THE INTERACTION OF MENTAL AND NEUROMUSCULAR FATIGUE AND THE IMPACT OF MENTAL FATIGUE ON FUNCTION ACROSS DIFFERENT AGE GROUPS

by

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DISSERTATION ABSTRACT

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Fatigue is a multidimensional concept with physical and psychological components. While neuromuscular fatigue has been studied extensively, its effects on cognitive function have been studied, few studies have focused on its impact on cognitive function. Further, the effect of mental fatigue on neuromuscular measures or physiological outcomes is not fully understood. Three studies were conducted to determine the interactions between mental and neuromuscular fatigue and the impact of mental fatigue on function and, to determine age related differences in these interactions.

Study one investigated neuromuscular function in the tibialis anterior of young and older adults (transcranial magnetic stimulation, electrical stimulation, and force measurements) before and after a 20-minute mental fatigue task. Results suggested that mental fatigue may cause increased cortical inhibition in both age groups and that 20 minutes of a mentally fatiguing task may cause a decrease in the ability to produce maximal force in young adults, providing evidence of an interaction between mental fatigue and physical function.

Study two examined the effect of neuromuscular fatigue on cognitive function in young and older adults. Measures of cognitive function (reaction time and errors during a 3-minute cognitive task) were taken before and after 16-minutes of intermittent isometric contraction of the ankle dorsiflexor muscles. Neuromuscular fatigue negatively affected cognitive function (slowed reaction time) in young adults only. Results suggested that a neuromuscular fatigue task may negatively affect cognitive function in young but not older adults.

Study three examined the postural response to force platform perturbations in young and older women in response to mental fatigue. Only young women experienced mental fatigue (slower reaction times) and this was accompanied by significantly faster center of pressure velocity during the mental fatigue condition compared with the control condition. Performance of the mental fatigue task, not necessarily development of mental fatigue, affects neuromuscular activation in young women only, but does not affect the magnitude of postural response to perturbation.

Taken together, these studies demonstrate that there is a complex and age-specific relationship between mental fatigue and physical function and physical fatigue and cognitive function.

This dissertation includes unpublished co-authored material.

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CHAPTER I

INTRODUCTION

Background and Significance

Fatigue is a multidimensional concept that has both physical and psychological components [1], and is reported by nearly half of the adult population throughout the course of a typical day [2]. While neuromuscular fatigue is a transient reduction in the ability of the muscle to produce force or power in response to contractile activity [3], mental fatigue is a psychophysiological state that occurs after or during prolonged periods of cognitive activity [4,5]. Mental fatigue is generally characterized by self-reported feelings of tiredness, lack of motivation, and decreased cognitive performance, [4,5] and is linked to several negative outcomes including: the development of physical fatigue, decreases in physical performance, poorer performance on cognitive tasks, and an inability to properly allocate attention [5–8]. Although neuromuscular fatigue has been studied extensively, few studies have focused on its impact on cognitive function. Further, the effect of mental fatigue on neuromuscular function or physiological outcomes is not fully understood. In order to truly understand the consequences of fatigue, it is necessary to examine its impacts across the multiple dimensions it affects. Understanding the neuromuscular and functional consequences of mental fatigue, as well as its interactions with neuromuscular fatigue, will fill a critical gap in our knowledge. Further, understanding the impact of mental fatigue and the interactions with neuromuscular fatigue across different age groups is important for our understanding of healthy aging.

Effect of Neuromuscular Fatigue on Cognitive Function

Just as the impact of mental fatigue on neuromuscular function is not known, the impact of neuromuscular fatigue on cognitive function is also poorly understood. Despite decades of work to characterize the effects of neuromuscular fatigue, there are very few studies documenting its impact on functional domains other than the motor system, such as cognition. Results from the limited existing studies indicate that neuromuscular fatigue has a negative effect on cognitive performance. For example, when participants performed a cognitive task with a simultaneous fatiguing submaximal contraction of the first dorsal interosseus, there was an increase in reaction time and cognitive errors compared to a cognitive task alone [7]. Additional evidence suggests that the impact of such contractions on cognitive performance is dependent upon the level of force produced [9], with higher force production resulting in increased errors and longer reaction time on a cognitive task [9]. These findings suggest an important association between neuromuscular fatigue and cognitive function, which warrants further investigation in this area.

Effect of Mental Fatigue on Physical Performance

It has consistently been demonstrated that mental fatigue can negatively affect whole body exercise. For example, in studies examining the effect of mental fatigue on cycling performance, decreased endurance time and losses in peak power have been reported in the presence of mental fatigue [5,10]. Similarly, decreases in running velocity, running distance, and speed and accuracy (during a soccer shot) have also been demonstrated with mental fatigue [11,12]. Collectively, these studies support the notion that

mental fatigue can negatively impact several aspects of whole body physical performance.

Similar results have been found with single joint exercise. Pageaux et al. (2013) demonstrated a 13% reduction in time to exhaustion during a knee extensor exercise with mental fatigue. Further, Bray et al. (2012) investigated the effects of a demanding cognitive task on maximal force production. Subjects were asked to perform either maximal voluntary contractions (MVC) every 3 minutes for 22 minutes, or perform a Stroop Task for 22 minutes, with an MVC every 3 minutes. They showed that the cognitive task condition resulted in greater declines in MVC force and increased ratings of mental exertion over the 22 minutes. Taken together, these studies suggest that mental fatigue can result in declines in motor output and performance during single joint exercise, similar to findings from whole body exercise. Although these results suggest a negative effect of mental fatigue on physical performance, the mechanisms leading to these deficits remain unclear.

To date, only three studies have examined changes in neuromuscular function in response to mental fatigue, and results vary [13–15]. In all studies, no changes in voluntary activation were noted following mental fatigue. Further, aside from one observation of an increased half-relaxation time [15] in response to mental fatigue, no changes in muscle contractile properties were reported (10,11). However, several limitations may have impacted results of these studies. For example, in one study, no changes in reaction time or errors on the cognitive task were noted, suggesting the task did not sufficiently cause mental fatigue [15]. In the other two studies, pauses in the cognitive task to take neuromuscular measures (10), or to transfer participants to the neuromuscular testing

device may have limited the ability to detect differences in neuromuscular function due to mental fatigue (11). Because of the inconsistencies in performing these studies and the variance in results, further research is necessary to determine how mental fatigue affects physical performance. Further, assessments of neuromuscular function have been largely limited to peripheral measures, with few assessments of changes in central factors, such as motor cortex function, which may offer important mechanistic insights.

Effect of Mental Fatigue on Executive Function

Executive functions include the ability to sustain attention, the ability to initiate and carry out behaviors, short term and working memory, stimulus detection, planning, and motor attention [16]. Mental fatigue influences brain regions associated with executive function, specifically the prefrontal cortex (PFC) and anterior cingulate cortex (ACC). Using various techniques (functional magnetic resonance imaging, and electroencephalography (EEG)), changes in activity in these regions in response to mental fatigue have been documented [6,17–20], suggesting their involvement in the process of mental fatigue.

One specific executive function that is negatively affected by mental fatigue is goal-directed attention. Such an impairment in goal-directed attention leads to a decrease in behavioral flexibility, and an inability to respond to unexpected stimuli [21]. Mental fatigue also leads to impaired action monitoring and failure to adjust performance in response to errors [22]. Further, the level of mental fatigue may contribute to the severity of error processing impairment and subsequently, sustained attention. Using EEG, Xiao et al. (2015) found that the degree of change in event related negativity (ERN) amplitude,

an index of error processing that can be used to predict sustained attention, was negatively affected by level of mental fatigue. Higher mental fatigue was significantly associated with larger changes in ERN amplitude, indicating poorer error processing and decreased sustained attention with higher levels of mental fatigue. Such negative impacts of mental fatigue on attention processing and action monitoring can lead not only to impaired cognitive processing, but can also affect physical functions, such as balance control.

Attention and Postural Stability

Attention, or the processing capacity of an individual, is limited and performing any task requires a portion of that attention [23]. The ability to properly allocate these attentional resources is important for postural stability [23]. Fewer attentional resources are available for balance control when subjects engage in a simultaneous cognitive task, leading to a decline in postural stability [24–27].

Research using a dual-task paradigm has demonstrated that: (1) cognitive tasks result in decrements in postural stability in both young and old adults and (2) older adults have less attentional processing ability leading to a greater impact of the cognitive task on balance control than in young adults [25–27]. Additionally, a study examining differences in healthy older adults and older adults classified as fallers, demonstrated that when postural stability was impaired (older fallers), even simple cognitive tasks can further decrease balance control [27].

Increased levels of mental fatigue could negatively impact postural stability as mental fatigue can negatively affect the ability to efficiently allocate attention and respond to unexpected stimuli. This could be especially important in older individuals, as their attentional resources and cognitive processing abilities are more limited than younger adults. However, the effect of mental fatigue on postural stability has not been studied.

Changes with Aging

Several physiological changes take place with aging, including declines in sensory system feedback, nerve conduction velocity, motor unit numbers, muscle mass, and central processing abilities [26]. There is also a reduction in brain volume and reduction in the size of neurons in the prefrontal cortex which begins earlier and is often more severe than in other areas of the brain [28].

Due to the many physiological changes across systems with aging, there is also a change in response to neuromuscular fatigue. Results from several studies indicate that older adults may be more fatigue resistant than young adults during isometric contractions, but more fatigable during dynamic contractions [29,30]. These differences in fatigability might be explained by changes in neuromuscular propagation (smaller M-wave) and contractile properties (slowing of half-relaxation time) of the muscle with aging [30].

In addition to physiological changes, cognitive changes occur with aging. The cost of cognitive activity increases as adults age. With cognitive demand, older adults experience greater increases in cardiovascular reactivity, muscle activation, and force

fluctuation (decreased steadiness) compared to younger adults [31–34]. Additionally, mental fatigue is commonly subjectively reported in older adults [35], with 28-55% of adults aged 65 or older experiencing subjective fatigue [36]. Subjective fatigue is a risk factor for various poor health outcomes in older adults including earlier onset of disability, slower gait speed, and increased risk of hospitalization [35,36]. Understanding more about the interactions between cognitive and motor functions and how these interactions change with age is important for our understanding of healthy aging and will be essential in developing evidence-based interventions to improve function and prevent falls in older adults.

Overall Goal and Specific Aims

Despite the important functional consequences of mental fatigue, the limited research in this area has been focused on subjective behavioral outcomes and little is known about the mechanisms behind how mental fatigue may affect motor function and postural stability. Further, the extent to which neuromuscular fatigue affects cognitive function is also largely unknown. As fatigue is a multidimensional concept, it is important to take a multifaceted approach to understanding its impacts.

The impacts of neuromuscular fatigue on cognitive function and of mental fatigue on neuromuscular function likely differs in older adults compared to young because aging affects both neuromuscular and cognitive processes. Further, though mental fatigue is highly reported in older adults, to our knowledge, there are no studies examining the possible age-related differences in the effects of mental fatigue.

The overall goal of this dissertation was to determine the interactions between mental and neuromuscular fatigue and the impact of mental fatigue on function and, importantly, to determine age related differences in these interactions. Four specific aims were identified. The first two aims focused on the interaction between mental fatigue and neuromuscular fatigue and the third aim focused on the impact of mental fatigue on function. The fourth aim focused on age related differences.

Aim 1: To determine the effects of mental fatigue on measures of neuromuscular function.

Aim 2: To determine the effects of neuromuscular fatigue on cognitive function.

Aim 3: To examine the effect of mental fatigue on postural stability.

Aim 4: To determine the age-related differences in neuromuscular function and postural stability in response to mental fatigue.

Hypotheses

Hypothesis 1: mental fatigue would negatively affect neuromuscular function.

Hypothesis 2: neuromuscular fatigue would negatively affect cognitive function.

Hypothesis 3: mental fatigue would increase postural instability.

Hypothesis 4: older adults would have worse neuromuscular function and postural instability with mental fatigue than younger adults.

Hypothesis 5: older adults would have worse cognitive function with neuromuscular fatigue than younger adults.

Flow of the Dissertation

This dissertation is in journal format for Chapters II through IV and includes co-authored material that has been prepared for submission to peer-reviewed scientific journals.

Chapter II examines the influence of mental fatigue on neuromuscular fatigue in young and older adults. This work has been prepared for submission to a peer-reviewed scientific journal. Anita Christie is a co-author.

Chapter III examines the influence of neuromuscular fatigue on cognitive function in young and older adults. This work has been prepared for submission to a peer-reviewed scientific journal. Anita Christie is a co-author.

Chapter IV examines the effect of mental fatigue on postural stability in young and older women. This work has been prepared for submission to a peer-reviewed scientific journal. Anita Christie is a co-author.

Chapter V summarizes the findings and provides recommendations for future research.

CHAPTER II

THE EFFECT OF MENTAL FATIGUE ON NEUROMUSCULAR FUNCTION

Amanda Morris contributed to the concept of the studies, recruited subjects, collected data, performed data analysis, and prepared the initial manuscript. Dr. Anita Christie contributed to the concept of the study, provided editorial support, and critically reviewed and revised the manuscript.

