasks

for a single individual. The COV can be calculated by dividing the ISD by mean performance for each individual (De Felice & Holland, 2018).

Behavioral IIV in Older Adults. There is evidence to suggest that IIV in behavior increases with age and can be used as a means of quantifying the presence and extent of cognitive aging (MacDonald et al., 2012; Strauss et al., 2007; West et al., 2002). Such increases in performance IIV, which have been associated with damage in frontal brain regions, are thought to be attributable to brief lapses in sustained attention and difficulties in the maintenance of executive control (Stuss et al., 2003). Furthermore, changes in IIV may precede changes in mean performance outcomes in older adults (Lovden et al., 2008).

The association between age and IIV in cognitive performance may be mediated by the level of cognitive demand inherent in a particular task. MacDonald and colleagues examined the impact of age on executive attention in a sample comprised of younger and older adults. They found that older adults demonstrated greater IIV in response latencies on tasks of high executive demand (i.e., high cognitive interference trials) as compared to younger adults. There were no differences in outcomes between age groups, however, on tasks of low executive demand (i.e., low cognitive interference trials) (MacDonald et al., 2012). As such, it appears that task difficulty is an important consideration when examining the impact of age on IIV in performance.

There is evidence to suggest that greater IIV in gait performance may be a marker of cognitive aging in a subset of older adults. Bunce and colleagues found that increased IIV in reaction time on a stepping task was associated with an increased risk of future falls amongst community-dwelling older adults with mild cognitive impairment (Bunce et al., 2017). In another study which utilized a dual-task walking paradigm, Reelick and colleagues found

that older adults with a history of recurrent falls exhibited increased IIV in gait performance (i.e., greater stride length COV) in the dual-task condition which was posited to reflect dysfunction in the neurocognitive control of locomotion. Additionally, amongst this study sample, IIV in stride length was found to be a more sensitive predictor of fall status than mean performance (Reelick et al., 2013).

Neural IIV in Aging. To date, only a handful of studies have examined the impact of age on changes in neural IIV (Garrett et al., 2013). Garrett and colleagues were among the first to use fMRI to examine age-related changes in IIV of the cortical hemodynamic response (i.e., BOLD SD) in a sample comprised of younger and older adults (Grady & Garrett, 2014). They found that, at rest, older adults demonstrated reduced neural IIV in most brain regions. In select frontal brain regions, however, older adults exhibited increased neural IIV as compared to their younger counterparts (Garrett et al., 2010). These findings suggest that the association between neural IIV and cognitive aging depends on the brain region being assessed.

The literature regarding the associations between neural IIV and task performance has also been mixed. Results of a recent fMRI study revealed that greater neocortical IIV was associated with younger age and more accurate performance on a spatial working memory task, while greater neural IIV in the hippocampus and subcortical brain regions was associated with older age and poorer performance (Guitart-Masip et al., 2016). In another study, Garrett and colleagues examined the impact of IIV of the cortical hemodynamic response on behavioral outcomes in a sample of younger and older adults. Study findings indicated that, within most cortical regions, greater neural IIV was associated with younger age as well as faster and less variable reaction times on a cognitive task (Garrett et al., 2011).

Taken together, results of these studies suggest that the association between neural IIV and cognitive performance also appears to depend on the brain region assessed. Nevertheless, it may be that reduced neural IIV in neocortical areas is a marker of cognitive aging, and therefore inefficiency.

Measuring Brain Activation During Active Walking

fNIRS is an effective method of measuring changes in the cortical hemodynamic response during active walking. This neuroimaging method uses blood oxygenation as a proxy measure of neural activity. The use of fNIRS is ideal for the examination of changes in PFC oxygenation in the context of complex motor paradigms (Leff et al., 2011). Recent review papers highlight the ways in which this optical imaging technique has been used thus far to examine neural correlates of locomotion (Gramigna et al., 2017; Udina et al., 2019). To date, fNIRS has been used to examine trajectories of PFC oxygenation both within and across repeated walking trials (Holtzer, Izzetogulu, et al., 2019; Holtzer, Kraut, et al., 2019). Studies that have utilized dual-task walking paradigms have consistently shown that individuals demonstrate increased PFC activation in the dual-task walk, as compared to the single-task walk, condition (Holtzer et al., 2011, 2015). These results support the assumption that dual-task walking requires a greater level of executive control as compared to single-task walking. Furthermore, in the context of such fNIRS studies, changes in PFC oxygenation have been found to be associated with walking performance. More specifically, in a study conducted with a sample of community-dwelling older adults, increased PFC oxygenation was found to be associated with greater stride length (Holtzer et al., 2015).

A recent study aimed to examine the moderating effects of cognitive status on the change in IIV in PFC oxygenation from single to dual-task walking conditions. Results of the

study, which was conducted in a sample of healthy older adults, revealed that individuals with cognitive impairment demonstrated a greater increase in fNIRS-derived IIV in PFC oxygenation from single to dual-task walking conditions (Holtzer et al., 2020). These results suggest that, when examining individual differences in the trajectory of change in neural IIV from single to dual-task walking, a greater increase may reflect an inefficient cortical response.

Rationale of Current Study

Pain is prevalent in aging and is known to be a mechanism for attention disruption (Patel et al., 2013; Moore et al., 2012). Pain is thought to impact aspects of attention (i.e., executive attention) via a shared reliance on prefrontal brain regions (Lorenz et al., 2003; Sevel et al., 2016). Dual-task walking paradigms provide a useful method for examining the impact of pain on executive attention/control as complex gait outcomes are known to be heavily reliant on such cognitive abilities (Coppin et al., 2006; Holtzer et al., 2006; Hausdorff et al., 2008). Furthermore, such paradigms are known to be sensitive to changes in the cortical hemodynamic response within prefrontal brain regions (Wagshul et al., 2019).

To date, there has been limited research examining the impact of pain on dual-task walking in older adults. While the literature regarding the direct and moderating effects of pain on gait performance have been mixed, there is some evidence to suggest that pain is associated with reduced gait variability during dual-task walking (Lamoth et al., 2008). Results of a single study also suggest that pain may moderate the change in gait variability in aging (Hamacher et al., 2014). In terms of the pain-related changes in PFC activation patterns during dual-task walking, there is a single study to suggest that perceived pain moderates cognitive control of locomotion in older adults (Pakray et al., 2021). As such, it may be that

pain contributes to neural inefficiency in aging. Furthermore, given emerging literature about differences in the cortical hemodynamic response to pain amongst males and females, the impact of pain on neural inefficiency in aging may differ by gender (Monroe et al., 2015; Straube et al., 2009). In order to fully understand this relationship, however, further research is needed to clarify the main and moderating effects of pain on behavioral and neural outcomes in aging and to assess whether these associations differ by gender.

Aims and Hypotheses

This study examined the associations of perceived pain with gait performance, cognitive accuracy, and PFC oxygenation assessed under Single-Task-Walk (STW), Cognitive Interference (Alpha), and Dual-Task-Walk (DTW) conditions in healthy, community-dwelling older adults. Pain was assessed using the Medical Outcomes Study-Pain Effects Scale (MOS-PES) and Pain Severity Scale (MOS-PSS). fNIRS was used to assess PFC oxygenation (i.e., HbO_2). Gait parameters were assessed using ProtoKinetics Movement Analysis Software technology. IIV in gait was assessed using the COV for stride variability. IIV in cortical control was assessed using the SD of HbO_2 values within the first 30-second period of each experimental condition. Furthermore, the impact of gender on these associations was also be assessed.

Aim 1: Examined the main and moderating effects of perceived pain on the change in IIV in fNIRS-derived PFC oxygenation from single to dual-task conditions.

> *Hypothesis 1a*. We hypothesized that the presence of pain would be associated with reduced neural IIV in the dual-task condition and a greater increase in IIV in PFC oxygenation from single to dual-task conditions.

Hypothesis 1b. We hypothesized that, amongst individuals with reported pain, greater perceived pain (i.e., high pain severity, high pain interference) would be associated with reduced neural IIV in the dual-task condition and a greater increase in IIV in PFC oxygenation from single to dual-task conditions.

Aim 2: Examined the main and moderating effects of perceived pain on the change in IIV in gait performance from single to dual-task walking conditions.

Hypothesis 1a. We hypothesized that the presence of pain would be associated with greater IIV in gait performance in the dual-task condition and a greater increase in IIV in gait performance from single to dual-task walking.

Hypothesis 1b. We hypothesized that, amongst individuals with reported pain, greater perceived pain (i.e., high pain severity, high pain interference) would be associated with greater IIV in gait performance in the dual-task condition and a greater increase in IIV in gait performance from single to dual-task walking.

Aim 3 [supplementary]: Examined the main and moderating effects of perceived pain on the change in cognitive accuracy from single to dual-task walking conditions.

Hypothesis 1a. We hypothesized that the presence of pain would be associated with reduced cognitive accuracy in the dual-task walking condition and a greater reduction in cognitive accuracy from single to dual-task conditions.

Hypothesis 1b. We hypothesized that, amongst individuals with reported pain, greater perceived pain (i.e., high pain severity, high pain interference) would be associated with reduced cognitive accuracy in the dual-task walking condition and a greater reduction in cognitive accuracy from single to dual-task conditions.

Aim 4 [exploratory]: Explored whether the main and moderating effects of pain on changes in IIV in prefrontal oxygenation and gait performance from single to dual-task conditions differed by gender.

Hypothesis: We did not provide a directional hypothesis as this was an exploratory aim.

Chapter II: Methods

Participants & Study Procedures

This study was a secondary analysis nested within a longitudinal, cohort study of community-dwelling older adults entitled Central Control of Mobility in Aging (CCMA) (Holtzer et al., 2014a; Holtzer et al., 2014b). The parent study, CCMA, was carried out within the Division of Cognitive and Motor Aging and Geriatrics in Albert Einstein College of Medicine (RO1AG036921, PI: Holtzer, R) and was approved by the Einstein IRB (protocol #: 2010-224). The overarching goals of the parent study included the identification of cognitive and neural predictors of mobility performance, decline, and disability in aging. Participants included individuals aged 65 years or older who were recruited from Westchester County, New York.

Participants were first contacted by letter and subsequently by telephone in order to determine their level of interest and eligibility for participation. Inclusion criteria required that participants be at least 65 years old, be free of any neurodegenerative conditions, and have the capacity for independent ambulation. Exclusion criteria included: an inability to speak English, a dementia diagnosis, and substantial audiovisual loss. Further exclusion criteria included: a prior history of neurological or psychiatric disease, ongoing hemodialysis, and/or the scheduling of any recent or upcoming medical procedures that could negatively impact mobility. Participants were first screened via a structured, telephone interview which consisted of verbal consent procedures, a brief medical history questionnaire, mobility

questions, and validated cognitive screens in order to exclude dementia (Baker et al., 2013; Galvin et al., 2005; Lipton et al., 2003). Cognitive status was determined by yearly review via a formal case conference diagnostic procedure (Holtzer et al., 2008).

Participants in this study were individuals who had complete cognitive, gait, and fNIRS data collected in their first year of participation (i.e., Wave 1). Dates of enrollment for the full study sample spanned from June of 2011 to October of 2017 as recruitment was continuous throughout the course of the study. The study sample was comprised of a total of 408 individuals with and without reported pain. While CCMA participants were asked to return for yearly follow-up visits, only data collected as baseline was used for the purposes of this study.

Measures

The proposed study examined data from a subset of measures that were included in the original, parent study.