Introduction

Mental fatigue is a psychophysiological state that occurs after or during prolonged periods of cognitive activity [4]; it is characterized by self-reported feelings of tiredness, lack of motivation, and decreased cognitive performance [37,38]. Several studies have examined the effect of mental fatigue on exercise performance and the perception of fatigue. Decreases in endurance time and loss of peak power during cycling in the presence of mental fatigue have been reported [5,10] as well as decreases in running velocity, running distance, and accuracy during a soccer shot [11,12]. Further, several studies using single joint exercises in the presence of mental fatigue have reported reductions in time to exhaustion and maximal force production [15,39]. All of these studies reported increases in ratings of perceived exertion with mental fatigue. Although these results suggest a negative effect of mental fatigue on physical performance and perception of exertion, the mechanisms leading to these deficits remain unclear.

Few studies have examined changes in neuromuscular function in response to mental fatigue, and results vary [13–15]. In these studies, no changes in voluntary activation were noted following mental fatigue. Further, aside from one observation of slowed

muscle relaxation time [15] in response to mental fatigue, no other changes in muscle contractile properties have been reported (10,11). However, several limitations may have impacted results of these studies. For example, in one study, no changes in reaction time or errors on the cognitive task were noted, suggesting the task did not sufficiently cause mental fatigue [15]. In the other two studies, pauses in the cognitive task to take neuromuscular measures (10) or to transfer participants to the neuromuscular testing device may have limited the ability to detect differences in neuromuscular function due to mental fatigue (11). Because of the inconsistencies in performing these studies and the variance in results, further research is necessary to determine how mental fatigue affects physical performance. Additionally, assessments of neuromuscular function in response to mental fatigue have been largely limited to peripheral measures, with few assessments of changes in central factors, such as motor cortex function, which may offer important mechanistic insights.

Any effects of mental fatigue on exercise performance and neuromuscular function may vary based on sex and/or aging. Women report significantly more mental and physical fatigue than men [40–42]. Older adults, especially older women, also report higher levels of subjective fatigue than young adults [41]. In older adults, self-reported fatigue is associated with earlier onset of disability, slower gait speed, and increased hospitalization risk [36,43]. Despite these important associations, little is known about the direct impact of mental fatigue on neuromuscular function in the older population. Additionally, numerous physiological changes take place with aging including: declines in sensory system feedback, nerve conduction velocity, motor unit numbers, muscle mass, and central processing abilities [26]. The impact of mental fatigue on neuromuscular

function may differ in older adults compared to young because aging affects both neuromuscular and cognitive processes. Although mental fatigue is highly reported in older adults, there are no studies examining the possible age-related differences in effects of mental fatigue. Understanding more about the interactions between cognitive and motor functions and how these interactions change with age is important for our understanding of healthy aging. Such information will be essential in developing evidence-based interventions to improve function and prevent falls in older adults.

The purpose of this study was to examine the effect of a mentally fatiguing task on neuromuscular and cortical functions in young and older adults. An exploratory aim of this study was to explore sex differences in these responses. Neuromuscular and cortical measures were obtained prior to and following a mentally fatiguing task. It was hypothesized that the mentally fatiguing task would negatively affect contractile properties of the muscle (increased half-relaxation time, decreased peak twitch force) and cortical measures (increased cortical inhibition and increased cortical excitability) in both age groups, with older adults showing augmented responses compared to the younger group.

Methods

Subjects

Seventeen young adults (9 females, Table 2.1) and 21 older adults (16 females, Table 2.1) participated in this study. Participants were healthy and free from any chronic disease, illness, condition, or medication that could impact balance. Exclusion criteria included: a positive screen for cognitive impairment, history of illness associated with fatigue (e.g. chronic fatigue syndrome, multiple sclerosis), history of cognitive deficiencies

(e.g. memory loss, difficulty concentrating), poor sleep habits, history of neurological impairment, history of musculoskeletal impairments, use of alcohol or central nervous system depressant pharmacological agents within 12 hours of performing tasks, or active substance abuse. All participants provided written informed consent and were asked to complete a brief medical history report, Pittsburgh Sleep Quality Index, Multidimensional Fatigue Index, and the Mini-Cog cognitive screening test. The procedures were reviewed and approved by the Institutional Review Board.

After completing sleep and fatigue questionnaires, neuromuscular measures (electrical stimulation) and cortical measures (transcranial magnetic stimulation (TMS)) were taken. Participants then performed a mentally fatiguing task for 20 minutes. The neuromuscular and cortical measures were repeated immediately following the mental fatigue task. The timeline for the experimental protocol is presented in Figure 2.1.

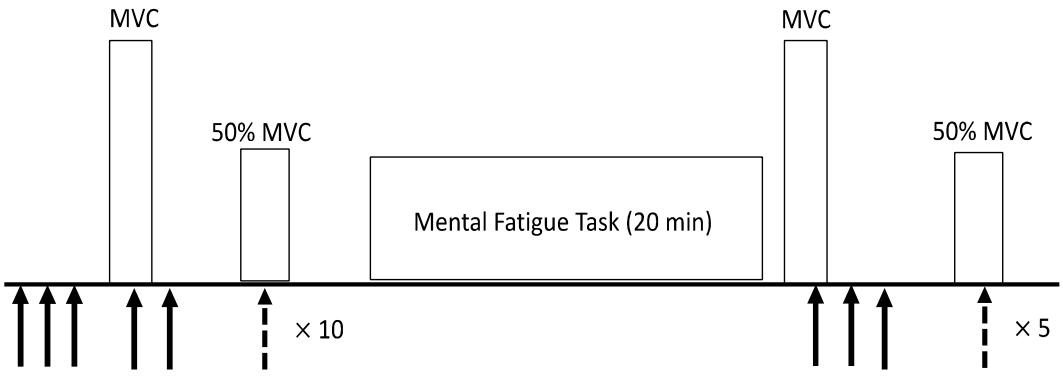

Figure 2.1. Overview for study one**.** Black solid line: electrical stimulation. Black dashed line: transcranial magnetic stimulation. Questionnaires were completed before and after the protocol.

Questionnaires

The Pittsburgh Sleep Quality Index (PSQI) was used to measure the sleep patterns and quality of sleep in seven domains subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, sleep medication use, and daytime dysfunction. The participants self-rated these aspects of sleep quality on a 0 to 3 scale, where 3 is negative. A total score, summed across all questions, of 5 or greater indicates a poor sleeper [44].

The Multidimensional Fatigue Inventory (MFI) is a 20 item, self-report instrument that measures fatigue in the following domains: general fatigue, physical fatigue, mental fatigue, motivation, and activity. Participants responded to each item on a scale of 1 to 7 and the total score was summed across all items. A higher total score corresponds to more acute levels of fatigue.

Neuromuscular Measures

Individuals were seated in a chair with their dominant foot placed in a custom-built device designed to measure dorsiflexion force. A strap was placed over the dorsum of the foot. Maximal voluntary force was determined by asking participants to pull as hard as they could by dorsiflexing their ankle and pulling their foot against the strap so that their maximal voluntary contraction force (MVC) was measured. They were asked to repeat this procedure an additional two times and were given at least 1 minute of rest between contractions. The highest value was taken as the MVC.

A preamplified, bipolar Ag-AgCl electrode (DE-2.1, Delsys Inc., Boston, MA), with an inter-electrode distance of 1 cm, was taped to the surface of the skin, over the belly of the tibialis anterior (TA) muscle. This electrode was connected to a portable

amplifier (Delsys Inc., Boston, MA), which further amplified and band-pass (20-450 Hz) filtered the signal. A ground electrode was applied to the ankle. The signal was sampled at 1 kHz with a 16-bit A/D converter (NI USB-6251, National Instruments, Austin, TX).

The maximal electrical response of the muscle was determined by placing a stimulating electrode on the side of the leg over the peroneal nerve and activating the nerve through brief (200 μs) electrical pulses. The intensity required to elicit a maximal electrical response (M-wave) of the muscle (recorded with the EMG electrodes) was determined and 3 stimulations were recorded at 120% of maximal intensity. M-wave peak-to-peak amplitude was used to examine electrical response of the muscle. Force responses to stimulations were used to examine contractile properties of the muscle and included: peak twitch force, time to peak twitch force, and half-relaxation time. Half-relaxation time was considered as the time from peak twitch force to the time force relaxed to 50% of the peak twitch force.

Single-pulse transcranial magnetic stimulation (TMS) was delivered using a 110 mm double cone magnetic stimulation coil placed on the head, over the motor cortex. This coil was used to activate the brain through brief magnetic pulses (100 μs). The response of the TA muscle was recorded with EMG. The optimal site for stimulation of the TA muscle was determined by moving the coil to find the location that presented the largest motor evoked potential (MEP) at 60% stimulator output. The resting motor threshold (RMT) of the muscle was determined by stimulating at decreasing stimulus intensity to find the threshold while the muscle is at rest. Threshold was defined as the stimulus intensity that produced a MEP of at least 50 μV in at least 5/10 trials [45]. The stimulus intensity was then set at 120% of RMT and responses were recorded while the

participant was contracting at 50% MVC. Ten responses were recorded before the mental fatigue task and 5 were recorded after. Cortical excitability was determined by the peak-to-peak amplitude of the active MEP, averaged across trials at each time point. Cortical inhibition was determined by the cortical silent period, measured as time between the end of the MEP and resumption of voluntary EMG activity, averaged across trials at each time point.

Mental Fatigue Task

To induce mental fatigue, participants were asked to perform the psychomotor vigilance task (PVT) for twenty minutes. The PVT is an objective, valid measure for assessing behavioral alertness and vigilant attention [46].The PVT is based on simple reaction time to stimuli that occur randomly [46]. Lapses in reaction time (RT > 500 ms) during this task are associated with subjective measures of physical fatigue and decline in energy [47,48]. When the task is performed for 20 minutes or more a time-on-task effect of increase in reaction time and/or decrease in accuracy over the task is observed, indicating a decrease in vigilance and presence of mental fatigue [37,38,49].

Participants were asked to visually fixate on a computer screen placed at eye level in front of them. They were asked to click the left button on a mouse as soon as a red number appeared on the screen. As soon as the button was pushed, a number was displayed on the screen for 500ms indicating reaction time and was then cleared and the next stimulus presented. Time between presentation of each stimulus varied randomly between 2 and 10 seconds. In addition to simple reaction time (RT), the program

recorded: false starts, anticipation (RT <100ms), minor lapses (RT ≥ 500ms), and major lapses (RT≥1000ms). Increases in reaction time and/or number of lapses indicated the presence of mental fatigue. This software was created by Biotechnology HPC Software Applications Institute and is run using MATLAB (MathWorks Inc., Natick, MA, USA).

Data Analysis

All data were analyzed with custom-written programs using MatLab software. To examine contractile properties of the muscle, the twitch force trace was used (Figure 2.2). Peak twitch force was the maximal force generated during the twitch (Figure 2.2, red arrow). Time to peak twitch force was calculated as the time from the beginning of the response to peak force (black arrow). Half-relaxation time (green arrow) was calculated by first determining half of peak force with the equation $peak\ force \div 2$. To calculate half-relaxation time, time of peak force was subtracted from the time when the force had relaxed to half of peak force. Twitch responses were then averaged across the three stimulations at baseline and one stimulation was analyzed at the end of the protocol.

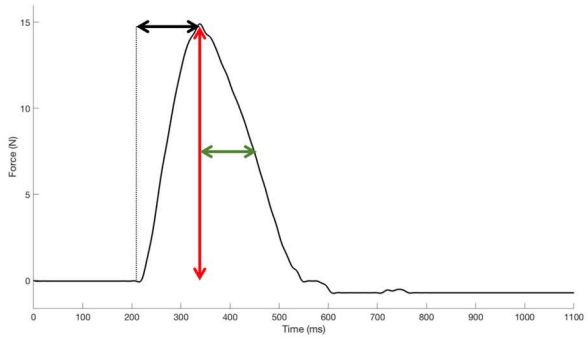

Figure 2.2. Representative trace of contractile properties of muscle. Black arrow: time to peak twitch force (ms); red arrow: peak twitch force (N); green arrow: half-relaxation time (ms).

M-wave amplitude (M_{Max}) was assessed using the EMG responses to electrical nerve stimulation (Figure 2.3, right). Peak-to-peak amplitude of the M-wave was calculated from the non-rectified signal as maximum EMG − minimum EMG. M-wave amplitude was then averaged across the three stimulations at baseline and only one stimulation was used at the end of the protocol.

Cortical excitability and inhibition were assessed using the EMG responses to TMS (Figure 2.3, left). Cortical excitability was determined by the peak-to-peak amplitude of the active MEP, normalized to M_{Max}. Cortical inhibition was indicated by the duration of the cortical silent period, measured as the time between the end of the MEP and resumption of voluntary EMG activity. These points were selected manually and averaged across trials at each time point.