MOS Pain Scales

All participants in this study had completed the Medical Outcomes Study Pain Effects Scale (MOS-PES) and Pain Severity Scale (MOS-PSS) at baseline. The MOS-PSS was utilized to determine pain status amongst the entire study sample as well as level of pain severity amongst the subset of individuals with reported pain. The MOS-PSS includes 5-items that assess frequency, duration, and intensity of pain. Response options are provided on a Likert scale, with values ranging from 1-6 for the first 3 items and 0-20 for the last 2 items. Pain status was determined by 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 based upon their response to this first item, with individuals who denied 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. Given that pain severity has a non-normal distribution within the study sample, it was then dichotomized by median split in order to categorize participants as having either "high pain severity" or "low pain severity." In a prior study conducted within this lab, the MOS-PSS was shown to have a Cronbach's alpha of 0.70 (Pakray et al., 2021). Furthermore, there is literature to suggest that the MOS-PSS exhibits robust convergent validity (Hays et al., 1995).

The MOS-PES includes 6 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 6 items and transforming the final value onto a 0-100 scale, with higher scores indicating higher levels of pain interference. Given that pain interference had a non-normal distribution amongst the study sample, it was dichotomized by median split, such that individuals were categorized as having "high pain interference" or "low pain interference." 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 to the MOS-PSS (Hays et al., 1995). In a prior study conducted within this

lab, the MOS-PES was shown to have a high level of internal consistency as determined by a Cronbach's alpha of 0.86 (Pakray et al., 2021).

Quantitative Gait Assessment

A 4 × 20 ft Zeno electronic walkway was used to assess stride length based on the location and mathematical parameters between footfalls, under STW and DTW conditions (Zenometrics, LLC; Peekskill, NY) (Lynall et al., 2017). ProtoKinetics Movement Analysis Software technology (PKMAS) was used to assess quantitative measures of gait and determine, algorithmically, entry and end points under STW and DTW conditions (England et al., 2015). Split-half intra-class correlations (ICC) for stride velocity in STW and DTW are indicative of excellent (i.e. > 0.95) internal consistency (Holtzer et al., 2015).

Gait Paradigm

Reliability and validity for the dual-task procedure utilized in the parent study have been well-established and described (Holtzer et al., 2014a; Holtzer et al., 2014b). 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 3 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. For the purposes of this study, the rate of correct letter generation served as the measure of cognitive performance during Alpha and DTW. The COV for stride length served as the measure of gait performance in STW 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 3 consecutive loops. Participants were instructed to pay

equal attention to both portions of the task- cognitive and motor. Test conditions were presented in a counter-balanced 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.

fNIRS System

The fNIRS sensor is designed to measure changes in oxygenation within the prefrontal cortex. The device allows for the detection of hemodynamic changes in response to cognitive and motor demands (Izzetoglu et al., 2005). For the purposes of this study, the fNIRS Imager 1100 (fNIRS Devices, LLC, Potomac, MD) 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 (Holtzer et al., 2015; Holtzer et al., 2016; Izzetoglu et al., 2005; Holtzer et al., 2017). System sampling rate was set at 2 Hz. The fNIRS sensor is comprised of ten 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. type L4X730/4X805/4X850-40Q96-I) contain three LEDs with peak wavelengths at 830, 805, and 850 nm and an overall outer diameter of 9.2 ± 0.2 mm. Sensor photodetectors (Bur Brown, type OPT101) are monolithic photodiodes featuring a single supply transimpedance amplifier. A standard sensor placement procedure, based upon landmarks from the international 10-20 system, was implemented (Ayaz et al., 2006).

Preprocessing and Hemodynamic Signal Extraction

Raw data from each of the 16 fNIRS channels under all experimental conditions were visually inspected in order to identify and remove raw intensity measurements that met saturation or dark current conditions. Then, using Daubechies 5 (db5) wavelet, wavelet de-noising was applied to the raw intensity measurements at 730 and 850 nm in order to facilitate suppression of spiky noise (Molavi & Dumont, 2012). Subsequently, the modified Beer-Lambert law (MBLL) was used to calculate changes in oxygenated hemoglobin (HbO_2) and deoxygenated hemoglobin (Hb) from artifact-removed raw intensity measurements. This procedure has been previously described in the literature (Izzetoglu & Holtzer, 2020). In MBLL, the previously published wavelength and chromophore dependent molar extinction coefficients by Prahl as well as wavelength adjusted differential pathlength factor (DPF) were used (Izzetoglu & Holtzer, 2020; Kim & Liu, 2007; Scholkmann & Wolf, 2013). Spline filtering and finite impulse response low-pass filter with cut-off frequency at 0.08 Hz were applied to remove possible baseline shifts and suppress physiological artifacts such as Mayer waves and respiration (Izzetoglu & Holzer, 2020; Scholkmann et al., 2010).

In this study, HbO_2 was used as a proxy for PFC activation as it is known to be more sensitive to locomotion-related changes in cerebral oxygenation as compared to other fNIRS-derived measures such as Hb (Harada et al., 2009; Miyai et al., 2001). Data epochs within each task condition were corrected relative to proximal 10-second baselines administered prior to each experimental condition in order to determine the relative task-related changes in HbO_2 concentrations (Holtzer et al., 2011, 2015, 2017; Holtzer, George, et al., 2018; Holtzer, Verghese, et al., 2016). HbO_2 measurements have previously been shown to have excellent internal consistency (Holtzer et al., 2015).

HbO_2 data were extracted for each participant separately for each task. Gait and fNIRS data acquisition were synchronized via the use of E-Prime 2.0 software within a central "hub" computer. This synchronization has previously been described in the literature (Holtzer et al., 2015; 2017; Holtzer, George, et al., 2018; Holtzer, Izzetoglu, et al., 2018; Holtzer, Verghese, et al., 2016; Holtzer, Yuan, et al., 2016).

The standard deviation (SD) of all data points collected during a 30-second time interval within each experimental condition was computed as a measure of intraindividual variability in fNIRS-derived HbO_2. Given the current fNIRS system's sampling rate of 2Hz, which results in data collection at 0.5 second intervals, 61 data points were available per channel (1-16) per experimental condition for calculation of the SD in fNIRS-derived HbO_2. To ensure temporal congruence across task conditions, data obtained from the first 30 seconds of the STW and DTW conditions was used to calculate the SD in fNIRS-derived HbO_2 for each participant. All data collected during the Alpha task, which was fixed at 30 seconds, was used to calculate the SD in fNIRS-derived HbO_2 for each participant.

Covariates

Demographic information, such as participant age, gender, ethnicity, and years of education, were collected via self-report at baseline and were included as covariates in adjusted models. More specifically, gender was used as a covariate in all analyses except those exploratory analyses which examined gender differences in study aims. 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 utilized as covariates in this proposed study (Duff et al., 2008; Yesavage et al., 1982). Global Health Score (GHS) is a disease comorbidity score

calculated based upon 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) (Holtzer et al., 2008). Patient self-report of disease has been demonstrated to be a valid and reliable measure of disease history in adults (Okura et al., 2004). GHS score was also included as a covariate in adjusted models. Mean HbO_2 was utilized as a covariate in analyses which examined the impact of task and pain on prefrontal cortex activation. Given their known impact on mean HbO_2, this was done in order to isolate the impact of these factors on IIV in prefrontal cortex activation (Pakray et al., 2021).

Statistical Analysis

Prior to conducting study aims, the distributions of all study variables were visually inspected and described (mean/standard deviation, n and %) in order to ensure that all model assumptions were met. Bivariate analyses were conducted to determine whether participant characteristics differed by pain status. The study was repeated measures in design with pain serving as the 2-level, between subject factor and task condition as the 3-level, within subject factor. IBM's SPSS Premium GradPack 26 was used to conduct all study analyses (IBM, Somers, NY). Alpha was set at .05 for all analyses. For all models, DTW was set as the reference task condition and either a positive pain status or high pain was selected as the reference pain group.

Aim 1a: A linear mixed effects model (LMEM) was conducted in order to examine the main and moderating effects of perceived pain on the change in IIV in PFC oxygenation from single to dual-task conditions. More specifically, the main effects and interaction of task and pain status were examined with relation to the change in IIV in fNIRS-derived HbO_2

from single to dual-task conditions (i.e. STW- DTW, Alpha-DTW). IIV in FNIRS-derived HbO_2 was calculated using the SD of all data points collected in a 30-second time interval within each experimental condition (61 total data points per condition). LMEM was selected as the preferred method of analysis given its robust nature in the face of missing data. Pain, the two-level between subject factor, was transformed from a continuous variable into a categorical variable (i.e., yes pain, no pain) based upon the presence of reported pain. Task served as the within-subject repeated measures factor (STW, Alpha, and DTW). IIV in prefrontal oxygenation was measured continuously and served as the dependent variable. Channels were treated as repeated random effects. A compound symmetry covariance structure was used.

Aim 1b: Two separate LMEMs were conducted in order to examine the main and moderating effects of perceived pain, within individuals with reported pain, on the change in IIV in PFC oxygenation from single to dual-task conditions. The first LMEM examined the interaction of perceived pain severity and task on the change in FNIRS-derived HBO_2 from single to dual-task conditions. Given that pain severity did not have a normal distribution amongst participants with reported pain, it was be transformed from a continuous variable into a categorical variable (i.e., high pain severity, low pain severity) via median split. Median split was the preferred method of dichotomization as it was most consistent with study aims (i.e., comparing high v. low severity). The second LMEM included pain interference as a predictor and this variable was transformed from a continuous to a categorical variable (i.e., high pain interference, low pain interference) via median split. The rationale for this dichotomization is consistent with the justification provided for pain severity (see above). IIV in prefrontal oxygenation was measured continuously and served as

the dependent variable in both LMEMs. Furthermore, task was the within-subject repeated measures variable in these analyses. Channels were treated as repeated random effects. A compound symmetry covariance structure was used.

Aim 2a: A LMEM was conducted to examine the main and moderating effects of perceived pain on the change in IIV in gait performance (i.e., stride length variability) from single to dual-task walking conditions (i.e., STW-DTW). IIV in gait performance was be calculated using the COV for stride length variability in all walking conditions (i.e., STW and DTW). Pain will be dichotomized (i.e., yes pain, no pain) and IIV in stride length was treated continuously. Task was the within-subject repeated measures variable in this analysis.

Aim 2b: Two separate LMEMs were conducted to examine the main and moderating effects of perceived pain, within individuals with reported pain, on the change in IIV in gait performance (i.e., stride length variability) from single to dual-task walking conditions (i.e., STW-DTW). The first LMEM examined the interaction of perceived pain severity (i.e., high pain severity, low pain severity) and task on the change in IIV in stride length from single to dual-task walking conditions. The second LMEM examined the interaction of perceived pain interference (i.e., high pain interference, low pain interference) and task on the change in IIV in stride length from single to dual-task walking conditions. As previously noted, the dichotomization of pain variables allowed statistical analyses to remain consistent with study aims (i.e., comparing high v low pain). Task was the within-subject repeated measures variable in these analyses.

Aim 3a: A LMEM was conducted to examine the main and moderating effects of perceived pain status on the change in cognitive accuracy from single to dual-task conditions (i.e. Alpha-DTW). Pain status was dichotomized based upon reported presence of pain (i.e.,

yes pain, no pain). Cognitive accuracy was assessed via the rate of correct letter generation in each task condition. Task was the within-subject repeated measures variable in this analysis.

Aim 3b: Two separate LMEMs were conducted to examine the main and moderating effects of perceived pain, within individuals with reported pain, on the change in cognitive accuracy (i.e., rate of correct letter generation) from single to dual-task conditions (i.e., Alpha-DTW). The first LMEM examined the effect of the interaction of perceived pain severity (i.e., high pain severity, low pain severity) and task on the change in cognitive accuracy from Alpha to DTW. The second LMEM examined the effect of the interaction of perceived pain interference (i.e., high pain interference, low pain interference) and task on the change in cognitive accuracy from Alpha to DTW. Task was the within-subject repeated measures variable in these analyses.

Aim 4: LMEMs were used to examine the impact of gender on the main and moderating effects of perceived pain on all study outcomes. Gender was assessed dichotomously (i.e., male, female) and all study analyses (previously described) were stratified by gender.

Power Analysis

Given the absence of an appropriate means of executing a power analysis for linear mixed effects models, we calculated the minimum sample size required to yield a medium effect size for a multiple linear regression model. The analysis was conducted for a linear regression model featuring 9 predictor variables (i.e., 1 predictor variable, 3 repeated measures variables, and 7 covariates). We used G*Power Version 3.1.9.4 to conduct the power analysis. Results of the power analysis indicated that, in order to achieve a medium

effect size index f^2 (0.15) for 0.95% power, a minimum sample size of 178 is required. Given the 408 participants in the current study sample, 266 of which endorsed some level of self-reported pain within the past month, we are expected to exceed the threshold of power needed to identify group differences at the medium effect side level.

Ethics

As previously noted, this study is a secondary analysis nested within a longitudinal, cohort study of community-dwelling older adults entitled Central Control of Mobility in Aging (CCMA). CCMA is approved by the Albert Einstein College of Medicine institutional review board (IRB protocol #2010-224). All research personnel involved in study operations were approved to work with human subjects by the Collaborative Institutional Training Initiative (CITI) program. All participants were provided with detailed information about the study and informed consent was collected prior to any data collection procedures at the time of the initial study visit. During the informed consent procedure, participants were informed of potential risks and benefits of the study. Potential risks were described as minimal and included fatigue, performance anxiety, and frustration.

Chapter III: Results

Participants

Study participants (N = 408; mean age = 76 ± 6.5ys; mean education = 14 ± 2.9ys; % female = 55.4) were individuals who had completed the dual task paradigm and self-report pain questionnaires at baseline. Based upon the presence of missing data, 68 individuals were excluded from the initial sample of 476 participants who completed baseline study procedures. Of the 408 participants included in the study, 83.3 % of the sample self-identified as Caucasian, 13.5% as Black, and the remaining 3.2% as belonging to another ethnicity. The sample was generally well-educated with an average of 14 years of education. Based upon the mean RBANS Index Score (91 ± 11.7), participants displayed an average level of overall cognition. The majority of participants (34.1%) endorsed a low-to-moderate level of disease comorbidity (GHS = 2), suggesting that the sample was relatively healthy. The presence of pain over the past month was reported by 65.1% (n = 266) of the sample.

Bivariate analyses revealed that ethnicity, gender, GHS, and RBANS Index Score differed significantly by pain status (Table 1). When compared to those without reported pain, participants with pain were more likely to be female (40.4% vs. 15.0%, $p < .001$). They were more likely to have a moderate global health score (25.2% vs. 8.8%, $p < .001$) suggesting a higher level of disease comorbidity. They were also more likely to have a higher RBANS Index Score (92 ± 11.2 vs. 90 ± 12.5, $p = .042$), which indicated a higher level of global cognitive functioning.

Insert Table 1

Aim 1: fNIRS-derived PFC IIV

The first LMEM aimed to replicate and extend prior findings with regards to the effects of this dual task paradigm on prefrontal oxygenation. Results of the adjusted model revealed the expected significant task effects whereby IIV in HbO_2 increased from STW (estimate = -0.034, 95% CI = -0.063 to -0.005, p = .022) and from Alpha (estimate = -0.049, 95% CI = -0.078 to -0.020], p < .001) to DTW. Results also revealed a significant pain effect whereby individuals with pain displayed lower IIV in HbO_2 across tasks (estimate = -0.032, 95% CI = -0.062 to -0.001, p = 0.037). Contrary to our hypothesis that the presence of pain would be associated with a greater increase in IIV in prefrontal oxygenation from single do dual-task conditions, the moderating effects of pain on the increase in HbO_2 from STW (estimate = 0.021, 95% CI = -0.013 to 0.057, p = .228) and Alpha (estimate = 0.020, 95% CI = -0.014 to 0.056, p = .248) to DTW were not significant. In terms of covariates, age, gender, and mean HbO_2 were significantly associated with HbO_2 (see Table 2).

The LMEM that examined the effects of task, pain severity, and their interaction on IIV in prefrontal oxygenation amongst individuals with reported pain revealed no significant increases in HbO_2 from STW (estimate = -0.018, 95% CI = -0.046 to 0.010], p = .220) and Alpha (estimate = -0.018, 95% CI = -0.046 to 0.009], p = .199) to DTW. The main effect of pain severity was non-significant (estimate = 0.006, 95% CI = -0.028 to 0.041, p = .706). Results of the interaction did not support our hypothesis that greater pain would be associated

with a greater increase in IIV in prefrontal cortex oxygenation from single to dual-task conditions. The moderating effects of pain on the increase in HbO_2 from STW (estimate = -0.000, 95% CI = -0.039 to 0.039, p = .993) and Alpha (estimate = -0.019, 95% CI = -0.058 to 0.020, p = .341) to DTW did not meet threshold for significance. Age and mean HbO_2 were significantly associated with IIV in prefrontal oxygenation (see Table 3).

The third LMEM aimed to examine the effects of task, pain interference, and their interaction on IIV in prefrontal oxygenation amongst individuals with reported pain. Results revealed a significant task effect whereby HbO_2 increased from Alpha to DTW (estimate = -0.030, 95% CI = -0.058 to -0.002, p = .034). While HbO_2 also increased from STW to DTW, this effect did not meet threshold for significance (estimate = -0.021, 95% CI = -0.050 to 0.007, p = .141). The main effect of pain interference was also non-significant (estimate = -0.009, 95% CI = -0.044 to 0.025, p = .594). Contrary to our hypothesis, the moderating effects of pain on the increase in HbO_2 from STW (estimate = 0.007, 95% CI = -0.032 to 0.047, p = .720) and Alpha (estimate = 0.005, 95% CI = -0.034 to 0.045, p = .783) to DTW were not significant. Age and mean HbO_2 were significantly associated with IIV in prefrontal oxygenation (see Table 3).

Insert Tables 2-3

Aim 2: Gait IIV

The LMEM that examined the effects of task, pain status, and their interaction on IIV in stride length in the total sample revealed a significant task effect such that stride length

variability increased from STW to DTW (estimate = -2.078, 95% CI = -2.977 to -1.179, $p <$ .001). The main effect of pain status was also significant, indicating that individuals with reported pain demonstrated reduced stride length variability across tasks (estimate = -1.180, 95% CI = -0.334 to 1.904, p = .006). While we hypothesized that individuals with pain would display a greater increase in stride length variability from STW to DTW, pain status did not moderate the association between task and stride length variability (estimate = 0.785, 95% CI = -0.334 to 1.904, p = .169). In terms of covariates, RBANS Index Score was significantly associated with IIV in stride length (see Table 4).

The LMEM that examined the effects of task, pain severity, and their interaction on IIV in stride length amongst those with reported pain revealed a non-significant task effect (estimate = -0.647, 95% CI = -1.517 to 0.222, p = .144) and a significant pain effect (estimate = 0.948, 95% CI = 0.022 to 1.875). Consistent with the study hypothesis, individuals with high pain severity demonstrated a greater increase in stride length variability from STW to DTW as compared to individuals with low pain severity (estimate = -1.301, 95% CI = -2.536 to -0.066, p = .039) (see Figure 1). Study covariates were not significantly associated with IIV in stride length in this model (see Table 5).

The LMEM that examined the effects of task, pain interference, and their interaction on IIV in stride length amongst those with reported pain revealed a significant task effect whereby stride length variability increased from STW to DTW (estimate = -1.159, 95% CI = -2.019 to -0.299, p = .008). The main effect of pain interference was non-significant (estimate = 0.336, 95% CI = -0.607 to 1.279, p = .484). Contrary to our study hypothesis, pain interference did not moderate the association between task and stride length variability

(estimate = -0.281, 95% CI = -1.527 to 9.964, p = .657). Study covariates were not significantly associated with IIV in stride length (see Table 5).

Insert Tables 4-5

Aim 3: Cognitive Accuracy

The LMEM that examined the effects of task, pain status, and their interaction on the rate of correct letter generation did not reveal significant main effects of task (estimate = -0.010, 95% CI = -0.045 to 0.024, p = .547) or pain (estimate = 0.026, 95% CI = -0.019 to 0.071). Pain status did not moderate the relationship between task and rate of correct letter generation (estimate = -0.011, 95% CI = -0.054 to 0.031). Education, ethnicity, gender, GHS score, and RBANS Index score were significantly associated with this outcome (see Table 6).

The LMEM that examined the effects of task, pain severity, and their interaction on the rate of correct letter generation amongst individuals with reported pain did not reveal a significant relationship between task and correct letter generation (estimate = -0.021, 95% CI = -0.058 to 0.015, p = .252). The main effect of pain severity was also non-significant (estimate = -0.000, 95% CI = -0.055 to 0.053, p = .982). Pain severity did not moderate the relationship between task and rate of correct letter generation (estimate = -0.001, 95% CI = -0.054 to 0.052, p = .965). Education and RBANS Index Score were significantly associated with this outcome (see Table 7).

The LMEM that examined the effects of task, pain interference, and their interaction on the rate of correct letter generation amongst individuals with reported pain did not reveal significant main effects of task (estimate = -0.028, 95% CI = -0.065 to 0.007, p = .119) or pain interference (estimate = -0.007, 95% CI = -0.063 to 0.048, p = .793). Pain interference did not moderate the relationship between task and rate of correct letter generation (estimate = 0.014, 95% CI = -0.038 to 0.068, p = .591). As above, education and RBANS Index Score were significantly associated with this outcome (see Table 7).

Insert Tables 6-7

Aim 4: Gender Differences

Gender & PFC IIV

Amongst females, the LMEM that examined the effects of task, pain status, and their interaction on IIV in prefrontal oxygenation revealed significant task effects such that IIV in HbO_2 increased from STW (estimate = -0.048, 95%CI = -0.089 to -0.008, p = .018) and Alpha (estimate = -0.043, 95% CI = -0.083 to -0.003, p = .031) to DTW. The main effect of pain was non-significant (estimate = -0.014, 95% CI = -0.055 to 0.026, p = .487). Pain status did not moderate the change in IIV in HbO_2 from STW (estimate = 0.033, 95% CI = -0.013 to 0.080, p = .158) and Alpha (estimate = 0.012, 95% CI = -0.033 to 0.059, p = .590) to DTW.

The LMEM that examined the effects of task, pain severity, and their interaction on IIV in HbO_2 amongst females with reported pain revealed non-significant task effects such

that there was no significant increase in prefrontal oxygenation from STW (estimate = -0.005, 95% CI = -0.040 to 0.029, p = .745) and Alpha (estimate = -0.014, 95% CI = -0.048 to 0.019, p = .401) to DTW. The main effect of pain severity was also non-significant (estimate = -0.011, 95% CI = -0.032 to 0.054, p = .619). Pain severity did not moderate the change in HbO_2 from STW (estimate = -0.022, 95% CI = -0.069 to 0.024, p = .344) and Alpha (estimate = -0.030, 95% CI = -0.077 to 0.016, p = .207).