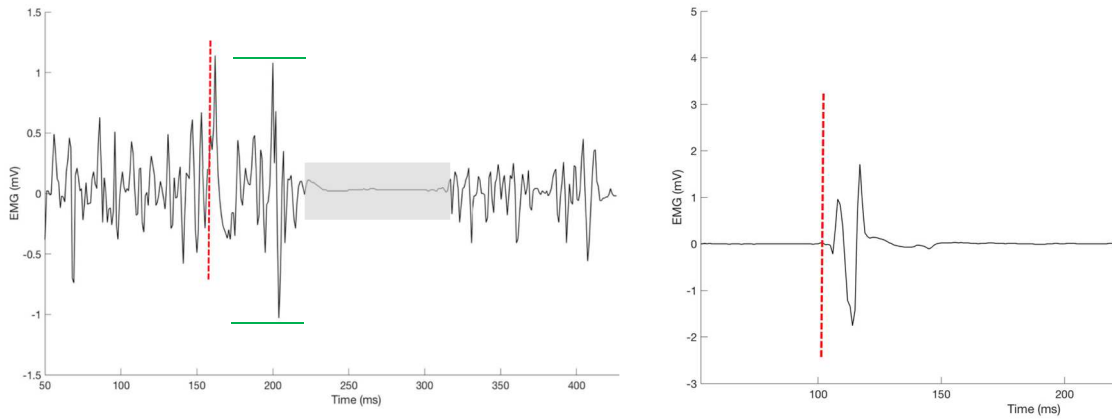

Figure 2.3. Representative trace of EMG responses. TMS (left) red dotted line: stimulation, green lines: MEP amplitude (mV), grey box: silent period. M-wave (right) red dotted line: stimulation

Statistical Analyses

The following quantitative outcome variables were obtained: mental fatigue: reaction time, number of lapses; neuromuscular function: MVC force, peak-to-peak amplitude of the M-wave; contractile properties of the muscle: time to peak force, peak force, half-relaxation time; cortical excitability: peak-to-peak amplitude of active motor evoked potential; cortical inhibition: cortical silent period duration.

Participant characteristics and all baseline measures were compared with 2-factor (age, sex) ANOVAs. To examine the impact of the mental fatigue protocol on each variable, 3-factor (age, sex, and time) repeated-measures ANOVAs were used. If significance was found, pairwise comparisons with a Bonferroni correction were used for post-hoc testing. Significance was set at $p \leq 0.05$.

Results

Participant Characteristics

Participant characteristics and scores (mean ± SD) for the Multidimensional Fatigue Inventory (MFI) and the Pittsburgh Sleep Quality Index (PSQI) are presented in Table 2.1. There was no significant interaction of sex and age (p=0.19) on total MFI, nor was there a main effect of sex (p=0.76). However, there was a significant effect of age (p=0.002) on MFI score, with older adults reporting higher scores than young adults. There was no significant interaction of sex and age (p=0.70) on PSQI scores, nor were there significant main effects of age (p=0.17) or sex (p=0.18). There was no significant interaction of sex and age (p=0.75) on subjective ratings of fatigue, nor were there significant main effects of age (p=0.12) or sex (p=0.42). There was no significant

interaction of sex and age (p=0.66) on subjective ratings of fatigue at baseline, nor were there any significant main effects of age (p=0.06) or sex (p=*0.*66).

Mean age, height and weight of participants is shown in Table 2.1. There was no significant age difference between sexes (p=0.06) but older adults were significantly older (p<0.001) than younger adults. There was a significant difference in height between sexes (p= 0.01) with males being taller than females, but no significant difference in height with age (p=0.54). There was no significant interaction of age and sex (p=0.14) on weight. However, males were heavier than females (p<0.001) and older adults were heavier than young adults (p=0.02).

Table 2.1. Participant characteristics

Variable	YF (n=9)	YM (n=8)	OF (n=16)	OM (n=5)
Age*	22.44 ± 2.88	23.80 ± 4.26	74.13 ± 6.30	68.80 ± 3.96
Height[#] (in)	65.40 ± 3.36	70.50 ± 1.29	64.12 ± 2.10	70.33 ± 2.62
Weight (kg)	272.36 ± 62.21	352.00 ± 28.79	293.23 ±42.56	438.53 ± 42.12
MFI*	48.10 ± 25.45	36.82 ± 29.54	55.00 ± 14.85	56.75 ± 13.34
PSQI	5.33 ± 2.78	4.50 ± 2.99	4.50 ± 2.07	3.00 ± 1.87
Subjective Fatigue Rating	3.33 ± 1.63	3.33 ± 1.63	2.00 ± 1.20	2.50 ± 1.87

MFI, Multidimensional Fatigue Index; PSQI, Pittsburgh Sleep Quality Index. Higher scores indicate more fatigue or poorer sleep quality. *****indicates a significant difference between age groups (p<0.05). [#] indicates a significant difference between sexes (p<0.05).

Baseline measures of neuromuscular function are presented in Table 2.2. There was no significant interaction of sex and age (p=0.62) on baseline maximal voluntary

contraction (MVC), nor was there a significant main effect of age (p=0.09). However, there was a significant main effect of sex (p=0.002) on MVC, with males being significantly stronger than females.

There was also no significant interaction of age and sex on baseline peak twitch force (p=0.15), time to peak twitch force (p=0.71), or half-relaxation time (p=0.76) (Table 2.2). There was no significant main effect of age on baseline peak twitch force (p=0.78), time to peak twitch force (p=0.29), nor on half-relaxation time (p=0.24). There was also no significant main effect of sex on baseline peak twitch force (p=0.12), time to peak twitch force (p=0.69), nor on half-relaxation time (p=0.62).

There was no significant interaction of sex and age (p=0.91) (Table 2.2) on baseline M-wave amplitude (M_{Max}), nor was there a significant main effect of sex (p=0.39). However, there was a significant main effect of age (p<0.001), with young adults having a greater amplitude.

There was no significant interaction of age and sex (p=0.72) on cortical silent period (CSP) duration at baseline, nor was there a significant main effect of age (p=0.11), sex (p=0.06), or interaction of age and sex (p=0.72). There was no significant interaction of age and sex (p=0.75) on MEP amplitude at baseline (Table 2.2). However, there was a significant main effect of age (p=0.05) on MEP amplitude, with older adults having larger MEP amplitudes.

Table 2.2. Baseline neuromuscular measures

Variable	YF (n=9)	YM (n=8)	OF (n=16)	OM (n=5)
MVC[#] (n)	205.38 ± 76.19	261.41 ± 32.11	164.00 ± 36.08	238.74 ± 45.69
PTF (n)	13.72 ± 5.54	18.55 ± 3.23	16.49 ± 2.19	16.67 ± 4.66
TTP (ms)	86.40 ± 16.82	91.00 ± 13.52	94.88 ±7.74	95.00 ± 19.34
HRT (ms)	98.54 ± 10.95	91.86 ±17.34	105.88 ± 23.03	104.36 ± 24.70
M_{Max} * (mV)	5.98 ± 1.23	6.33 ± 1.97	3.99 ± 0.77	4.46 ± 0.69
MEP (%M_{Max})	27.84 ± 8.03	30.46 ± 19.16	42.87 ± 15.21	42.27 ± 16.94
CSP (ms)	74.42 ± 6.33	106.38 ± 58.03	101.36 ± 26.96	123.62 ± 34.84

MVC, maximal voluntary contraction; PTF, peak twitch force; TTP, time to peak twitch force; HRT, half relaxation time; M_{Max}, m-wave; MEP, motor evoked potential; CSP, cortical silent period. *indicates a significant difference between ages. [#] indicates a significant difference between sexes (p<0.05).

Mental Fatigue

Likert ratings of subjective fatigue are shown in Figure 2.4. There was no significant interaction of time, age, and sex (p=0.87), nor were there significant interactions between time and sex (p=0.76), time and age (p=0.19), or sex and age (p=0.52). However, there was a significant main effect of time (p <0.001); ratings after mental fatigue were significantly higher than ratings at baseline (p <0.001). Additionally, there was a significant main effect of age (p=0.002), with older adults reporting lower fatigue than younger adults (3.71 ± 1.55 vs 5.83 ± 1.64).

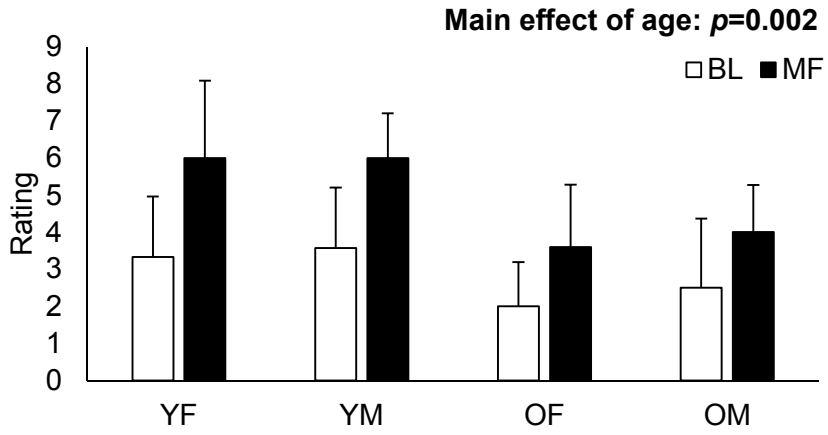

Figure 2.4. Subjective fatigue ratings. Higher values indicate higher feelings of fatigue. After the mental fatigue task (MF), ratings were significantly higher (p<.001) than ratings at baseline (BL). Older adults reported lower fatigue than younger adults (p=0.002).

There was no significant interaction of time, sex, and age (p=0.34) for reaction time , nor were there interactions of time and sex (p=0.75) or time and age (p=0.26 (Figure 2.5). However, there was a significant main effect of time (pre versus post mental fatigue) (p=0.001) on reaction time in the PVT, with the post-mental fatigue time point having significantly longer reaction times than baseline (Figure 2.5). There were no significant main effects of age (p=0.68) or sex (p=0.88).

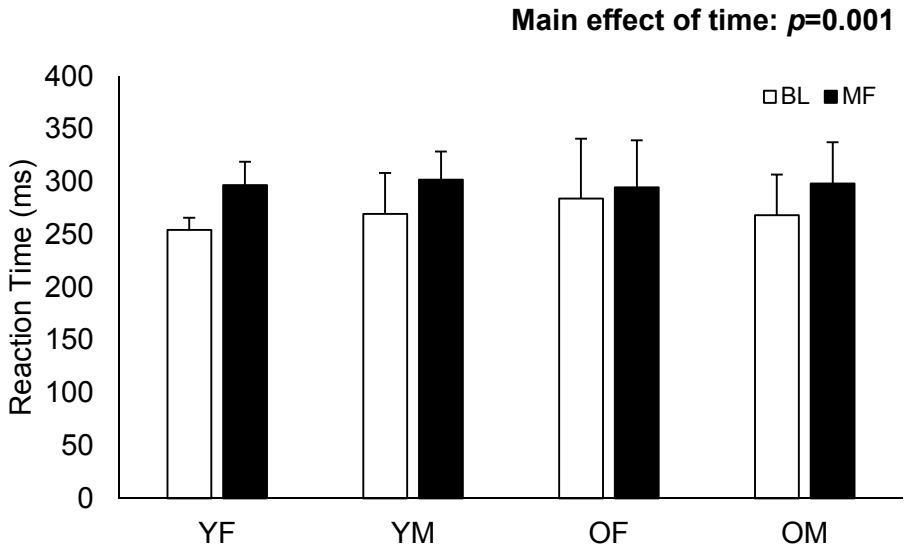

Figure 2.5. Psychomotor vigilance task reaction time. YF=young female, YM = young male, OF = older female, OM = older male, BL = baseline, MF = mental fatigue. MF times were significantly slower than BL (p=0.001).

False starts and lapses are presented in Table 2.3. There was no significant main effect of sex (p=0.24) and no significant interaction of age and sex (p=0.29) false starts. However, there was a significant main effect of age (p=0.001) on number of false starts, with older adults having significantly more false starts than young adults. There was no significant interaction of sex and age (p=0.75) on number of lapses (RT > 500ms), nor was there a significant main effect of sex (p=0.85) or age (p=0.64).

Table 2.3. False starts and lapses during the PVT

Variable	YF (n=9)	YM (n=8)	OF (n=16)	OM (n=5)
False Starts*	1.67 ± 0.82	2.00 ± 1.90	7.47 ± 6.39	12.67 ± 9.83
Lapses	3.67 ± 1.86	3.83 ± 5.60	3.47 ± 3.07	2.83 ± 1.72

* indicates a significant difference between age groups (p=0.001).

Force

There was a significant interaction of time, age, and sex (p=0.03) on MVC force; old males (p=0.03) and young females (p=0.004) had a significant decline in MVC force after mental fatigue (Figure 2.6). There was a significant main effect of time on MVC (p=0.002), with lower MVC force values post mental fatigue, compared with baseline. There was also a significant main effect of sex (p=0.001) with males producing more force than females. There was no significant main effect of age (p=0.09), nor were there any significant interactions of time and age (p=0.83), time and sex (p=0.41), or age and sex (p=0.89).