When examining the effects of task, pain interference, and their interaction on IIV in HbO_2 amongst females with reported pain, there was a significant increase in prefrontal oxygenation from Alpha to DTW (estimate = -0.048, 95% CI = -0.084 to -0.013, p = .007) but not from STW to DTW (estimate = -0.018, 95% CI = -0.055 to 0.017, p = .305). The main effect of pain interference was non-significant (estimate = -0.020, 95% CI = -0.064 to 0.023, p = .355). Females with high pain interference did not display a significant change in IIV in HbO_2 from STW (estimate = 0.001, 95% CI = -0.046 to 0.048, p = .962) and Alpha (estimate = 0.032, 95% CI = -0.014 to 0.080, p = .174) to DTW.

Amongst males, the LMEM that examined the effects of task, pain status, and their interaction on IIV in prefrontal oxygenation revealed a significant task effect in the change in IIV in HbO_2 from Alpha to DTW (estimate = -0.047, 95% CI = -0.089 to -0.005, p = .027) but not from STW to DTW (estimate = -0.020, 95% CI = -0.063 to 0.022, p = .353). There was a significant main effect of pain such that males with reported pain displayed reduced IIV in HbO_2 across tasks (estimate = -0.049, estimate = -0.095 to -0.002, p = .037). Pain status did not moderate the change in prefrontal cortex oxygenation from STW (estimate = 0.007, 95% CI = -0.049 to 0.063, p = .805) and Alpha (estimate = 0.027, 95% CI = -0.028 to 0.083, p = .334) to DTW.

The LMEM that examined the effects of task, pain severity, and their interaction on IIV in HbO_2 amongst males with reported pain revealed non-significant task effects such that there was no significant increase in prefrontal oxygenation from STW (estimate = -0.032, 95% CI = -0.081 to 0.017, p = .208) and Alpha (estimate = -0.019, 95% CI = -0.067 to 0.028, p = .420) to DTW. The main effect of pain severity was also non-significant (estimate = -0.003, 95% CI = -0.064 to 0.057, p = .917). Pain severity did not moderate the change in IIV in HbO_2 from STW (estimate = 0.034, 95% CI = -0.038 to 0.106, p = .354) and Alpha (estimate = -0.001, 95% CI = -0.073 to 0.070, p = .967) to DTW.

When examining the effects of task, pain interference, and their interaction on IIV in HbO_2 amongst males with reported pain, there was no significant increase in prefrontal oxygenation from STW (estimate = -0.022, 95% CI = -0.070 to 0.025, p =.358) and Alpha (estimate = -0.005, 95% CI = -0.052 to 0.041, p = .824) to DTW. The main effect of pain interference was non-significant (estimate = 0.003, 95% CI = -0.057 to 0.064, p = .915). Males with high pain interference did not display a significant change in IIV in HbO_2 from STW (estimate = 0.015, 95% CI = -0.057 to 0.088, p = .678) and Alpha (estimate = -0.035, 95% CI = -0.108 to 0.036, p = .329) to DTW.

Results of the six LMEMs referenced above revealed significant associations between mean HbO_2 and IIV in HbO_2 (see Tables 8-10).

Insert Tables 8-10

Gender & Gait IIV

Amongst females, the LMEM that assessed for effects of task, pain status, and their interaction on IIV in stride length revealed a significant main effect of task such that IIV in gait performance increased from STW to DTW (estimate = -2.747, 95% CI = -4.138 to -1.355, $p < .001$). There was a significant pain effect such that females with reported pain demonstrated reduced IIV in stride length across tasks (estimate = -1.712, 95% CI = -2.979 to -0.445, $p = .008$). Pain status did not moderate the change in gait performance from STW to DTW (estimate = 1.358, 95% CI = -0.273 to 2.991, $p = .102$). Study covariates were not significantly associated with this outcome (see Table 11).

The LMEM that examined the effects of task, pain severity, and their interaction on IIV in gait amongst females with reported pain did not reveal a significant task effect (estimate = -0.606, 95% CI = -1.744 to 0.531, $p = .294$), but did reveal a significant pain effect (estimate = 1.435, 95% CI = 0.220 to 2.649, $p = .021$). The moderating effect of pain trended towards significance such that females with high pain severity showed a greater increase in gait IIV from STW to DTW (estimate = -1.488, 95% CI = -3.059 to 0.082, $p = .063$). Study covariates were not significantly associated with this outcome (see Table 12).

When examining the effects of task, pain interference, and their interaction on IIV in stride length amongst females with reported pain, there was a significant task effect such that gait IIV increased from STW to DTW (estimate = -1.210, 95% CI = -2.352 to -0.067, $p = .038$). The main effect of pain interference was non-significant (estimate = 0.160, 95% CI = -

1.089 to 1.410, p = .800). Pain interference did not moderate the association between task and IIV in stride length (estimate = -0.342, 95% CI = -1.929 to 1.243, p = .670). As above, study covariates were not significantly associated with this outcome (see Table 12).

Amongst males, the LMEM that assessed for effects of task, pain status, and their interaction on IIV in stride length revealed a significant task effect such that IIV in stride length increased from STW to DTW (estimate = -1.582, 95% CI = -2.763 to -0.402, p = .009). The main (estimate = -0.825, 95% CI = -1.945 to 0.294, p = .148) and moderating (estimate = 0.448, 95% CI = -1.154 to 2.050, p = .582) effects of pain were non-significant. RBANS Index Score was significantly associated with IIV in gait performance (see Table 11).

The LMEM that examined the effects of task, pain severity, and their interaction on IIV in stride length amongst males with reported pain revealed non-significant task (estimate = -0.706, 95% CI = -2.082 to 0.670, p = .311) and pain (estimate = 0.175, 95% CI = -1.321 to 1.671, p = .818) effects. Pain severity did not moderate the association between task and IIV in stride length (estimate = -0.957, 95% CI = -3.014 to 1.100, p = .358). Education was significantly associated with this study outcome (see Table 13).

When examining the effects of task, pain interference, and their interaction on IIV in stride length amongst males with reported pain, there were no significant main effects of task (estimate = -1.090, 95% CI = -2.423 to 0.243, p = .108) and pain interference (estimate = 0.489, 95% CI = -1.051 to 2.029, p = .532). Pain interference did not moderate the association between task and gait performance (estimate = -0.110, 95% CI = -2.202 to 1.982, p = .917). As above, education was significantly associated with IIV in stride length (see Table 13).

Insert Tables 11-13

Gender & Cognitive Accuracy

Amongst females, the LMEM that assessed the effects of task, pain status, and their interaction on rate of correct letter generation revealed non-significant task (estimate = 0.004, 95% CI = -0.047 to 0.056, p = .862) and pain (estimate = -0.012, 95% CI = -0.075 to 0.049, p = .688) effects. Pain did not moderate the association between task and cognitive accuracy (estimate = -0.002, 95% CI = -0.063 to 0.059, p = .939).

The LMEM that examined the effects of task, pain severity, and their interaction on rate of correct letter generation amongst females with reported pain revealed non-significant task (estimate = 0.016, 95% CI = -0.029 to 0.062, p = .473) and pain (estimate = 0.038, 95% CI = -0.030 to 0.107, p = .276) effects. Pain severity did not moderate the association between task and cognitive accuracy (estimate = -0.028, 95% CI = -0.093 to 0.036, p = .387).

When examining the effects of task, pain interference, and their interaction on rate of correct letter generation amongst females with reported pain, results revealed non-significant task (estimate = 0.007, 95% CI = -0.039 to 0.053, p = .764) and pain (estimate = 0.008, 95% CI = -0.064 to 0.080, p = .832) effects. Pain interference was not a moderator of the association between task and cognitive accuracy (estimate = -0.009, 95% CI = -0.074 to 0.055, p = .782). In the models above, females demonstrated significant associations in

education, ethnicity, and RBANS Index score with rate of correct letter generation (see Tables 14-15).

Amongst males, the LMEM that examined the effects of task, pain status, and their interaction on rate of correct letter generation revealed a non-significant task effect (estimate = 0.334, 95% CI = -0.069 to 0.023, p = .334). There was a significant pain effect such that males with reported pain demonstrated a higher rate of correct letter generation across tasks (estimate = 0.073, 95% CI = 0.005 to 0.141, p = .034). Pain did not moderate the association between task and cognitive accuracy (estimate = -0.040, 95% CI = -0.102 to 0.021, p = .202). Education, GHS, and RBANS Index Score were significantly associated with rate of correct letter generation (see Table 14).

The LMEM that examined the effects of task, pain severity, and their interaction on rate of correct letter generation amongst males with reported pain revealed a significant task effect such that cognitive accuracy increased from Alpha to DTW (estimate = -0.079, 95% CI = -0.141 to -0.017, p = .013). The main (estimate = -0.032, 95% CI = -0.124 to 0.058, p = .481) and moderating (estimate = 0.036, 95% CI = -0.055 to 0.128, p = .434) effects of pain severity were non-significant. Education and RBANS Index Score were significantly associated with rate of correct letter generation (see Table 16).

When examining the effects of task, pain interference, and their interaction on rate of correct letter generation amongst males with reported pain, results of the LMEM revealed a significant task effect whereby cognitive accuracy increased from Alpha to DTW (estimate = -0.077, 95% CI = -0.136 to -0.018, p = .010). The main (estimate = -0.011, 95% CI = -0.104 to 0.081, p = .809) and moderating (estimate = 0.037, 95% CI = -0.056 to 0.131, p = .433)

effects of pain interference were non-significant. Education and RBANS Index Score were significantly associated with rate of correct letter generation (see Table 16).

Insert Tables 14-16

Chapter IV: Discussion

Despite the high prevalence of pain in aging, there has been little research examining the impact of pain on dual-task performances amongst older adults. Furthermore, of the studies that have been done, few have examined the concurrent effects of perceived pain on neural and behavioral outcomes. Given the known associations between pain and PFC activation patterns as well as the sensitivity of dual-task walking paradigms to changes in the cortical hemodynamic response within the PFC, such research is well-warranted (Holtzer et al., 2011; Lorenz et al., 2003; Lovden et al., 2008; Moore et al., 2012). The current study aimed to bridge this gap in the literature by examining the impact of perceived pain on IIV in PFC oxygenation, IIV in stride length, and cognitive accuracy in a sample of healthy, community dwelling older adults. In light of emerging evidence of differential patterns of PFC activation amongst males and females, we also explored the impact of gender on these associations (Monroe et al., 2015; Straube et al., 2009). Overall, we found pain to be associated with reduced IIV in PFC oxygenation and stride length in the dual-task walking condition. Pain was also found to be associated with a greater change in IIV of stride length from single- to dual-task conditions. Results of exploratory analyses revealed gender differences in some of these associations.

Summary of Major Findings

Consistent with results of prior literature demonstrating increased IIV in PFC oxygenation from single- to dual-task conditions (Holtzer et al., 2020), our

results showed a similar increase in IIV in PFC oxygenation from STW and Alpha to DTW. In light of prior fMRI studies that have utilized experimental pain paradigms to demonstrate the association between pain and functional changes in the PFC (Monroe et al., 2015; Straube et al., 2009), our results serve to provide further support for such an association. Furthermore, our study extends the generalizability of these results beyond an experimental pain paradigm and demonstrates similar effects amongst healthy older adults with perceived pain.