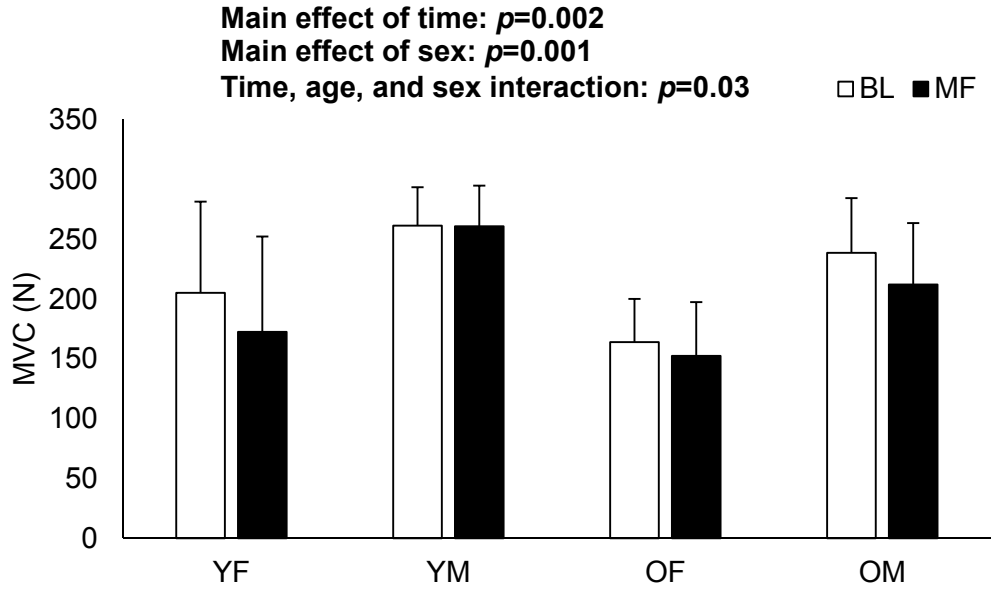

Figure 2.6. Baseline (BL) and mental fatigue (MF) maximal voluntary contraction (MVC) force values. YF=young female, YM = young male, OF = older female, OM = older male. There was a significant decrease (p<0.002) in MVC with MF. Males produced more force than females (p=0.001*).*

The force, relative to MVC, at the end of the mental fatigue protocol is presented for each group in Figure 2.7. There was a significant age and sex interaction (p=0.05); young females reached a significantly lower percent of their MVC after mental fatigue than young males (p=0.02). There was no main effect of age (p=0.88) or sex (p=0.17) relative

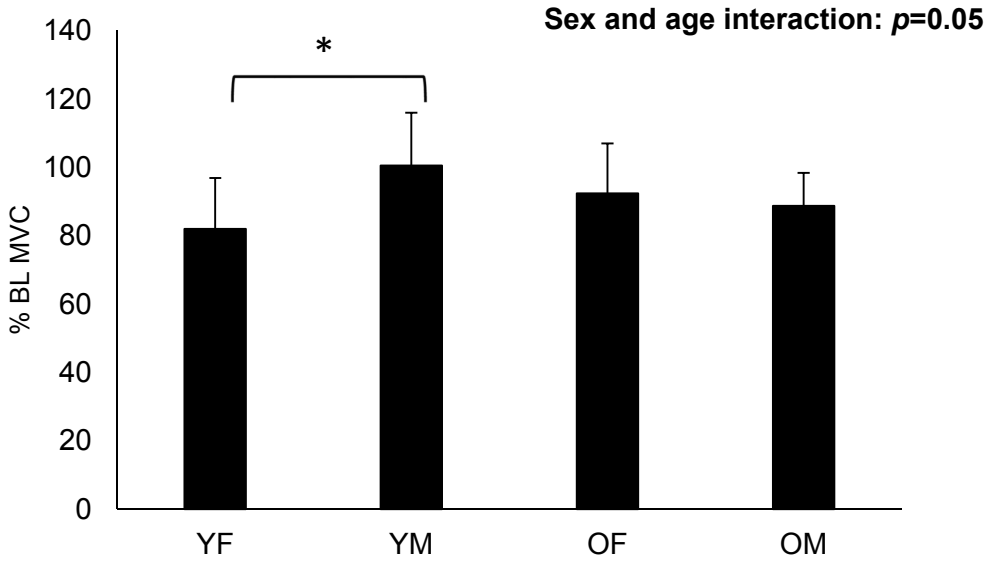

Figure 2.7. Maximal voluntary contraction (MVC) force after mental fatigue (MF) protocol. Data presented as percent of BL MVC after MF. YF=young female, YM = young male, OF = older female, OM = older male. * YF reached a significantly lower percent of their MVC after MF than YM (82.10 ± 21.20 vs. 100.6 ± 21.00%).

Peripheral Neuromuscular Measurements

There was no significant interaction of time, sex and age (p=0.22), time and age (p=0.08), or time and sex (p=0.48) on peak twitch force (PTF) (Table 2.4). There was a significant interaction of sex and age (p=0.03) with young males having higher PTF than young females (p=0.006) and old males (p=0.03). There was also a significant main effect of sex with males having greater PTF than females (p=0.05).

There were no significant interactions of time and age (p=0.95) time and sex (p=0.43), sex and age (p=0.45), or time, sex, and age (p=0.76) on time to peak force twitch (Table 2.4). Further, there was no significant main effect of time (p=0.09), sex (p=0.78), or age (p=0.32).

Similarly, there were no significant interactions of time and age (p=0.62), time and sex (p=0.72), age and sex (p=0.59), or time, sex, and age (p=0.09) on half-relaxation time. Nor were there any significant main effects of time (p=0.26), sex (p=0.89), or age (p=0.11).

There were no significant interactions of time and age (p=0.30), time and sex (p=0.46), age and sex (p=0.26) or time, sex, and age (p=0.17) on M-wave amplitude (Table 2.4). There were no significant main effects of time (p=0.93) or sex (p=0.16) on M-wave amplitude. However, there was a significant main effect of age (p=0.02) with young adults having significantly larger M-wave amplitudes than old.

Table 2.4. Neuromuscular measures before and after mental fatigue

Variable	YF (n=9)		YM (n=8)		OF (n=16)		OM (n=5)	
	BL	MF	BL	MF	BL	MF	BL	MF
PTF (N)	13.72 ± 5.54	12.03 ± 2.55	18.55 ± 3.23	21.56 ± 8.07	16.49 ± 2.19	13.50 ± 5.03	16.67 ± 4.66	12.38± 5.22
TTP (ms)	86.40 ± 16.82	88.80 ± 13.52	91.00 ± 13.52	81.67 ± 11.86	94.88± 7.74	84.75 ± 12.01	95.00 ± 19.34	92.60 ± 12.34
HRT (ms) °	98.54 ± 10.95	88.99 ± 14.84	91.86± 17.34	88.33 ± 8.65	105.88 ± 23.03	91.82 ± 23.69	104.36 ± 24.70	103.81 ± 30.45
M_{Max}* (mv)	5.98 ± 1.23	5.62 ± 1.33	6.33 ± 1.97	5.57 ± 1.43	3.99 ± 0.77	3.54 ± 1.19	4.46 ± 0.69	5.87 ± 4.87

PTF, peak twitch force; TTP, time to peak twitch force; HRT, half-relaxation time, M_{Max}, M-wave. ° indicates a significant difference post MF (p<0.05). * indicates a significant difference between ages (p<0.05).

Cortical Neuromuscular Measurements

There were no significant interactions of time and age (p=0.73), time and sex (p=0.99), age and sex (p=0.64), or time, sex and age (p=0.47) on CSP duration, nor were there significant main effects of sex (p=0.08) or age (p=0.13). However, there was a significant main effect of time on CSP duration (p=0.004) with the CSP being longer after mental fatigue than baseline (Figure 2.8).

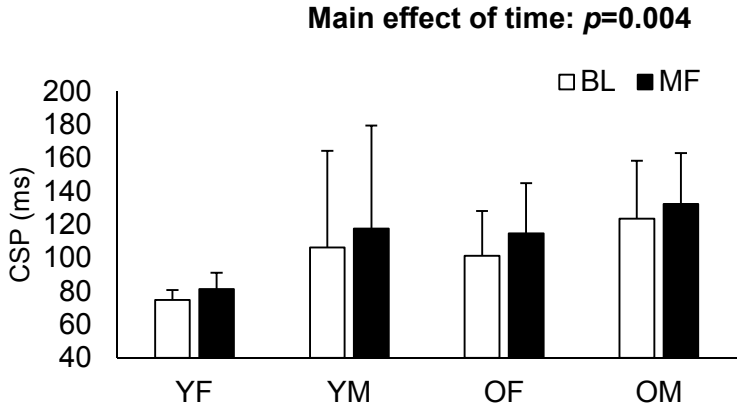

Figure 2.8. Baseline (BL) and mental fatigue (MF) cortical silent period (CSP). YF=young female, YM = young male, OF = older female, OM = older male. The mental fatigue condition had significantly longer (p=0.004) CSP duration than baseline.

There were no significant interactions of time and age (p=0.08), time and sex (p=0.63), age and sex (p=0.63), or time, sex and age (p=0.61) on MEP amplitudes, nor were there any significant main effects of sex (p=0.81) or time (p=0.92). However, there was a significant main effect of age on MEP amplitude (p=0.03) with older adults having larger MEP amplitudes than young (Figure 2.9).

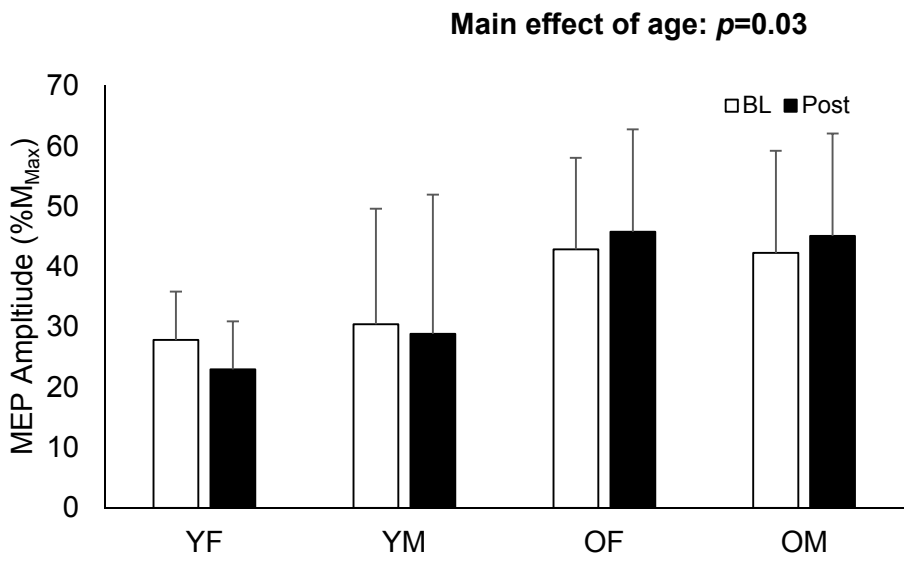

Figure 2.9. Baseline (BL) and mental fatigue (MF) motor evoked potential (MEP). MEP presented as a percentage of m-wave. YF=young female, YM = young male, OF = older female, OM = older male. Older adults had significantly larger (p=0.03) MEP amplitudes.

Discussion

The purpose of this study was to examine the effect of mental fatigue on neuromuscular function. The results of this study suggest that mental fatigue may influence the ability to produce force in young adults. After the mental fatigue task, young females produced significantly less force than at baseline. Contrary to our hypothesis, neuromuscular function measures and measures of cortical excitability did not change with mental fatigue. However, cortical inhibition increased after mental fatigue.

Baseline Measurements

As sleep quality can affect the PVT [50], the PSQI was administered to determine if there were any differences in sleep quality between groups. There was no significant

difference between age groups or sexes in sleep ratings, indicating that at baseline, there was no difference between groups in sleep quality. However, older adults reported significantly higher amounts of subjective fatigue on the Multidimensional Fatigue Index. This agrees with results found by Schwarz et al. [51], who also found that older adults scored significantly higher on the MFI than young adults.

There was no significant difference between young and older adults in ability to produce force. Several studies have reported similar results in the ankle dorsiflexors [52–54]. For example, McNeil et al. [53,55], found no difference in MVC torque in the TA between young (23-32 years) and older (61-69 years) men. However, the same group of studies had a "very old" group (80-90 years) of men who were significantly weaker than the young men. The older adults in the present study were fairly young (~68-74 years old) and since no differences in strength were found, this may suggest that major strength changes in the TA do not occur until much later in life [52,53]. The lack of difference between age groups may be explained by the muscle fiber composition of the tibialis anterior; the TA is composed of 70-80% Type I muscle fibers [56–58] and Type I fibers seem to be less affected by aging [57]. In the current study, there was also a sex difference in MVC, as women did not produce as much force as the men. This observed sex difference is consistent with results from Kent-Braun and Ng [59], who also examined strength in the tibialis anterior and reported that women produced less force than men. Studies examining the TA report that men have a larger muscle cross sectional area, larger muscle fibers, and more Type II fibers than women [60,61], all of which could contribute to men being able to produce more force.

There were no significant differences in contractile properties of the muscle (TTP,PTF,HRT) between age groups, indicating that contractile properties in the TA are unaffected by aging. However, older adults had significantly smaller amplitude M-waves. These results are in agreement with a study by Klass et al. [62] who demonstrated no difference in peak twitch torque or half-relaxation time but significantly smaller amplitude M-waves in the tibialis anterior between young and older adults. Changes in the neuromuscular system with aging such as decreases in muscle fiber number and size, as well as decreases in conduction velocity with aging could contribute to a decreased M-wave amplitude in older adults, while not producing substantial changes in the contractile properties [63,64].

In the present study, CSP trended toward a difference in age group, with older adults having longer duration CSP than young adults. However, the difference was not significant, suggesting that cortical inhibition may not differ between young and older adults. These results are similar to those in a study examining corticospinal excitability in the quadriceps of young and older adults in which researchers found no difference in CSP duration between the age groups [65]. In the current study, older adults had significantly larger MEPs than young adults, suggesting higher cortical excitability at baseline. This is similar to results found by Bernard & Seidler [66], who showed larger amplitude MEPs in the first dorsal interosseous muscle in older adults compared with young. Higher levels of cortical excitability in the older adults could be a compensation for previously discussed declines in the aging neuromuscular system as well as increased cortical inhibition. Previous research exploring motor cortical representation and brain region recruitment in older adults indicates that older adults have more dispersed motor cortical representation

and less specific patterns of brain region recruitment when performing cognitive tasks, which could lead to a larger MEP amplitude in older adults [66,67].

Mental Fatigue and Force Output

Twenty minutes of the PVT induced a significant increase in both subjective fatigue rating and reaction time, indicating the presence of mental fatigue. This is consistent with previous studies that used the PVT to induce mental fatigue [68,69]. There was no difference between age groups or sexes in reaction time, but older adults reported lower levels of subjective fatigue overall. This may suggest that while both groups experienced mental fatigue (overall increase in reaction time and subjective fatigue rating) younger adults felt more fatigued (higher subjective fatigue ratings in young adults). Force output in the mentally fatigued state significantly decreased to 82% of baseline MVC in the young females only, suggesting that mental fatigue affects physical function in young adults but not older adults. This may be explained by the changes in cortical functions, as described below.

None of the peripheral neuromuscular function measures (M_{Max}, TTP, PTF, HRT) changed with mental fatigue. Older adults tended to have increased MEP amplitudes after mental fatigue (F 6%, M 7%) whereas young adults tended to have decreased MEP amplitudes (F -18.5%, M -6%). Although these changes were not statistically significant, the tendency for reduced excitability in the young females in particular, may help to explain the reduced MVC force observed in this group following mental fatigue.

There was also a significant increase in CSP duration in all groups, indicating an increase in cortical inhibition. Increases in CSP duration with mental fatigue could be due

to changes in dopamine release. Results from a study using positron emission tomography to examine dopamine release during sustained attention tasks suggest that there may be an attention related increase in dopamine release during the sustained attention tasks [70]. Previous research indicates that dopamine lengthens the duration of CSP [71,72]. Therefore, the increase in CSP in the present study could be attributed to an increased release of dopamine during the PVT which is a sustained attention task.

We did not observe significant changes in contractile properties of the muscle, or in M_{Max} . Therefore, we can assume that changes in force output in young females with mental fatigue were more likely caused by supraspinal mechanisms (suboptimal output from the motor cortex [3]) than by mechanisms at the muscle or of neuromuscular transmission. In contrast, older adults may have compensated for the increased inhibition from mental fatigue by increasing cortical excitability (though not significant) to maintain corticomotor drive to the muscle and reach MVC values that were similar to baseline.

Limitations

There is high intra-individual and inter-subject variability in MEP amplitude. Location and orientation of the coil can affect MEP amplitude [73]. In the present study, once the optimal site for TMS was found, location of this site, as well as an outline of the coil, was marked on a wig cap and the same researcher applied the stimulation each time to minimize movement of the TMS coil. Further, MEP variability decreases with increasing contraction intensity [73] and participants were contracting to 50% during these recordings, which should help to minimize variability. Lastly, MEP was normalized to

M_{Max} which should account for potential differences in MEP amplitude that are due to the size of the muscle or neuromuscular transmission that are not related to cortical excitability itself. The low number of older men in the study may have impacted the results related to sex differences. Additional work with equal samples sizes across groups is warranted.

Conclusions

Results from the present study suggest that 20 minutes of a mentally fatiguing task may cause a decrease in the ability to produce maximal force in young but not older adults. Significant decreases in MVC force were seen only in young women. However, cortical silent period was increased in both young and older groups, suggesting that mental fatigue may cause increased cortical inhibition. Measures of neuromuscular function (contractile properties of the muscle, M_{Max}) did not change, suggesting that changes in force production with mental fatigue are more likely due to supraspinal than peripheral mechanisms. To our knowledge, this is the first study using TMS to examine the effects of mental fatigue on neuromuscular function. These findings provide further evidence of an interaction between mental fatigue and physical function [5,11,12].

Bridge

Chapter II examined the effect of a mentally fatiguing task on neuromuscular function. In the next chapter, we examine the effect of a neuromuscular fatigue task on cognitive function.

CHAPTER III

THE EFFECT OF NEUROMUSCULAR FATIGUE ON COGNITIVE FUNCTION

Amanda Morris contributed to the concept of the studies, recruited subjects, collected data, performed data analysis, and prepared the initial manuscript. Dr. Anita Christie contributed to the concept of the study, provided editorial support, and critically reviewed and revised the manuscript.

Introduction

Although neuromuscular fatigue has been studied extensively, few studies have focused on its impact on cognitive function. In order to truly understand the consequences of neuromuscular fatigue, it is necessary to examine its impacts across the multiple dimensions it affects. Understanding both the neuromuscular and cognitive consequences of neuromuscular fatigue will fill a critical gap in our knowledge.

Despite decades of work to characterize the effects of neuromuscular fatigue, there are few studies documenting its impact on functional domains other than the motor system, such as cognition. Results from the limited existing studies indicate that neuromuscular fatigue has a negative effect on cognitive performance. For example, when participants performed a cognitive task with a simultaneous fatiguing submaximal contraction of the first dorsal interosseus, there was an increase in reaction time and cognitive errors compared to a cognitive task alone [7]. Additional evidence suggests that the impact of such contractions on cognitive performance is dependent upon the level of force produced [9], with higher force production resulting in increased errors and longer reaction time on a cognitive task [9]. These findings suggest an important association

between neuromuscular fatigue and cognitive function, which warrants further investigation.

Numerous physiological changes take place with aging including: declines in sensory system feedback, nerve conduction velocity, motor unit numbers, muscle mass, and central processing abilities [26]. These changes alter the response to neuromuscular fatigue. For example, results from several studies indicate that older adults may be more fatigue resistant than young adults during isometric contractions, but more fatigable during dynamic contractions [29,30]. These differences in fatigability might be explained by changes in neuromuscular propagation (smaller M-wave), contractile properties (slowing of half-relaxation time) of the muscle, and fiber type changes (Type I fibers less affected with age [57]) with aging [30]. Cognitive changes, such as an increase in the cost of cognitive activity, also occur with aging; with cognitive demand, older adults experience greater increases in cardiovascular reactivity, muscle activation, and force fluctuation (decreased steadiness) compared to younger adults [31–34]. These declines across multiple systems may further alter cognitive function in response to neuromuscular fatigue in older adults.

The sex of the participants can also impact the response to neuromuscular fatigue. For example, women typically have greater resistance to fatigue than men during submaximal contractions [74]. Many explanations have been proposed such as: hormonal differences, muscle mass, neural activation pattern, muscle type differences, and preferred metabolic system [74]. There is little research on differences in cognitive function between sexes. However, during choice reaction time tasks, men are significantly faster than women while women are significantly more accurate than men, indicating a possible

difference in the speed-accuracy tradeoff between sexes [75,76]. Due to differences across the neuromuscular system and response to reaction time tasks, it is important to investigate how neuromuscular fatigue may affect cognition differently in men and women. The purpose of this study was to examine the effect of neuromuscular fatigue on cognitive function in young and older adults. An exploratory aim was to examine sex differences in these responses. Cognitive function was assessed through reaction time during two minutes of the psychomotor vigilance task (PVT) before and after a neuromuscular fatigue task. Neuromuscular and cortical measurements were also taken to evaluate the expected decline in force production with neuromuscular fatigue. It was hypothesized that neuromuscular fatigue would result in an increase in reaction time and errors during a cognitive task and that older adults would experience a larger increase in reaction time and errors during a cognitive task than younger adults with neuromuscular fatigue

Methods

The same participants from Study 1 participated in Study 2; study order was randomized and separated by at least 3 days. Seventeen young adults (9 females, Table 3.1) and 21 older adults (16 females, Table 3.1) participated in this study. Participants were healthy and free from any chronic disease, illness, condition, or medication that could impact balance. Exclusion criteria included: a positive screen for cognitive impairment, history of illness associated with fatigue (e.g. chronic fatigue syndrome, multiple sclerosis), history of cognitive deficiencies (e.g. memory loss, difficulty concentrating), poor sleep habits, history of neurological impairment, history of musculoskeletal impairments, use of alcohol or central nervous system depressant

pharmacological agents within 12 hours of performing tasks, or active substance abuse. The procedures were reviewed and approved by the Institutional Review Board. All participants provided written informed consent and were asked to complete a brief medical history report, Pittsburgh Sleep Quality Index, Multidimensional Fatigue Index, and the Mini-Cog cognitive screening test.

After completing sleep and fatigue questionnaires, neuromuscular measures were taken and included voluntary contractions, electrical nerve stimulation and transcranial magnetic stimulation (TMS). Then, participants performed a cognitive task for 3 minutes followed by a neuromuscular fatigue task for 16 minutes. The neuromuscular measures were repeated immediately following the neuromuscular fatigue task. The same cognitive task was performed for 2 minutes at the end of the protocol. The timeline for these procedures is presented in Figure 3.1

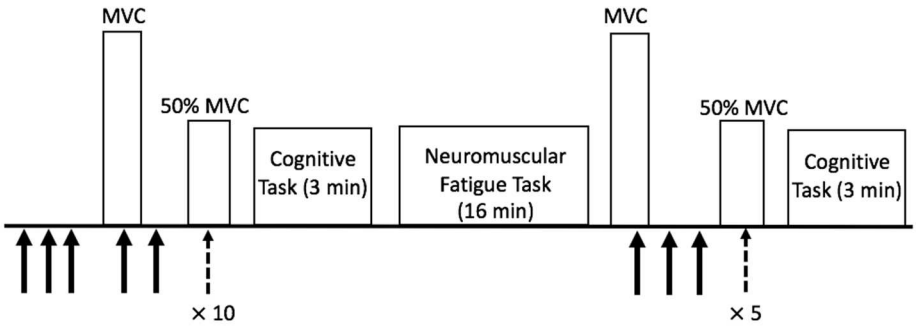

Figure 3.1: Overview for study two. Black solid line: electrical stimulation. Black dashed line: transcranial magnetic stimulation. Questionnaires will be completed before and after the protocol.

Questionnaires

The Pittsburgh Sleep Quality Index (PSQI) was used to measure the sleep patterns and quality of sleep in seven domains subjective sleep quality, sleep latency, sleep

duration, habitual sleep efficiency, sleep disturbances, sleep medication use, and daytime dysfunction. The participants self-rated these aspects of sleep quality on a 0 to 3 scale, where 3 is negative. A total score, summed across all questions, of 5 or greater indicates a poor sleeper [44].

The Multidimensional Fatigue Inventory (MFI) is a 20 item, self-report instrument that measures fatigue in the following domains: general fatigue, physical fatigue, mental fatigue, motivation, and activity. Participants responded to each item on a scale of 1 to 7 and the total score was summed across all items. A higher total score corresponds to more acute levels of fatigue.

Neuromuscular Measures

Methods for collecting neuromuscular measures are the same as methods for the study described in Chapter 2, but descriptions are provided again below.

Individuals were seated in a chair with their dominant foot placed in a custom-built device designed to measure dorsiflexion force. A strap was placed over the dorsum of the foot. Maximal voluntary force was determined by asking participants to pull as hard as they could by dorsiflexing their ankle and pulling their foot against the strap so that their maximal voluntary contraction force (MVC) was measured. They were asked to repeat this procedure an additional two times and were given at least 1 minute of rest between contractions. The highest value was taken as the MVC.

A preamplified, bipolar Ag-AgCl electrode (DE-2.1, Delsys Inc., Boston, MA), with an inter-electrode distance of 1 cm, was taped to the surface of the skin, over the belly of the tibialis anterior (TA) muscle. This electrode was connected to a portable

amplifier (Delsys Inc., Boston, MA), which further amplified and band-pass (20-450 Hz) filtered the signal. A ground electrode was applied to the ankle. The signal was sampled at 1 kHz with a 16-bit A/D converter (NI USB-6251, National Instruments, Austin, TX).

The maximal electrical response of the muscle was determined by placing a stimulating electrode on the side of the leg over the peroneal nerve and activating the nerve through brief (200 μs) electrical pulses. The intensity required to elicit a maximal electrical response (M-wave) of the muscle (recorded with the EMG electrodes) was determined and 3 stimulations were recorded at 120% of maximal intensity. M-wave peak-to-peak amplitude was used to examine electrical response of the muscle. Force responses to stimulations were used to examine contractile properties of the muscle and included: peak twitch force, time to peak twitch force, and half-relaxation time. Half-relaxation time was considered as the time from peak twitch force to the time force relaxed to 50% of the peak twitch force.