Consistent with study hypotheses, we found that the presence of perceived pain was associated with reduced IIV in fNIRS-derived PFC oxygenation in the dual-task condition. As pain is a known mechanism of attention disruption with associated effects on PFC activation patterns, we had postulated that self-reported pain would be associated with an inefficient brain response (Eccleston & Crombez, 1999; Lorenz et al., 2003; Moore et al., 2012). Our findings are consistent with results of recent fMRI studies which have shown reduced neocortical IIV to be associated with older age and more variable reaction times, thereby identifying it as a potentially inefficient response pattern (Garret et al., 2011; Guitart-Masip et al., 2016). Furthermore, there is evidence to suggest that reduced cortical IIV during tasks of high cognitive load may reflect a brain that is less flexible and adaptive to environmental stimuli (Grady & Garett, 2014). As such, it may be that older adults with pain experience a suboptimal hemodynamic response within the PFC when faced with walking tasks that feature a high degree of executive demand.

Contrary to study hypotheses, which were based on limited research suggesting that a greater increase in IIV in PFC oxygenation from single to dual-task walking conditions is associated with cognitive impairment and therefore a potentially inefficient cortical response,

we did not find perceived pain to be a moderator of the change in IIV of fNIRS-derived PFC oxygenation (Holtzer et al., 2020). In considering the absence of this moderating effect, it may be that more research is needed to clarify whether a greater increase in IIV of fNIRS-derived PFC oxygenation truly represents an inefficient brain response. Alternatively, it may be that the disruptive effects of pain on neural IIV are only apparent during tasks of high executive demand (i.e., DTW) and therefore best captured in terms of main, rather than moderating, effects.

Amongst the entire study sample, IIV in stride length increased from single- to dual-task conditions commensurate with a corresponding increase in task demands. Contrary to the study hypothesis, the presence of reported pain was associated with reduced IIV in stride length during the dual-task, as compared to single-task, walking condition. Based upon prior literature showing an association between increased IIV in gait performance during DTW and an elevated risk of falls in aging, we had hypothesized that individuals with pain would demonstrate a similar, and likely inefficient, behavioral response (Bunce et al., 2016; Reelick et al., 2013). Nevertheless, our findings suggest that reduced IIV in stride length may also represent a suboptimal behavioral response amongst older adults with pain. Given the broad associations between pain and motor dysfunction (Leveille et al., 2009; Patel et al., 2013), it may be that pain-related reductions in stride length variability reflect a maladaptive pattern of gait inflexibility with less room for adaptation to unexpected environmental changes (Lamoth et al., 2008). From this perspective, individuals with pain may demonstrate greater cognitive regulation of gait as a compensatory mechanism for reduced automaticity in walking.

Consistent with our study hypothesis, high pain severity was associated with a greater increase in IIV in stride length from single- to dual-task walking conditions although this

same effect was not found amongst those with high pain interference. As executive functions are known to regulate gait performance and increased gait variability has known associations with unsteadiness (Springer et al., 2006), it may be that a greater increase in gait variability across tasks of rising executive demand reflects the destabilizing effects of pain on walking performance. Although previously demonstrated amongst adults with chronic low back pain (Hamacher et al., 2014), the moderating effect of pain on gait variability had not previously been documented in healthy aging. These results are novel in that they provide evidence for pain-related changes in stride length IIV across walking tasks of increasing demand and complexity amongst healthy, community-dwelling older adults.

Cognitive accuracy, as assessed by rate of correct letter generation, did not change as a function of task. Furthermore, there were no differences in cognitive accuracy as a function of pain status or pain level (i.e., pain severity, pain interference). Contrary to expectations, pain did not moderate the change in cognitive accuracy from Alpha to DTW amongst those with reported pain as well as amongst individuals with high levels of pain severity and interference. Given that pain is known to be a mechanism of attention disruption (Eccleston & Crombez, 1999), we had hypothesized that perceived pain would be associated with reduced cognitive accuracy in DTW and a greater decline in cognitive accuracy from Alpha to DTW. The absence of these effects in our study sample may be a function of the level of task difficulty inherent in study procedures, as there is evidence to suggest that pain selectively impacts attention when task demands are high (Moore et al., 2012).

Overall, study analyses revealed a number of major findings to suggest that the presence of perceived pain is associated with inefficient neural and behavioral response patterns in normal aging. Healthy older adults with self-reported pain exhibited reduced IIV

in fNIRS-derived PFC oxygenation in DTW, suggesting that the effects of perceived pain on IIV in cortical control of gait are apparent when task demands are high. Those with self-reported pain also exhibited reduced IIV in stride length in DTW, suggesting that pain is associated with maladaptive tightening of gait control during tasks of high executive demand. And finally, those with high levels of self-reported pain (i.e., high pain severity) exhibited a greater increase in stride length IIV from STW to DTW, consistent with prior literature showing similar effects in older adults with chronic low back pain (Hamacher et al., 2014).

Summary of Gender Differences in Study Results

Analyses conducted utilizing the entire study sample, as well as those conducted utilizing only individuals with reported pain, revealed a number of significant associations between perceived pain and study outcomes. These results were further clarified in stratified analyses that explored the moderating impact of pain on study outcomes amongst males and females, separately.

While no significant association between pain and neural IIV was observed in females, there was a significant main effect of pain on PFC IIV in males such that those with perceived pain showed reduced IIV in fNIRS-derived PFC oxygenation in DTW. Prior studies that have examined gender differences with regards to the effects of pain on the cortical hemodynamic response in the PFC have yielded significant, yet differing, results (Monroe et al., 2015; Straube et al., 2009). This literature suggests that women are particularly sensitive to the neural effects of pain, but that the directionality of this effect within the PFC may depend on the specific area within that brain region that is being assessed. Our results are novel in that they show that, at least amongst healthy older adults, males appear to be more sensitive to the effects of pain on IIV in PFC activation, especially

during a complex and demanding walking task. These results are somewhat consistent with those of another study which found that the presence of cognitive impairments and being a male were independently associated with greater increases in IIV in PFC activation from single to dual-task walking conditions (Holtzer et al., 2020). Taken together, these findings suggest that older males are more susceptible to showing inefficient responses in neural IIV within the PFC in response to pain.

Although males did not show an association between pain and IIV in stride length, females did display such a relationship and those with reported pain presence displayed reduced IIV in stride length in DTW as compared to STW. As previously mentioned, this was interpreted as an inefficient response pattern characterized by a maladaptive tightening of gait control during a cognitively challenging walking task. Although not found in the larger sample of females with reported pain presence nor amongst those with high reported pain interference, females with high reported pain severity showed a greater increase in IIV in stride length from STW to DTW. This was also interpreted to be an inefficient behavioral response that had previously been documented amongst older adults with chronic low back pain (Hamacher et al., 2014). The presence of such behavioral effects in females is surprising as it was males who were identified as showing an inefficient neural response to pain. Nevertheless, given prior research to suggest that females display greater pain sensitivity (Fillingim et al., 2009; Monroe et al., 2015) and greater levels of pain-related, self-attention (Straube et al., 2009), it may be that these factors contribute to their greater likelihood of behavioral modification in response to pain.

While females did not display an association between pain and rate of correct letter generation, males did demonstrate an association such that those with reported pain presence

displayed increased cognitive accuracy in DTW as compared to alpha. This result is also unexpected, given that pain is known to function as a mechanism for attention disruption (Eccleston & Crombez, 1999). It is rather unclear as to why males with reported pain presence demonstrated improved cognitive performance during a walking task of high executive demand. Nevertheless, this finding provides further support for the idea that older males are not prone to demonstrating poorer behavioral performances in response to pain.

Limitations and Future Directions

This study has several limitations to consider. Firstly, an fNIRS system was used to assess for changes in the cortical hemodynamic response during single- and dual-tasks. While this system has a number of strengths including enhanced portability and a means for assessing changes in cerebral oxygenation during active walking, it does also have limitations in terms of depth of penetration and special resolution. Nevertheless, results of a recent MRI fNIRS co-registration study support the use of this system among older adults (Chen et al., 2017). Furthermore, there are several recent studies confirming associations between MRI and fNIRS-derived data. More specifically, these studies demonstrated that poor white matter integrity, smaller gray matter volume, and thinner cortex were associated with reduced neural efficiency (Lucas et al., 2019; Wagshul et al., 2019; Ross et al., 2021).

Secondly, as this study was cross-sectional in design, a direct causal link was not able to be established between perceived pain and study outcomes. As such, future studies may consider examining these associations longitudinally in order to facilitate greater understanding of the impact of self-reported pain on cognitive and behavioral outcomes amongst healthy older adults. Thirdly, this study did not consider the impact of pain location on study outcomes. Thus, we were unable to assess whether the location of pain had any

bearing on the association of pain with brain and behavioral outcomes. This study also did not account for the number of pain locations in order to assess the impact of multisite pain on study outcomes. Given literature to suggest that multisite pain is a sensitive predictor of lower extremity function, future studies should consider utilizing self-report pain measures that assess for multisite pain in order to examine its relationship with gait in aging (Eggermont et al., 2009).

This study did not examine whether the impact of pain on study outcomes differed by clinical pain type (e.g., neuropathic, radicular, etc.). There is literature to suggest the presence of gait abnormalities in various clinical pain groups, including both neuropathic and musculoskeletal pain (Lalli et al., 2013; Sawa et al., 2017). As such, it would be clinically impactful to determine whether the neural and behavioral effects of pain in aging differ by pain type, and therefore likely as a function of etiology. Furthermore, as we used a pain measure that required participants to aggregate their experiences over the course of one month, the impact of current pain was not assessed. Future studies may consider utilizing pain measures that allow for a more detailed examination of these factors.

As pain is prevalent in many primary neurological diseases, future studies may wish to assess the effects of perceived pain on neural and behavioral outcomes in older adults with such conditions (Borsook, 2011). Examining these relationships in Parkinson's disease, in particular, may be clinically useful as individuals with this disorder have been shown to demonstrate greater dual-task costs while walking (O'Shea et al., 2002). Furthermore, pain is known to be both prevalent and functionally impactful with regards to health-related quality of life in this population. The presence of various clinical pain types within Parkinson's disease (i.e., musculoskeletal, radicular-neuropathic, dystonic, central) also presents a unique

opportunity for assessing whether study outcomes differ by pain type within a single nervous system disorder (Rana et al., 2013)

While these study results highlight self-reported pain presence and pain severity as sensitive predictors of neural and behavioral outcomes, the impact of the affective response to pain was not assessed. Future studies should explore the relationship between pain-related fear in aging and gait outcomes as individuals who tend to perceive pain in a catastrophic manner may be more likely to engage in patterns of less adaptive motor movement modification (James & France, 2007). These findings are consistent with the Fear-Avoidance Model of Pain which suggests that pain-related disability is associated with the perception of threat such that individuals who perceive pain to be a source of threat are more likely to engage in activity avoidance and behavioral modification (Leeuw et al., 2006). In examining the impact of pain-related fear on behavior in aging, future studies may wish to assess the role of pain catastrophizing as it is known to be associated with pain-related disability and activity intolerance (Peters et al., 2005).

Lastly, as measures of performance variability have been shown to be more sensitive predictors of long-term physical function in community-dwelling older adults (Hausdorff et al., 2001), future studies may consider looking at additional measures of gait variability (e.g., swing time variability, double support time variability, etc.). Additionally, although this study was not able to assess the impact of pain on cognitive variability, future studies may consider utilizing a dual-task walking paradigm to examine this relationship further.

Clinical Implications

This study highlights the importance of the clinical use of routine pain assessments with community-dwelling older adults. The current findings revealed that the presence of

pain was associated with reduced IIV in stride length and in the cortical hemodynamic response during dual-task walking. Furthermore, amongst those with reported pain, individuals with high pain severity demonstrated a greater increase in IIV in stride length from single- to dual-task walking conditions. Taken together, these findings suggest that perceived pain over the past month is associated with inefficient patterns of neural and behavioral responding amongst healthy, community-dwelling older adults.