Single-pulse transcranial magnetic stimulation (TMS) was delivered using a 110 mm double cone magnetic stimulation coil placed on the head, over the motor cortex. This coil was used to activate the brain through brief magnetic pulses (100 μs). The response of the TA muscle was recorded with EMG. The optimal site for stimulation of the TA muscle was determined by moving the coil to find the location that presented the largest motor evoked potential (MEP) at 60% stimulator output. The resting motor threshold (RMT) of the muscle was determined by stimulating at decreasing stimulus intensity to find the threshold while the muscle is at rest. Threshold was defined as the stimulus intensity that produced a MEP of at least 50 μV in at least 5/10 trials [45]. The stimulus intensity was then set at 120% of RMT and responses were recorded while the

participant was contracting at 50% MVC. Ten responses were recorded before the mental fatigue task and 5 were recorded after. Cortical excitability was determined by the peak-to-peak amplitude of the active MEP. Cortical inhibition was determined by the cortical silent period, measured as time between the end of the MEP and resumption of voluntary EMG activity.

Neuromuscular Fatigue Task

To induce neuromuscular fatigue, participants were asked to perform a series of isometric dorsiflexion contractions starting at a target force of 10% MVC (4 seconds of contraction, 6 seconds of rest) and incrementing by 10% every 2 minutes for a total of 16 minutes [59]. A MVC was performed at the beginning of each 2-minute stage to assess the level of fatigue. Fatigue was assessed by examining decrease in MVC.

Cognitive Task

To assess cognitive function at baseline and after performing the neuromuscular fatigue task, participants were asked to perform the psychomotor vigilance task (PVT) for three minutes. The PVT was described in Chapter 2 but is presented below as well. The PVT is an objective, valid measure for assessing behavioral alertness and vigilant attention [46]. The PVT is based on reaction time to stimuli that occur at random interstimulus intervals, over a period of time [46,77]. The PVT relies on sampling many responses as opposed to just one simple reaction time, representing the vigilance portion of the PVT[77]. Lapses in reaction time (RT > 500 ms) during this task are associated with subjective measures of fatigue and decline in energy [47,48].

Participants were asked to visually fixate on a computer screen placed at eye level in front of them. They were asked to click the left button on a mouse as soon as a red number appeared on the screen. As soon as the button was pushed, a number was displayed on the screen for 500ms indicating reaction time and was then cleared and the next stimulus was presented. Time between presentation of each stimulus varied randomly between 2 and 10 seconds. In addition to simple reaction time (RT), the program recorded: false starts, anticipation (RT <100ms), minor lapses (RT ≥ 500ms), and major lapses (RT≥1000ms). This software was created by Biotechnology HPC Software Applications Institute and was run using MATLAB (MathWorks Inc., Natick, MA, USA).

Data Analysis

Neuromuscular Measures

Neuromuscular fatigue was assessed through the decline in maximal voluntary contraction (MVC) from the beginning to the end of the 16-minute neuromuscular fatigue task.

The twitch force response was used to examine contractile properties of the muscle. Peak twitch force was calculated as the maximal force achieved. Time to peak force was calculated as the time between the start of the force response and peak twitch force. Half-relaxation time was calculated as the time from the peak until the twitch force relaxed to 50% of the peak twitch force. Contractile properties at baseline were averaged

across the three baseline stimulations whereas only one twitch was taken at the end of the fatigue protocol.

M-wave amplitude (M_{Max}) was assessed using the EMG data. The data were rectified to help identify the response. An area around the M-wave response was manually selected and peak-to-peak amplitude of the M-wave was calculated from the non-rectified signal as maximum EMG − minimum EMG. M-wave amplitude was then averaged across the three baseline stimulations whereas only one stimulation was taken at the end of the fatigue protocol.

Cortical Measures

Cortical excitability and inhibition were assessed using the EMG responses to TMS. Cortical excitability was determined by the peak-to-peak amplitude of the active MEP, normalized to M_{Max}. Cortical inhibition was indicated by the duration of the cortical silent period, measured as the time between the end of the MEP and resumption of voluntary EMG activity. These points were selected manually and averaged across trials at each time point.

Cognitive Function

Changes in cognitive function were assessed through reaction time, number of lapses, number of false starts on the PVT. The reaction time values were averaged across the 3-minute trial before and after the neuromuscular fatigue protocol.

Statistical Analyses

The following quantitative outcome variables were obtained: cognitive function: reaction time, number of lapses, number of false starts; neuromuscular function: MVC force, voluntary activation, peak-to-peak amplitude of the M-wave; contractile properties of the muscle: time to peak force, peak force, half-relaxation time; cortical excitability: peak-to-peak amplitude of active motor evoked potential; cortical inhibition: cortical silent period duration.

Participant characteristics and baseline measurements were analyzed using a 2-factor ANOVA (age and sex). To examine the impact of the neuromuscular fatigue protocol on each variable, 3-factor (age, sex, and time) repeated-measures ANOVAs were used. If significance was found, post-hoc testing with a Bonferroni correction was used. Significance was set at $p \leq 0.05$.

Results

Participant Characteristics

Participant characteristics and scores (mean ± SD) for the Multidimensional Fatigue Inventory (MFI) and the Pittsburgh Sleep Quality Index (PSQI) are presented in Table 3.1. There was no significant age difference between sexes ($p=0.06$) but older adults were significantly older ($p<0.001$) than younger adults. Males were significantly taller ($p= 0.01$) and heavier ($p<0.001$) than females. There was no main effect of age on height ($p=0.54$) but, there was a main effect of age on weight, with older adults being heavier than young adults ($p=0.02$).

There was no significant interaction of sex and age (p=0.15) on total MFI scores, nor were there any significant main effects of age (p=0.54) or sex (p=0.65). There was no significant interaction of sex and age (p=0.70) on PSQI scores, nor were there any significant main effects of age (p=0.17) or sex (p=0.18), There was no significant effect interaction of sex and age (p=0.75), nor were there any significant main effects of age (p=0.12) or sex (p=0.42) on baseline subjective ratings of fatigue.

Table 3.1. Participant characteristics

Variable	YF (n=9)	YM (n=8)	OF (n=16)	OM (n=5)
Age*	22.44 ± 2.88	23.80 ± 4.26	74.13 ± 6.30	68.80 ± 3.96
Height[#] (in)	65.40 ± 3.36	70.50 ± 1.29	64.12 ± 2.10	70.33 ± 2.62
Weight (kg)	272.36 ± 62.21	352.00 ± 28.79	293.23 ±42.56	438.53 ± 42.12
MFI	60.22 ± 5.26	58.40 ± 6.24	58.71 ± 5.68	62.17 ± 2.79
PSQI	5.33 ± 2.78	4.50 ± 2.99	4.50 ± 2.07	3.00 ± 1.87
Subjective Fatigue Rating	3.40 ± 2.30	2.67 ± 1.32	2.15 ± 1.91	1.83 ± 1.17

MFI, Multidimensional Fatigue Index; PSQI, Pittsburgh Sleep Quality Index. Higher scores indicate more fatigue or poorer sleep quality. *indicates a significant difference between age groups (p<0.001). [#] indicates a significant difference between sexes (p<0.05).

Baseline values for tests of neuromuscular function are presented in Table 3.2. There was no significant interaction of sex and age (p=0.75) on baseline maximal voluntary contraction (MVC) nor was there a significant main effect of age (p=0.25). However, males produced significantly more force than females (p=0.01)

There was no significant interaction of age and sex (p=0.08) on peak twitch force (PTF) at baseline (Table 3.2). There was also no significant main effect of sex (p=0.29) or age (p=0.80) on PTF.

There was no significant interaction of sex and age (p=0.99) on baseline half-relaxation time nor were there any significant main effects of age (p=0.61) or sex (p=0.31). There was no significant interaction of age and sex (p=0.60) on baseline time to peak twitch force nor was there a significant main effect of age (p=0.28) or sex (p=0.66).

There was no significant interaction of sex and age (p=0.22) on baseline M-wave amplitude (Table 3.2). However, older adults had significantly smaller (p=0.008) M-wave (M_{Max}) amplitudes than young adults and females had significantly smaller M_{Max} amplitudes than males (p<0.001).

There was no significant interaction of age and sex (p=0.54) on cortical silent period (CSP) duration at baseline, nor were there significant main effects of age (p=0.52) or sex (p=0.15). There was also no significant interaction of age and sex (p=0.20) on motor evoked potential (MEP) amplitude at baseline, nor were there significant main effects of age (p=0.16) or sex (p=0.27).

Table 3.2. Baseline neuromuscular measures

Variable	YF (n=9)	YM (n=8)	OF (n=16)	OM (n=5)
MVC[#] (N)	206.47 ± 64.23	251.49 ± 54.87	177.62 ± 58.10	235.03 ± 46.06
PTF (N)	13.59 ± 2.63	18.97 ± 6.63	17.48 ± 2.81	16.02 ±3.43
TTP (ms)	90.00 ± 6.93	90.44 ± 19.24	98.25 ± 16.12	94.00 ± 11.40
HRT (ms)	95.40 ± 15.41	91.67 ± 12.39	101.50 ± 26.29	99.40 ± 23.32
M_{Max} [*#] (mV)	4.44 ± 0.71	6.61 ± 1.38	3.81 ± 0.49	5.01 ± 1.40
MEP	35.62 ± 6.75	35.64 ± 20.39	44.45 ± 15.21	36.95 ± 27.84
CSP (ms)	92.21 ± 24.87	98.57 ± 52.16	86.55 ± 23.27	117.08 ± 33.61

MVC, maximal voluntary contraction; PTF, peak twitch force; TTP, time to peak twitch force; HRT, half-relaxation time; M_{Max} , m-wave; MEP, motor evoked potential; CSP, cortical silent period. [#] indicates a significant difference between sexes (p<0.05). *indicates a significant difference between ages (p<0.05).

Baseline cognitive function values are shown in Table 3.4. There was no significant interaction of sex and age (p=0.56) on reaction time during the PVT at baseline, nor was there a main effect of sex (p=0.86) or age (p=0.06).

There was no significant interaction of sex and age (p=0.51) on false starts, nor was there a significant main effect of sex (p=0.14). However, there was a significant main effect of age (p=0.05) on the number of false starts at baseline, with older adults having a higher number of false starts.

There was a significant interaction of sex and age (p=0.04) on number of lapses (RT>500 ms) at baseline. Older females had more lapses than both older men (p=0.003)

and young women (p=0.005). There was a main effect of sex (p=0.04), with women having more lapses than men, and age (p=0.04), with older adults having more lapses than young adults.

Force

There were no significant interactions of sex and age (p=0.59), time and sex (p=0.10), time and age (p=0.10), or time, sex, and age (p=0.11) on MVC force. There was a significant main effect of time on MVC force (p<0.0001), with post NMF MVC values being lower than baseline (Figure 3.2). There was a significant main effect of sex (p=0.001), with females producing less force than males, and age (p=0.04), with younger adults producing more force than older adults.

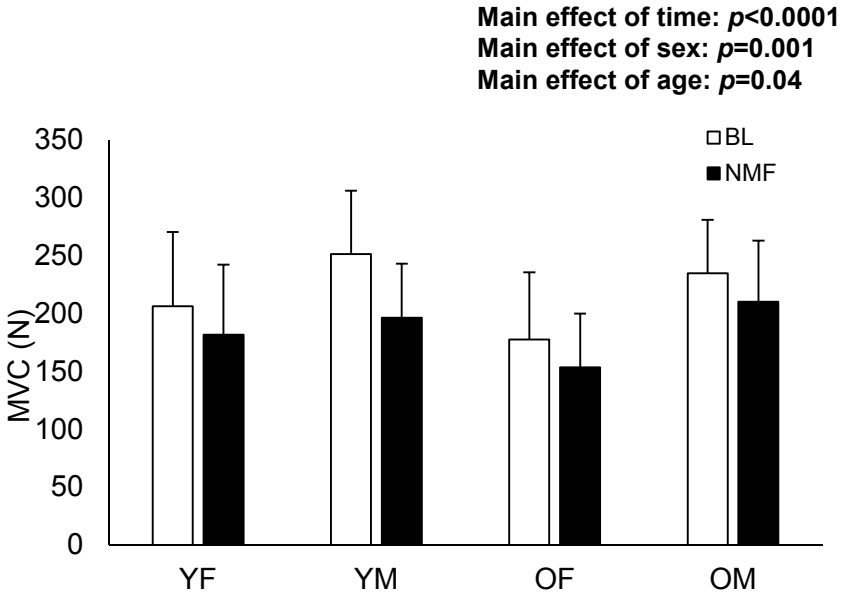

Figure 3.2. Baseline (BL) and neuromuscular fatigue (NMF) maximal voluntary contraction (MVC) force values. YF=young female, YM = young male, OF = older female, OM = older male. There was a significant decrease (p<0.001) in MVC with NMF. Females produced less force than males (p=0.001). Younger adults produced more force than older adults (p=0.04).

The force, relative to MVC, at the end of the neuromuscular fatigue protocol is presented for each group in Figure 3.3. There was no significant age and sex interaction (p=0.37), nor were there main effects of age (p=0.25) or sex (p=0.38) on relative force at the end of the protocol, indicating a similar level of fatigue across all groups.

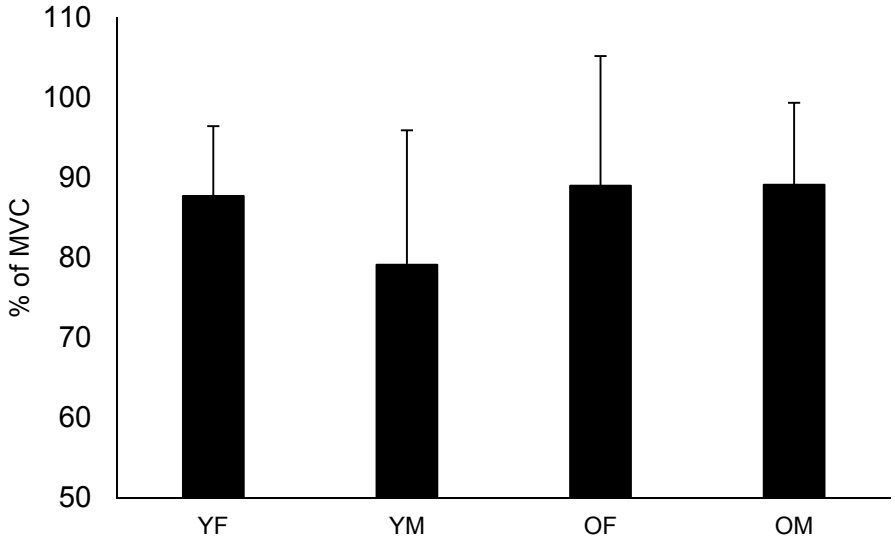

Figure 3.3. Maximal voluntary contraction (MVC) force after neuromuscular fatigue (NMF) protocol. Data presented as % MVC after NMF. YF=young female, YM = young male, OF = older female, OM = older male.

Peripheral Neuromuscular Measures

There were no significant interactions of time, sex, and age (p=0.97) or time and sex (p=0.76) on peak twitch force (PTF). There was a significant interaction of time and age (p=0.003) for PTF, with young adults having significantly larger PTF after neuromuscular fatigue (p<0.0001). There was also a significant interaction of sex and age (p=0.04), with young males having larger PTF than older males (p=0.05) (Table 3.3). There was also a significant main effect of time (p=0.007), as PTF was higher following

the fatiguing protocol. There was no significant main effect of sex (p=0.24) or age (p=0.46).

There were no significant interactions of time and sex (p=0.68), time and age (p=0.15), sex and age (p=0.55) or time, sex and age (p=0.98) (Table 3.3) on time to peak twitch force (TTP), nor were there any significant main effects of time (p=0.47) or sex (p=0.35). However, older adults had a significantly slower (p=0.004) time to peak force (TTP) than younger adults.

There were no significant interactions of time and sex (p=0.25), time and age (p=0.85), sex and age (p=0.97) or time, sex and age (p=0.85) (Table 3.3) on half-relaxation time (HRT). However, half-relaxation time (HRT) was slower after neuromuscular fatigue (p=0.01). There were no significant main effects of sex (p=0.39) or age (p=0.94), nor were there any significant interactions of

There were no significant interactions of time and age (p=0.92), time and sex (p=0.24), age and sex (p=0.39), or time, sex and age (p=0.59) on M-wave amplitude (M_{Max}). M_{Max} was significantly smaller after neuromuscular fatigue (p=0.001). Additionally, males had significantly larger M_{Max} than females (p=0.002) and younger adults had significantly larger M_{Max} than older adults (p=0.005).

Table 3.3. Neuromuscular measures at baseline (BL) and after the neuromuscular fatigue protocol (NMF)

Variable	YF (n=9)		YM (n=8)		OF (n=16)		OM (n=5)	
	BL	NMF	BL	NMF	BL	NMF	BL	NMF
PTF (N) °*	11.83 ± 4.53	17.84 ± 9.00	18.97 ± 6.63	24.34 ± 7.65	17.66 ± 3.04	17.62 ± 2.52	16.01 ±3.43	15.49 ±4.09
TTP (ms) *	90.00 ± 6.93	88.40 ± 13.12	90.44 ± 19.24	85.11 ± 10.19	98.25 ± 16.12	110.88 ± 14.65	94.00 ± 11.40	102.40 ± 26.62
HRT (ms) °	95.40 ± 15.41	100.20 ± 25.37	91.67 ± 12.39	104.56 ± 13.26	101.50 ± 26.29	106.25 ± 21.78	99.40 ± 23.32	110.00 ± 18.76
M_{Max} °* (mv)	4.44 ± 0.71	3.83 ± 1.03	6.61 ± 1.38	4.90 ± 1.45	3.81 ± 0.49	2.81 ± 1.57	5.01 ± 1.40	3.59 ± 1.93

PTF, peak twitch force; TTP, time to peak twitch force; HRT, half relaxation time. ° indicates a significant difference post NMF (p<0.05). * indicates a significant difference between ages (p<0.05). # indicates a significant difference between sexes.

Cortical Neuromuscular Measures

There were no significant interactions of time and age (p=0.91), time and sex (p=0.58), sex and age (p=0.76), or time, sex, and age (p=0.75) on motor evoked potential (MEP) amplitude. However, MEP amplitude was significantly lower (p=0.02) after neuromuscular fatigue (Figure 3.4). There was no significant main effect of age (p=0.42) or sex (p=0.46)

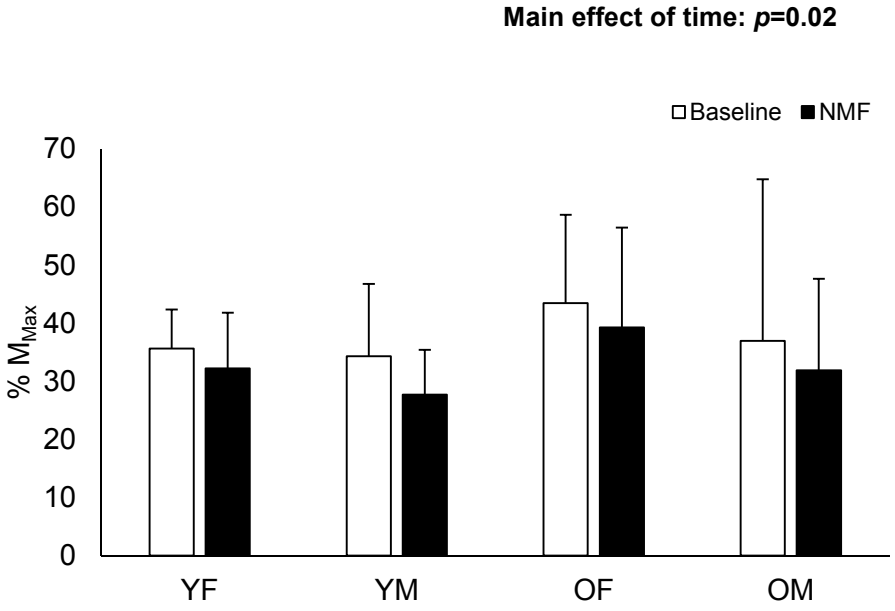

Figure 3.4. Motor evoked potential (MEP) before and after neuromuscular fatigue (NMF) protocol. Data presented as percent of baseline (BL) MEP after NMF. YF=young female, YM = young male, OF = older female, OM = older male. There was a significant increase in MEP with NMF (p=0.02).

There was a significant main effect of time (p<0.0001) on cortical silent period (CSP) duration (Figure 3.5), with an overall longer CSP duration after the fatiguing protocol. There was no significant main effect of age (p=0.63) or sex (p=0.13) nor were there significant interactions of time and age (p=0.38), time and sex (p=0.38), or sex and age (p=0.36).However, there was a significant interaction of time, age and sex (p=0.05), as younger females (p=0.01), young males (p=0.003) and older males (p=0.001), but not older females (p=0.11), had significantly longer CSP after neuromuscular fatigue (Figure 3.5).

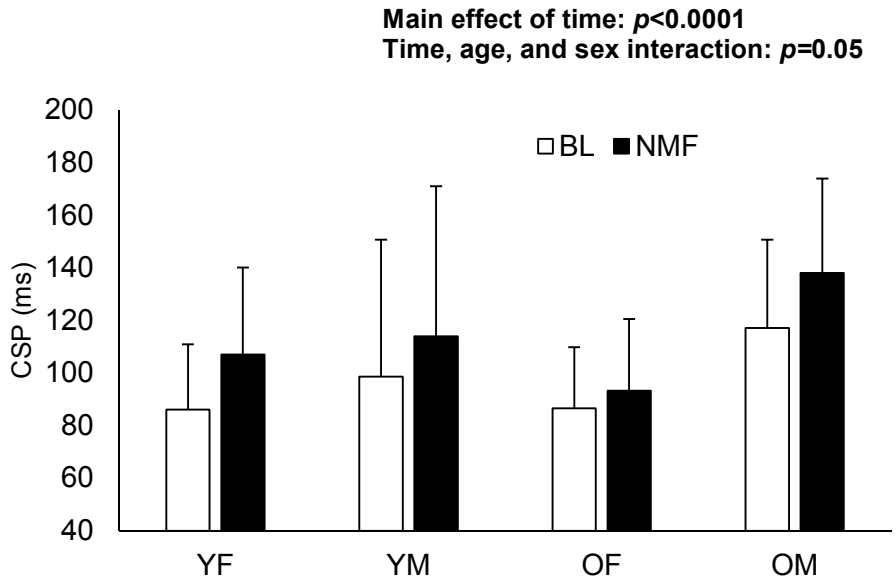

Figure 3.5. Cortical silent period (CSP) before and after neuromuscular fatigue (NMF) protocol. There was a significant increase in CSP with NMF for YF, YM, and OM (p<0.01). YF=young female, YM = young male, OF = older female, OM = older male.

Cognitive Function After Neuromuscular Fatigue

Likert ratings of subjective fatigue are shown in Figure 3.6. There were no significant interactions of time and sex (p=0.51), time and age (p=0.91), sex and age (p=0.77), or time and age and sex (p=0.97) on subjective fatigue ratings. After the neuromuscular fatigue protocol, ratings of subjective fatigue were significantly higher (p=0.002) than at baseline. There were no significant main effects of sex (p=0.33) or age (p=0.12).

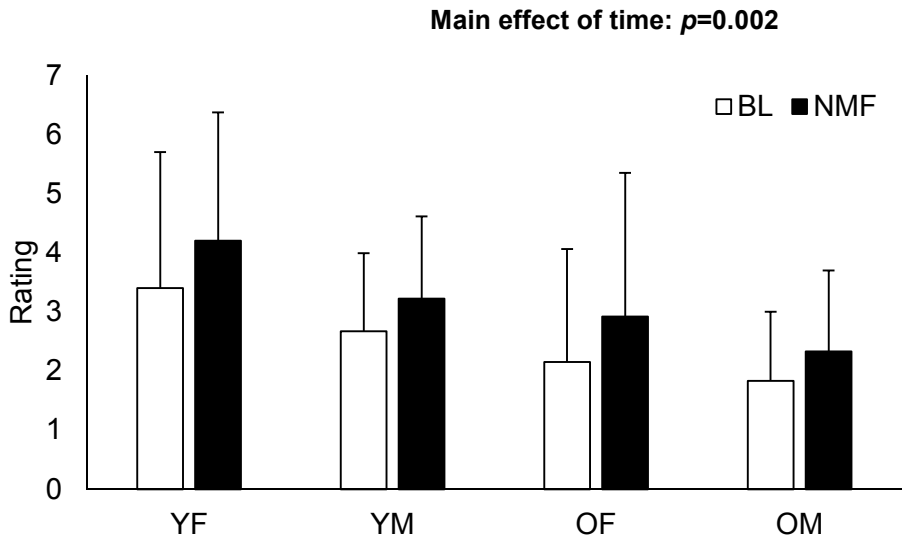

Figure 3.6. Subjective fatigue ratings before and after neuromuscular fatigue protocol. NMF = neuromuscular fatigue. Higher values indicate higher feelings of fatigue. After NMF, ratings were significantly higher (p=0.002) than ratings at baseline.

There were no significant interactions of time by sex (p=0.89), sex by age (p=0.42), or time by sex by age (p=0.64) on reaction time during the PVT. However, there was a significant interaction of time and age (p=0.004) as young adults (p=0.001), but not old (p=0.69) experienced a significant slowing in reaction time after the neuromuscular fatigue protocol (Figure 3.7). There was a significant main effect of time on reaction time during the PVT (p=0.02), with reaction times after neuromuscular fatigue being slower than baseline (Figure 3.7). There was no significant main effect of age (p=0.33) or sex (p=0.81).