These findings indicate that assessing the presence of pain in isolation may be insufficient in terms of identifying individuals at risk of gait dysfunction. Rather, it appears that assessing level of pain severity is also an important indicator of walking performance. Furthermore, our results suggest that self-reported pain is associated with study outcomes when assessed over a one-month period. As such, it is unclear whether assessing pain at a single time-point (i.e., current pain) would be a sensitive predictor of IIV in stride length and in the cortical hemodynamic response. Future studies may wish to consider examining the association between self-reported pain of differing durations on study outcomes in order to determine which temporal assessments are most sensitive in aging.

Beyond increased assessment of pain, these findings provide further support for the importance of effective and timely treatment of pain amongst otherwise healthy older adults. There are recent review papers describing the growing evidence base for utilization of psychosocial interventions (i.e., cognitive behavioral therapy, emotional disclosure, mind-body interventions) amongst older adults (Keefe et al., 2013; Pu et al., 2018). These interventions are particularly relevant in aging given the potential for benefit without any associated, major risks. Such interventions may also have a resultant impact on gait

performance, as walking speed has been found to be associated with fear avoidance beliefs amongst older adults with chronic low back pain (Camacho-Soto et al., 2012).

Repetitive transcranial magnetic stimulation (rTMS) is another potential avenue for pain management with a known impact on the cortical hemodynamic response (Li et al., 2019). While this modality is currently only FDA-approved for treatment of depression, there is increasing evidence to support its use in pain populations (Leung et al., 2014; Martin et al., 2013). More specifically, when directed over the prefrontal cortex, rTMS has been shown to be associated with reduced subjective pain ratings in response to thermal stimulation (Martin et al., 2013). Furthermore, studies that have examined its use in aging suggest that it is a safe and well-tolerated intervention amongst older adults with minimal risk of harm to cognitive status (Houde et al., 2018; Iriarte & George, 2018).

Conclusion

In sum, these study findings further our knowledge with regards to the impact of perceived pain over a one-month period on cognitive and behavioral performances across tasks of increasing cognitive load amongst healthy, community-dwelling older adults. In our study sample, individuals with pain showed reduced IIV in the cortical hemodynamic response as well as reduced IIV in stride length in the DTW as compared to single-task conditions. Gender stratified analyses revealed that these main effects of pain were driven by males and females, respectively. Additionally, individuals with high pain severity showed a greater increase in IIV in stride length from STW to DTW. Stratified analyses clarified that this effect was significant in females, but not in males. Overall, these results suggest that older adults with perceived pain demonstrate less efficient patterns of neural and behavioral

responding. Furthermore, it appears that males are more susceptible to the neural effects of pain, while females are more susceptible to demonstrating behavioral effects of pain under attention-demanding conditions. The current study emphasizes the clinical need for use of routine assessments and, when necessary, intervention strategies, for effective and timely treatment of pain in aging.

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Table 1: Demographics stratified by pain status.

Variable	Total N= 408	No Pain N= 142	Pain N=266	Significance
	M(SD), Mdn(IQR) or N(%)	M(SD), Mdn(IQR) or N(%)	M(SD), Mdn(IQR) or N(%)	*p*
Age	76(6.5)	77(6.4)	75(6.6)	0.071
Education	14(2.9)	13(2.8)	14.5(2.9)	0.059
Ethnicity				0.017
Caucasian	340(83.3%)	118(28.9%)	222(54.4%)	
Black	55(13.5%)	15(3.7%)	40(9.8%)	
Other	13(3.2%)	9(2.2%)	4(1.0%)	
Gender				<0.001
Male	182(44.6%)	81(19.9%)	101(24.8%)	
Female	226(55.4%)	61(15.0%)	165(40.4%)	
GHS				<0.001
0	64(15.7%)	30(7.4%)	34(8.3%)	
1	126(30.9%)	54(13.2%)	72(17.6%)	
2	139(34.1%)	36(8.8%)	103(25.2%)	
3	63(15.4%)	20(4.9%)	43(10.5%)	
4	13(3.2%)	1(0.2%)	12(2.9%)	
5	3(0.7%)	1(0.2%)	2(0.5%)	
RBANS	91(11.7)	90(12.5)	92(11.2)	0.042
Mean HBO_2				
STW	0.2(0.5)	0.2(0.6)	0.2(0.5)	0.573
Alpha	0.6(0.5)	0.6(0.5)	0.6(0.5)	0.525
DTW	0.6(0.7)	0.7(0.9)	0.6(0.6)	0.102

Note: GHS= Global Health Score; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status, Total Scaled Score; STW = Single Task Walk; Alpha = Cognitive Interference; DTW = Dual Task Walk

Table 2: Effects of task and pain status on HbO_2 SD.

Variable	Estimate	t	95% CI	*p*
Task				
STW v DTW	-0.03	-2.29	-0.06 to -0.00	0.022
Alpha v DTW	-0.04	-3.37	-0.07 to -0.02	<0.001
Pain Status				
Pain Yes v No	-0.03	-2.09	-0.06 to -0.00	0.037
Task X Pain				
STW v DTW x Pain Yes v No	0.02	1.20	-0.01 to 0.05	0.228
Alpha v DTW x Pain Yes v No	0.02	1.15	-0.01 to 0.05	0.248
Covariates				
Age	-0.00	-3.36	-0.00 to -0.00	<0.001
Mean HBO_2	0.08	13.23	0.07 to 0.10	<0.001
Education	-0.00	-1.07	-0.00 to 0.00	0.285
GDS	-0.00	-0.27	-0.00 to 0.00	0.782
Gender	-0.03	-3.01	-0.05 to -0.01	0.003
GHS	-0.00	-0.56	-0.01 to 0.00	0.575
RBANS	0.00	1.29	-0.00 to 0.00	0.197

Note: GDS= Geriatric Depression Scale; GHS= Global Health Score; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status, Total Scaled Score; STW = Single Task Walk; Alpha = Cognitive Interference; DTW = Dual Task Walk; Results of model adjusted for age, mean HbO_2, gender, education, depression (i.e., GDS), comorbidity status (i.e., GHS), and RBANS total index score.

Table 3: Effects of task, pain severity, and pain interference on HBO_2 SD.

Variable	Estimate	t	95% CI	*p*
Model 1				
Task				
STW v DTW	-0.01	-1.22	-0.04 to 0.01	0.220
Alpha v DTW	-0.01	-1.28	-0.04 to 0.00	0.199
Pain Severity				
High v Low	0.00	0.37	-0.02 to 0.04	0.706
Task X Severity				
STW v DTW x Severity High v Low	-0.00	-0.00	-0.03 to 0.03	0.993
Alpha v DTW x Severity High v Low	-0.01	-0.95	-0.05 to 0.02	0.341
Covariates				
Age	-0.00	-2.75	-0.00 to -0.00	0.006
Mean HBO_2	0.07	8.72	0.05 to 0.090	<0.001
Education	-0.00	-0.22	-0.00 to 0.00	0.822
Ethnicity	0.01	1.13	-0.01 to 0.04	0.259
GDS	0.00	0.40	-0.00 to 0.00	0.688
Gender	-0.02	-1.52	-0.04 to 0.00	0.128
GHS	0.00	0.23	-0.01 to 0.01	0.818
RBANS	0.00	1.22	-0.00 to 0.00	0.223
Model 2				
Task				
STW v DTW	-0.02	-1.47	-0.05 to 0.00	0.141
Alpha v DTW	-0.03	-2.12	-0.05 to -0.00	0.034
Pain Interference				
High v Low	-0.00	-0.53	-0.04 to 0.02	0.594
Task X Interference				
STW v DTW x Interference High v Low	0.00	0.35	-0.03 to 0.04	0.720
Alpha v DTW x Interference High v Low	0.00	0.27	-0.03 to 0.04	0.783
Covariates				
Age	-0.00	-2.77	-0.00 to -0.00	0.006
Mean HBO_2	0.07	8.75	0.05 to 0.09	<0.001
Education	-0.00	-0.22	-0.00 to 0.00	0.821
Ethnicity	0.01	1.12	-0.01 to 0.04	0.261
GDS	0.00	0.50	-0.00 to 0.00	0.611
Gender	-0.02	-1.46	-0.04 to 0.00	0.145
GHS	0.00	0.28	-0.01 to 0.01	0.778
RBANS	0.00	1.21	-0.00 to 0.00	0.225

Note: GDS= Geriatric Depression Scale; GHS= Global Health Score; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status, Total Scaled Score; STW = Single Task Walk; Alpha = Cognitive Interference; DTW = Dual Task Walk. Model 1 evaluated effects of task and pain severity; Model 2 evaluated effects of task and pain interference; Results of models adjusted for age, mean HBO_2, gender, ethnicity, education, depression (i.e., GDS), comorbidity status (i.e., GHS), and RBANS total index score.

Table 4: Effects of task and pain status on COV for stride length**.**

Variable	Estimate	t	95% CI	*p*
Task				
STW v DTW	-2.07	-4.54	-2.97 to -1.17	<0.001
Pain Status				
Pain Yes v No	-1.18	-2.75	-2.02 to -0.33	0.006
Task X Pain				
STW v DTW x Pain Yes v No	0.78	1.37	-0.33 to 1.90	0.169
Covariates				
Age	0.01	0.62	-0.03 to 0.58	0.535
Education	0.01	0.27	-0.08 to 0.11	0.786
Ethnicity	-0.04	-0.19	-0.51 to 0.42	0.848
GDS	0.06	1.56	-0.01 to 0.13	0.119
Gender	-0.46	-1.54	-1.05 to 0.12	0.124
GHS	-0.02	-0.21	-0.30 to 0.24	0.829
RBANS	-0.03	-2.46	-0.05 to -0.00	0.014

Note: GDS= Geriatric Depression Scale; GHS= Global Health Score; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status, Total Scaled Score; STW = Single Task Walk; DTW = Dual Task Walk. Results of model adjusted for age, gender, education, ethnicity, depression (i.e., GDS), comorbidity (i.e., GHS), and RBANS total index score.

Table 5: Effects of task, pain severity, and pain interference on COV of stride length.

Variable	Estimate	t	95% CI	*p*
Model 1				
Task				
STW v DTW	-0.64	-1.46	-1.51 to 0.22	0.144
Pain Severity				
High v Low	0.94	2.01	0.02 to 1.87	0.045
Task X Severity				
STW v DTW x Severity High v Low	-1.30	-2.07	-2.53 to -0.06	0.039
Covariates				
Age	0.04	1.54	-0.01 to 0.09	0.124
Education	0.06	1.13	-0.05 to 0.18	0.257
Ethnicity	0.50	1.48	-0.16 to 1.17	0.140
GDS	0.05	1.30	-0.02 to 0.14	0.194
Gender	-0.67	-1.91	-1.36 to 0.01	0.057
GHS	0.09	0.60	-0.22 to 0.41	0.543
RBANS	-0.01	-0.69	-0.04 to 0.01	0.488
Model 2				
Task				
STW v DTW	-1.15	-2.65	-2.01 to -0.29	0.008
Pain Interference				
High v Low	0.33	0.70	-0.60 to 1.27	0.484
Task X Interference				
STW v DTW x Interference High v Low	-0.28	-0.44	-1.52 to 9.96	0.657
Covariates				
Age	0.04	1.54	-0.01 to 0.93	0.123
Education	0.06	1.03	-0.05 to 0.18	0.301
Ethnicity	0.49	1.44	-0.18 to 1.16	0.151
GDS	0.05	1.23	-0.03 to 0.14	0.217
Gender	-0.67	-1.90	-1.36 to 0.02	0.058
GHS	0.11	0.69	-0.20 to 0.42	0.488
RBANS	-0.01	-0.73	-0.04 to 0.01	0.460

Note: GDS= Geriatric Depression Scale; GHS= Global Health Score; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status, Total Scaled Score; STW = Single Task Walk; DTW = Dual Task Walk. 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, ethnicity, education, depression (i.e., GDS), comorbidity status (i.e., GHS), and RBANS total index score.

Table 6: Effects of task and pain status on rate of letter generation.

Variable	Estimate	t	95% CI	*p*
Task				
Alpha v DTW	-0.01	-0.60	-0.04 to 0.02	0.547
Pain Status				
Pain Yes v No	0.02	1.11	-0.01 to 0.07	0.266
Task X Pain				
Alpha v DTW x Pain Yes v No	-0.01	-0.51	-0.05 to 0.03	0.606
Covariates				
Age	-0.00	-0.40	-0.00 to 0.00	0.687
Education	0.01	5.64	0.01 to 0.02	<0.001
Ethnicity	-0.04	-2.40	-0.07 to -0.00	0.017
GDS	0.00	1.18	-0.00 to 0.00	0.238
Gender	0.04	2.39	0.00 to 0.08	0.017
GHS	-0.02	-2.52	-0.03 to -0.00	0.012
RBANS	0.00	7.23	0.00 to 0.00	<0.001

Note: GDS= Geriatric Depression Scale; GHS= Global Health Score; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status, Total Scaled Score; Alpha = Cognitive Interference; DTW = Dual Task Walk. Results of model adjusted for age, gender, ethnicity, education, depression (i.e., GDS), comorbidity status (i.e., GHS), and RBANS total index score.

Table 7: Effects of task, pain severity, and pain interference on rate of correct letter generation.

Variable	Estimate	t	95% CI	*p*
Model 1				
Task				
Alpha v DTW	-0.02	-1.14	-0.05 to 0.01	0.252
Pain Severity				
High v Low	-0.00	-0.02	-0.05 to 0.05	0.982
Task X Severity				
Alpha v DTW x Severity High v Low	-0.00	-0.04	-0.05 to 0.05	0.965
Covariates				
Age	0.00	0.19	-0.00 to 0.00	0.844
Education	0.02	5.25	0.01 to 0.02	<0.001
Ethnicity	-0.03	-1.45	-0.08 to 0.01	0.148
GDS	0.00	0.61	-0.00 to 0.00	0.537
Gender	0.03	1.41	-0.01 to 0.07	0.148
GHS	-0.01	0.14	-0.03 to 0.00	0.141
RBANS	0.00	5.68	0.00 to 0.00	<0.001
Model 2				
Task				
Alpha v DTW	-0.02	-1.56	-0.06 to 0.00	0.119
Pain Interference				
High v Low	-0.00	-0.26	-0.06 to 0.04	0.793
Task X Interference				
Alpha v DTW x Interference High v Low	0.01	0.53	-0.03 to 0.06	0.591
Covariates				
Age	0.00	0.18	-0.00 to 0.00	0.851
Education	0.02	5.26	0.01 to 0.02	<0.001
Ethnicity	-0.03	-1.45	-0.08 to 0.01	0.148
GDS	0.00	0.57	-0.00 to 0.00	0.568
Gender	0.03	1.41	-0.01 to 0.07	0.158
GHS	-0.01	-1.52	-0.03 to 0.00	0.130
RBANS	0.00	5.69	0.00 to 0.00	<0.001

Note: GDS= Geriatric Depression Scale; GHS= Global Health Score; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status, Total Scaled Score; Alpha = Cognitive Interference; DTW = Dual Task Walk. 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, ethnicity, education, depression (i.e., GDS), comorbidity status (i.e., GHS), and RBANS total index score.

Table 8: Gender stratified: Effects of task and pain status on HBO_2 SD.

Variable	Estimate	t	95% CI	*p*
Females				
Task				
STW v DTW	-0.04	-2.37	-0.08 to -0.00	0.018
Alpha v DTW	-0.04	-2.16	-0.08 to -0.00	0.031
Pain Status				
Pain Yes v No	-0.01	-0.69	-0.05 to 0.02	0.487
Task X Status				
STW v DTW x Pain Yes v No	0.03	1.41	-0.01 to 0.08	0.158
Alpha v DTW x Pain Yes v No	0.01	0.54	-0.03 to 0.05	0.590
Covariates				
Age	-0.00	-1.86	-0.00 to 0.00	0.064
Mean HBO_2	0.06	7.46	0.05 to 0.08	<0.001
Education	-0.00	-1.55	-0.00 to 0.00	0.121
Ethnicity	0.00	0.74	-0.01 to 0.03	0.456
GDS	-0.00	-0.50	-0.00 to 0.00	0.612
GHS	0.00	0.62	-0.00 to 0.01	0.533
RBANS	0.00	1.09	-0.00 to 0.00	0.277
Males				
Task				
STW v DTW	-0.02	-0.93	-0.06 to 0.02	0.353
Alpha v DTW	-0.04	-2.21	-0.08 to -0.00	0.027
Pain Status				
Pain Yes v No	-0.04	-2.09	-0.09 to -0.00	0.037
Task X Status				
STW v DTW x Pain Yes v No	0.00	0.24	-0.04 to 0.06	0.805
Alpha v DTW x Pain Yes v No	0.02	0.96	-0.02 to 0.08	0.334
Covariates				
Age	-0.00	-2.89	-0.00 to -0.00	0.004
Mean HBO_2	0.10	10.64	0.08 to 0.12	<0.001
Education	0.00	0.47	-0.00 to 0.00	0.635
Ethnicity	0.02	1.57	-0.00 to 0.04	0.116
GDS	0.00	0.33	-0.00 to 0.00	0.735
GHS	-0.01	-1.35	-0.02 to 0.00	0.177
RBANS	0.00	0.24	-0.00 to 0.00	0.805

Note: GDS= Geriatric Depression Scale; GHS= Global Health Score; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status, Total Scaled Score; STW = Single Task Walk; Alpha = Cognitive Interference; DTW = Dual Task Walk. Results of models adjusted for age, mean HBO2, education, ethnicity, depression (i.e., GDS), comorbidity status (i.e., GHS), and RBANS total index score.

Table 9: Effects of task, pain severity, and pain interference on HBO_2 SD in females.

Variable	Estimate	t	95% CI	*p*
Model 1				
Task				
STW v DTW	-0.00	-0.32	-0.04 to 0.02	0.745
Alpha v DTW	-0.01	-0.84	-0.04 to 0.01	0.401
Pain Severity				
High v Low	0.01	0.49	-0.03 to 0.05	0.619
Task X Severity				
STW v DTW x Severity High v Low	-0.02	-0.94	-0.06 to 0.02	0.344
Alpha v DTW x Severity High v Low	-0.03	-1.26	-0.07 to 0.01	0.207
Covariates				
Age	-0.00	-2.08	-0.00 to -0.00	0.039
Mean HBO_2	0.06	5.89	0.04 to 0.08	<0.001
Education	-0.00	-1.35	-0.01 to 0.00	0.178
Ethnicity	0.01	0.72	-0.02 to 0.04	0.472
GDS	0.00	0.52	-0.00 to 0.00	0.601
GHS	0.00	0.55	-0.01 to 0.02	0.578
RBANS	0.00	0.63	-0.00 to 0.00	0.527
Model 2				
Task				
STW v DTW	-0.01	-1.02	-0.05 to 0.01	0.305
Alpha v DTW	-0.04	-2.70	-0.08 to -0.01	0.007
Pain Interference				
High v Low	-0.02	-0.92	-0.06 to 0.02	0.355
Task X Interference				
STW v DTW x Interference High v Low	0.00	0.04	-0.04 to 0.04	0.962
Alpha v DTW x Interference High v Low	0.03	1.36	-0.01 to 0.08	0.174
Covariates				
Age	-0.00	-2.06	-0.00 to -0.00	0.041
Mean HBO_2	0.06	5.91	0.04 to 0.08	<0.001
Education	-0.00	-1.33	-0.01 to 0.00	0.183
Ethnicity	0.01	0.74	-0.02 to 0.04	0.458
GDS	0.00	0.62	-0.00 to 0.00	0.534
GHS	0.00	0.55	-0.01 to 0.01	0.578
RBANS	0.00	0.69	-0.00 to 0.00	0.490

Note: GDS= Geriatric Depression Scale; GHS= Global Health Score; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status, Total Scaled Score; STW = Single Task Walk; Alpha = Cognitive Interference; DTW = Dual Task Walk. Model 1 evaluated effects of task and pain severity; Model 2 evaluated effects of task and pain interference; Results of models adjusted for age, mean HBO_2, ethnicity, education, depression (i.e., GDS), comorbidity status (i.e., GHS), and RBANS total index score.

Table 10: Effects of task, pain severity, and pain interference on HBO_2 SD in males.

Variable	Estimate	t	95% CI	*p*
Model 1				
Task				
STW v DTW	-0.03	-1.26	-0.08 to 0.01	0.208
Alpha v DTW	-0.01	-0.80	-0.06 to 0.02	0.420
Pain Severity				
High v Low	-0.00	-0.10	-0.06 to 0.05	0.917
Task X Severity				
STW v DTW x Severity High v Low	0.03	0.93	-0.03 to 0.10	0.354
Alpha v DTW x Severity High v Low	-0.00	-0.04	-0.07 to 0.07	0.967
Covariates				
Age	-0.00	-1.88	-0.00 to 0.00	0.062
Mean HBO_2	0.09	6.64	0.06 to 0.12	<0.001
Education	0.00	1.31	-0.00 to 0.01	0.192
Ethnicity	0.01	0.66	-0.02 to 0.05	0.506
GDS	0.00	0.33	-0.00 to 0.00	0.741
GHS	-0.00	-0.31	-0.02 to 0.01	0.752
RBANS	0.00	0.95	-0.00 to 0.00	0.344
Model 2				
Task				
STW v DTW	-0.02	-0.92	-0.07 to 0.02	0.358
Alpha v DTW	-0.00	-0.22	-0.05 to 0.04	0.824
Pain Interference				
High v Low	0.00	0.10	-0.05 to 0.06	0.915
Task X Interference				
STW v DTW x Interference High v Low	0.01	0.41	-0.05 to 0.08	0.678
Alpha v DTW x Interference High v Low	-0.03	-0.97	-0.10 to 0.03	0.329
Covariates				
Age	-0.00	-1.94	-0.00 to 0.00	0.055
Mean HBO_2	0.09	6.73	0.06 to 0.12	<0.001
Education	0.00	1.30	-0.00 to 0.01	0.194
Ethnicity	0.01	0.63	-0.02 to 0.05	0.531
GDS	0.00	0.42	-0.00 to 0.00	0.673
GHS	-0.00	-0.22	-0.02 to 0.01	0.822
RBANS	0.00	0.99	-0.00 to 0.00	0.322

Note: GDS= Geriatric Depression Scale; GHS= Global Health Score; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status, Total Scaled Score; STW = Single Task Walk; Alpha = Cognitive Interference; DTW = Dual Task Walk. Model 1 evaluated effects of task and pain severity; Model 2 evaluated effects of task and pain interference; Results of models adjusted for age, mean HBO_2, ethnicity, education, depression (i.e., GDS), comorbidity status (i.e., GHS), and RBANS total index score.

Table 11: Gender stratified: Effects of task and pain status on COV of stride length.

Variable	Estimate	t	95% CI	*p*
Females				
Task				
STW v DTW	-2.74	-3.89	-4.13 to -1.35	<0.001
Pain Status				
Pain Yes v No	-1.71	-2.65	-2.97 to -0.44	0.008
Task X Severity				
STW v DTW x Pain Yes v No	1.35	1.64	-0.27 to 2.99	0.102
Covariates				
Age	0.02	0.79	-0.04 to 0.09	0.425
Education	-0.02	-0.29	-0.18 to 0.13	0.767
Ethnicity	-0.13	-0.38	-0.80 to 0.54	0.704
GDS	0.04	0.79	-0.06 to 0.15	0.427
GHS	-0.05	-0.26	-0.45 to 0.34	0.790
RBANS	-0.01	-0.96	-0.05 to 0.01	0.338
Males				
Task				
STW v DTW	-1.58	-2.64	-2.76 to -0.40	0.009
Pain Status				
Pain Yes v No	-0.82	-1.44	-1.94 to 0.29	0.148
Task X Interference				
STW v DTW x Pain Yes v No	0.44	0.55	-1.15 to 2.05	0.582
Covariates				
Age	0.00	0.12	-0.05 to 0.05	0.900
Education	0.08	1.33	-0.04 to 0.22	0.184
Ethnicity	0.14	0.43	-0.51 to 0.79	0.668
GDS	0.08	1.72	-0.01 to 0.18	0.086
GHS	-0.02	-0.12	-0.38 to 0.34	0.902
RBANS	-0.06	-3.27	-0.09 to -0.02	0.001

Note: GDS= Geriatric Depression Scale; GHS= Global Health Score; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status, Total Scaled Score; STW = Single Task Walk; DTW = Dual Task Walk. Results of models adjusted for age, education, ethnicity, depression (i.e., GDS), comorbidity status (i.e., GHS), and RBANS total index score.

Table 12: Effects task, pain severity, and pain interference on COV of stride length in females.

Variable	Estimate	t	95% CI	*p*
Model 1				
Task				
STW v DTW	-0.60	-1.05	-1.74 to 0.53	0.294
Pain Severity				
High v Low	1.43	2.32	0.22 to 2.64	0.021
Task X Severity				
STW v DTW x Severity High v Low	-1.48	-1.87	-3.05 to 0.08	0.063
Covariates				
Age	0.02	0.72	-0.04 to 0.09	0.469
Education	-0.04	-0.48	-0.20 to 0.12	0.627
Ethnicity	0.46	1.00	-0.45 to 1.38	0.317
GDS	0.04	0.77	-0.06 to 0.15	0.440
GHS	-0.01	-0.08	-0.43 to 0.40	0.935
RBANS	-0.00	-0.24	-0.04 to 0.03	0.807
Model 2				
Task				
STW v DTW	-1.21	-2.09	-2.35 to -0.06	0.038
Pain Interference				
High v Low	0.16	0.25	-1.08 to 1.41	0.800
Task X Interference				
STW v DTW x Interference High v Low	-0.34	-0.42	-1.92 to 1.24	0.670
Covariates				
Age	0.03	0.88	-0.04 to 0.10	0.377
Education	-0.04	-0.59	-0.21 to 0.11	0.556
Ethnicity	0.42	0.98	-0.46 to 1.38	0.324
GDS	0.05	0.98	-0.05 to 0.17	0.324
GHS	0.03	0.16	-0.38 to 0.45	0.868
RBANS	-0.00	-0.45	-0.04 to 0.02	0.649

Note: GDS= Geriatric Depression Scale; GHS= Global Health Score; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status, Total Scaled Score; STW = Single Task Walk; DTW = Dual Task Walk. Model 1 evaluated effects of task and pain severity; Model 2 evaluated effects of task and pain interference; Results of models adjusted for age, ethnicity, education, depression (i.e., GDS), comorbidity status (i.e., GHS), and RBANS total index score.

Table 13: Effects of task, pain severity, and pain interference on COV of stride length in males.

Variable	Estimate	t	95% CI	*p*
Model 1				
Task				
STW v DTW	-0.70	-1.01	-2.08 to 0.67	0.311
Pain Severity				
High v Low	0.17	0.23	-1.32 to 1.67	0.818
Task X Severity				
STW v DTW x Severity High v Low	-0.95	-0.92	-3.01 to 1.10	0.358
Covariates				
Age	0.03	0.80	-0.04 to 0.10	0.421
Education	0.22	2.57	0.05 to 0.40	0.012
Ethnicity	0.54	1.09	-0.44 to 1.53	0.275
GDS	0.10	1.54	-0.03 to 0.24	0.125
GHS	0.26	1.06	-0.22 to 0.75	0.289
RBANS	-0.02	-0.96	-0.08 to 0.02	0.336
Model 2				
Task				
STW v DTW	-1.09	-1.62	-2.42 to 0.24	0.108
Pain Interference				
High v Low	0.48	0.62	-1.05 to 2.02	0.532
Task X Interference				
STW v DTW x Interference High v Low	-0.11	-0.10	-2.20 to 1.98	0.917
Covariates				
Age	0.04	1.17	-0.03 to 0.12	0.243
Education	0.21	2.44	0.04 to 0.39	0.016
Ethnicity	0.58	1.17	-0.40 to 1.56	0.244
GDS	0.08	1.17	-0.05 to 0.22	0.243
GHS	0.20	0.85	-0.27 to 0.69	0.396
RBANS	-0.02	-1.06	-0.08 to 0.02	0.288

Note: GDS= Geriatric Depression Scale; GHS= Global Health Score; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status, Total Scaled Score; Alpha = Cognitive Interference; DTW = Dual Task Walk. Model 1 evaluated effects of task and pain severity; Model 2 evaluated effects of task and pain interference; Results of models adjusted for age, ethnicity, education, depression (i.e., GDS), comorbidity status (i.e., GHS), and RBANS total index score.

Table 14: Gender stratified: Effects of task and pain status on rate of correct letter generation.

Variable	Estimate	t	95% CI	*p*
Females				
Task				
Alpha v DTW	0.00	0.17	-0.04 to 0.05	0.862
Pain Status				
Pain Yes v No	-0.01	-0.40	-0.07 to 0.04	0.688
Task X Severity				
Alpha v DTW x Pain Yes v No	-0.00	-0.07	-0.06 to 0.05	0.939
Covariates				
Age	-0.00	-0.14	-0.00 to 0.00	0.883
Education	0.01	4.35	0.01 to 0.02	<0.001
Ethnicity	-0.08	-4.10	-0.12 to -0.04	<0.001
GDS	0.00	0.71	-0.00 to 0.00	0.473
GHS	-0.00	-0.75	-0.03 to 0.01	0.450
RBANS	0.00	5.91	0.00 to 0.00	<0.001
Males				
Task				
Alpha v DTW	-0.02	-0.96	-0.06 to 0.02	0.334
Pain Status				
Pain Yes v No	0.07	2.13	0.00 to 0.14	0.034
Task X Interference				
Alpha v DTW x Pain Yes v No	-0.04	-1.28	-0.10 to 0.02	0.202
Covariates				
Age	-0.00	-0.23	-0.00 to 0.00	0.819
Education	0.01	3.92	0.00 to 0.02	<0.001
Ethnicity	0.03	1.03	-0.02 to 0.08	0.303
GDS	0.00	1.25	-0.00 to 0.01	0.212
GHS	-0.03	-2.56	-0.06 to -0.00	0.011
RBANS	0.00	3.82	0.00 to 0.00	<0.001

Note: GDS= Geriatric Depression Scale; GHS= Global Health Score; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status, Total Scaled Score; Alpha = Cognitive Interference; DTW = Dual Task Walk. Results of models adjusted for age, education, ethnicity, depression (i.e., GDS), comorbidity status (i.e., GHS), and RBANS total index score.

Table 15: Effects of task, pain severity, and pain interference on rate of correct letter generation in females.

Variable	Estimate	t	95% CI	*p*
Model 1				
Task				
Alpha v DTW	0.01	.72	-0.02 to 0.06	0.473
Pain Severity				
High v Low	0.03	1.09	-0.03 to 0.10	0.276
Task X Severity				
Alpha v DTW x Severity High v Low	-0.02	-0.86	-0.09 to 0.03	0.387
Covariates				
Age	-0.00	-0.53	-0.00 to 0.00	0.593
Education	0.01	3.11	0.00 to 0.02	0.002
Ethnicity	-0.09	-3.17	-0.15 to -0.03	0.002
GDS	0.00	0.51	-0.00 to 0.00	0.607
GHS	-0.01	-1.07	-0.04 to 0.01	0.286
RBANS	0.00	4.59	0.00 to 0.00	<0.001
Model 2				
Task				
Alpha v DTW	0.00	0.30	-0.03 to 0.05	0.764
Pain Interference				
High v Low	0.00	0.22	-0.06 to 0.08	0.823
Task X Interference				
Alpha v DTW x Interference High v Low	-0.00	-0.27	-0.07 to 0.05	0.782
Covariates				
Age	-0.00	-0.42	-0.00 to 0.00	0.673
Education	0.01	3.08	0.00 to 0.02	0.002
Ethnicity	-0.09	-3.16	-0.15 to -0.03	0.002
GDS	0.00	0.56	-0.00 to 0.00	0.573
GHS	-0.01	-0.91	-0.03 to 0.01	0.361
RBANS	0.00	4.51	0.00 to 0.00	<0.001

Note: GDS= Geriatric Depression Scale; GHS= Global Health Score; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status, Total Scaled Score; Alpha = Cognitive Interference; DTW = Dual Task Walk. Model 1 evaluated effects of task and pain severity; Model 2 evaluated effects of task and pain interference; Results of models adjusted for age, ethnicity, education, depression (i.e., GDS), comorbidity status (i.e., GHS), and RBANS total index score.

Table 16: Effects of task, pain severity, and pain interference on rate of correct letter generation in males.

Variable	Estimate	t	95% CI	*p*
Model 1				
Task				
Alpha v DTW	-0.07	-2.54	-0.14 to -0.01	0.013
Pain Severity				
High v Low	-0.03	-0.70	-0.12 to 0.05	0.481
Task X Severity				
Alpha v DTW x Severity High v Low	0.03	0.78	-0.05 to 0.12	0.434
Covariates				
Age	0.00	0.16	-0.00 to 0.00	0.874
Education	0.02	4.33	0.01 to 0.03	<0.001
Ethnicity	0.07	1.79	-0.00 to 0.15	0.076
GDS	0.00	0.38	-0.00 to 0.01	0.701
GHS	-0.01	-0.85	-0.04 to 0.01	0.394
RBANS	0.00	2.16	0.00 to 0.00	0.033
Model 2				
Task				
Alpha v DTW	-0.07	-2.62	-0.13 to -0.01	0.010
Pain Interference				
High v Low	-0.01	-0.24	-0.10 to 0.08	0.809
Task X Interference				
Alpha v DTW x Interference High v Low	0.03	0.78	-0.05 to 0.13	0.433
Covariates				
Age	0.00	0.25	-0.00 to 0.00	0.798
Education	0.02	4.37	0.01 to 0.03	<0.001
Ethnicity	0.07	1.86	-0.00 to 0.15	0.066
GDS	0.00	0.25	-0.00 to 0.01	0.800
GHS	-0.01	-0.97	-0.05 to 0.01	0.333
RBANS	0.00	2.12	0.00 to 0.00	0.037

Note: GDS= Geriatric Depression Scale; GHS= Global Health Score; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status, Total Scaled Score; Alpha = Cognitive Interference; DTW = Dual Task Walk. Model 1 evaluated effects of task and pain severity; Model 2 evaluated effects of task and pain interference; Results of models adjusted for age, ethnicity, education, depression (i.e., GDS), comorbidity status (i.e., GHS), and RBANS total index score.