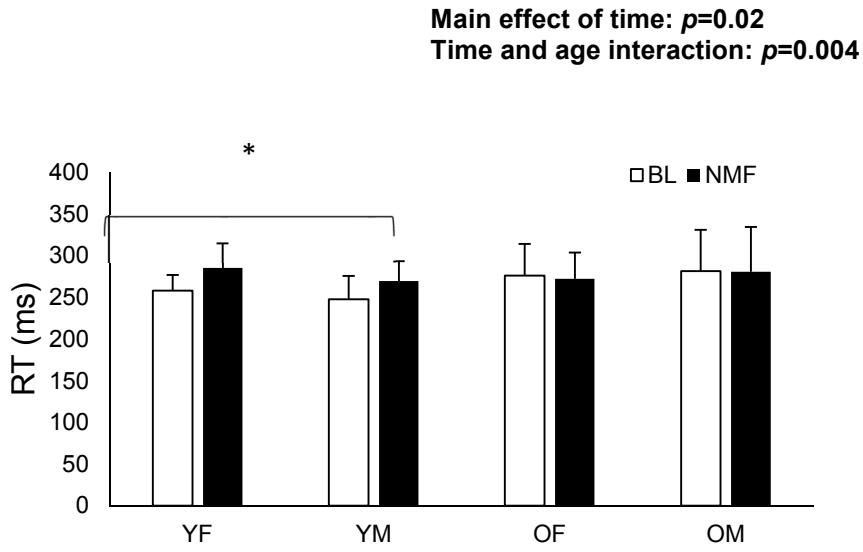

Figure 3.7. Psychomotor vigilance task reaction time (RT) before and after neuromuscular fatigue protocol. YF=young female, YM = young male, OF = older female, OM = older male, BL = baseline, NMF = neuromuscular fatigue. NMF times were significantly slower than BL (p=0.02). *Young adults had significantly slower reaction times during the NMF time point (p=0.004).

There were no significant interactions of time and sex (p=0.45), time and age (p=0.31), sex and age (p=0.52), or time, sex, and age (p=0.83) on the number of false starts during the PVT, nor was there a significant main effect of time (p=0.63) or sex (p=0.22) (Table 3.4). However, there was a significant main effect of age (p=0.001) on false starts, with older adults having more false starts than young adults.

There were no significant interactions of time and sex (p=0.95), time and age (p=0.28), sex and age (p=0.33), or time, sex, and age (p=0.19), nor was there a significant main effect of age (p=0.23) or time (p=0.25) on number of lapses (Table 3.4). However, females had significantly more lapses than males (p=0.04).

Table 3.4. False starts and lapses during the PVT

Variable	YF (n=9)		YM (n=8)		OF (n=16)		OM (n=5)	
	BL	NMF	BL	NMF	BL	NMF	BL	NMF
False Starts*	0.20 ± 0.45	0.20 ± 0.47	0.56 ± 0.88	0.22 ± 0.44	0.77 ± 1.36	1.54 ± 1.71	1.67 ± 1.03	1.83 ± 1.33
Lapses*#	0.00 ± 0.00	0.40 ± 0.55	0.00 ± 0.00	0.11 ± 0.33	0.54 ± 0.52	0.38 ± 0.65	0.00 ± 0.00	0.17 ± 0.41

BL = baseline; NMF = neuromuscular fatigue. *indicates a significant difference between age groups (p=0.001). # indicates a significant difference between sexes (p=0.04).

Discussion

The purpose of this study was to examine the effect of neuromuscular fatigue on cognitive function. The results of this study suggest that neuromuscular fatigue may influence cognitive function in young and older adults. After the neuromuscular fatigue task, subjective ratings of fatigue, as well as reaction time during the cognitive task increased.

Baseline Peripheral and Cortical Neuromuscular Measurements

In the current study, there was no significant difference between young and older adults in the ability to produce ankle dorsiflexion force. This is similar to results found in several studies examining age differences in strength in the tibialis anterior [52,53] and is likely attributed to this muscle being relatively well preserved during aging [57]. Women were unable to produce as much force as men, which is a similar finding to previous studies [74]. There were no significant differences in contractile properties of the muscle (TTP,PTF,HRT) between age groups or sexes. However, older adults had significantly smaller M_{Max} amplitudes than young adults and females had significantly smaller amplitude M_{Max} than males. A significant difference in M_{max} amplitude between ages

might be attributed to the multiple changes that take place in the neuromuscular system with aging, specifically a slowing in the rate of neuromuscular transmission [78].

In the present study, women had significantly smaller amplitude M-waves than men. This could be due to the differences in muscle fiber type and cross sectional area between men and women. Median frequency and conduction velocity are linearly related to muscle fiber type and muscle fiber cross sectional area; muscles with a higher percentage of type II fibers have higher median frequency and faster conduction velocities [79]. Studies examining the TA report that men have a larger muscle cross sectional area, larger muscle fibers, and more Type II fibers than women [60,61]. These factors could have contributed to the difference in M-wave amplitude that we saw in the present study.

There was no significant difference in CSP duration between age groups or sexes. These results match those found by Stevens-Lapsley et al. [65], who found no difference in CSP duration in the vastus lateralis between young and older adults. Additionally, there was no significant difference at baseline in MEP amplitude between young and older adults or between sexes. Several studies examining MEP amplitude in the hand report no difference in amplitude between young and old adults [80–82] and similar results have been found in both the vastus lateralis [65] and tibialis anterior [83]. Taken together, these cortical measurements suggest that, in the present study at baseline, there was no difference in cortical excitability or inhibition between young and older participants, nor between males and females.

Baseline Cognitive Measurements

There was no difference between sexes or age groups in ratings of fatigue on the Multidimensional Fatigue Index. There was also no difference in reaction time on the cognitive task between age groups or sexes, indicating similar levels of cognitive function between groups at baseline. The lack of difference in reaction times in the present study could be due to the fact that the older adults in this study were habitually active. Previous research suggests that there is a link between physical fitness and cognitive function. Rogers et al. 1990, examined active and sedentary older adults and observed maintained levels of cerebral blood flow and better scores on cognitive tasks in the active older adults [84]. Additionally, a meta-analysis focusing on physical fitness and cognitive function in older adults demonstrated that fitness training had benefits for cognition, specifically executive function in older adults [85].

Although reaction time was not different between age groups, at baseline older females had more lapses than both older males and younger females and older adults had more false starts than young adults. False starts during the PVT indicate impaired executive function and an inability to inhibit responses [47]. In the present study, this could indicate that while older adults may have had more trouble inhibiting incorrect responses, it did not impair their reaction time.

Neuromuscular Fatigue: Neuromuscular and Cortical Measures

There was a significant reduction in MVC force after the neuromuscular fatigue task. This reduction in force suggests that fatigue occurred but the fatigue (% of BL MVC) was not significantly different between groups. Previously, several studies have

reported that women are more fatigue resistant than men [28,86–88]. Discordant findings between previous research and the present findings could be due to differences in: muscle group studied and/or fatiguing task. Many of the studies demonstrating a difference in fatigue between men and women examined muscle groups such as the elbow flexors, hand muscles, and knee extensors [28,86–88]. Alternatively, Avin et al. [89], examined sex differences in fatigue resistance in both the elbow flexors and ankle dorsiflexors, suggesting that women were more fatigue resistant than males at the elbow but not at the ankle. Additionally, when using an incremental, isometric fatigue task in the dorsiflexors, Kent-Braun and Ng [54] found no difference between men and women in fatigue. Both muscle group and task could affect amount of perfusion of the muscle during contraction which could affect response to fatigue; reduced perfusion results in task failure due to increased metabolite buildup and lack of oxygen delivery [60,90].

Men are typically stronger than women, leading to greater intramuscular pressure and, therefore, less perfusion of the muscle [91–93]. Further, typically women have higher levels of capillarization due to their larger proportion of Type I muscle fibers [90] which would presumably lead to higher levels of perfusion in women than men. However, in the tibialis anterior, capillarization is not significantly different between men and women [60]. Additionally, many of the studies that demonstrated sex differences in fatigue, relied on sustained contractions; whereas, the current study utilized incremental isometric contractions. Sustained contractions over 50% MVC reduce muscle perfusion [94]; the use of incremental isometric contractions in the present study could have caused little to no attenuation in muscle perfusion, which would have eliminated sex differences in

intramuscular pressure (muscle mass dependent), allowing for a similar fatigue response between men and women.

Several studies have demonstrated fatigue resistance in older adults [52,95,96]. In the present study, older adults were able to reach a higher percentage of their pre-fatigue MVC (89% vs. 83%) than young adults but this was not significant. The lack of demonstration of fatigue resistance in older adults, could be due to differences in the fatiguing task, muscle group used, and force level. However, other studies have also reported a lack of difference in fatigue between ages. For example, Lanza et al. [97] found similar levels of fatigue between young and older men after a 60-second maximal isometric contraction in the ankle dorsiflexors. Additionally, Allman and Rice [98] demonstrated no difference rate of force loss or time to recovery between young and older adults in the elbow flexors.

Neuromuscular fatigue was accompanied by changes in the contractile properties of the muscle, as well as the M-wave. Specifically, while TTP twitch force did not change, HRT was significantly slower, indicating slowed contractile properties after fatigue, and PTF was significantly larger in the young group, but not the older group. The M_{Max} amplitude was also significantly smaller after neuromuscular fatigue. Behm and St.Pierre [99], examined the effects of neuromuscular fatigue in the tibialis anterior and soleus in young adults; results were similar to the present study and demonstrated a ~15% decrease in M_{Max} amplitude along with a ~16% increase in PTF, ~16% decrease in HRT and no change in TTP. A possible explanation for the lack of change in TTP accompanied by a change in HRT could be due to effects of muscle metabolism during fatigue. Sequestering of Ca^{2+} by the sarcoplasmic reticulum, represented by HRT,

involves ATP [100] whereas release of Ca^{2+}, represented by TTP, does not (46). Re-synthesis of ATP during fatigue may be hindered with low intramuscular pH [101] during fatigue. Having less ATP available may slow Ca^{2+} sequestering, thus increasing HRT, whereas Ca^{2+} release (because it is passive) would not be affected thus leaving TTP unchanged.

Taken together, results from the present study, indicate that NMF was present, and it may be partially attributed to both a decline in neuromuscular transmission (neuromuscular junction) [78,102,103] and a slowing of contractile properties of the muscle [74,103].

In the present study, older adults did not experience increases in PTF with fatigue. Previous studies examining twitch potentiation, in older versus young adults, after fatigue in both the first dorsal interosseous [104] and tibialis anterior [105], demonstrated higher levels of potentiation in younger adults. One possible explanation for this difference is that younger adults typically have a greater proportion of type II fibers [57] and type II fibers have greater twitch potentiation than type I fibers [106]. However, as mentioned above, the TA is relatively unaffected by age so this may not explain the difference found in the present study [57]. Vandervoort et al.[107], examined twitch potentiation in the tibialis anterior and plantarflexors after voluntary contraction; results demonstrated that brief MVCs potentiated the twitich in the tibialis anterior and the potentiation was still detectable 8-10 minutes after MVC. In the present study, because we were trying to capture the effect of neuromuscular fatigue, our post-fatigue measures were obtained several seconds, not minutes, following the final MVC. This could have led to the increased PTF after NMF that we see in the young group in the present study.

MEP amplitude was significantly lower after neuromuscular fatigue. However, this was not different between groups. Studies examining TMS responses after fatigue, have found similar reductions in MEP amplitude after fatigue in the abductor digiti minimi [108], wrist flexors [109], tibialis anterior [110,111], and whole body exercise to fatigue [112]. At the cortical level, decreases in MEP represent a decrease in cortical excitability. However, the MEP is representative of the entire neuromuscular pathway; any changes in the periphery could also affect the MEP amplitude. For example, in the present study, there was a decrease in M_{Max} amplitude (representing a decline in neuromuscular transmission) and an increase in half-relaxation time (indicating a slowing of contractile properties of the muscle) after fatigue and these decreases in function at the level of the peripheral neuromuscular system may have contributed to a decrease in the amplitude of the MEP.

Every group, except the older females, had significantly longer CSP after NMF, indicating greater intracortical inhibition. Previous studies examining the elbow flexors [113,114] and hand muscles [115] during fatigue also found increases in CSP duration. The present results are similar to those found by McKay et al. [116], who showed a ~40% increase in CSP duration after a fatiguing MVC in the tibialis anterior. Further, Taylor et al. [113] demonstrated that CSP lengthens after a 5 second MVC and continues to lengthen if additional exercise is performed before complete recovery. The increase in CSP duration along with the decrease in MEP amplitude, in the present study, suggest that neuromuscular fatigue results in a net decrease in cortical excitability after neuromuscular fatigue. Fatigue related afferents (III/IV) may influence inhibition in the motor cortex. Kennedy et al.[117] examined fatiguing MVCs in the knee extensors during

firing of group III/IV afferents by occluding blood flow post-exercise; results demonstrated a failure of recovery of the CSP during post-exercise ischemia indicating that III/IV afferents may have influence inhibition in the motor cortex. Further, Hilty et al. [118], examined the quadriceps after fatiguing exercise under two conditions: blocked III/IV afferent feedback using fentanyl and unblocked III/IV afferent feedback using a placebo. CSP duration increased during the placebo condition but did not increase with fatigue when fentanyl was administered. This suggests that III/IV afferents may contribute to the fatigue induced increase in CSP duration. Additionally, there is evidence that exercise causes an increase in levels of dopamine in the central nervous system [119] and dopamine lengthens the duration of CSP [71,72]. Therefore, in the present study increases in CSP duration could also be attributed to an increased level of dopamine resulting from exercise. Intracortical inhibition, as indicated by increased CSP duration, could result in decreased force output due to a decrease in drive to the motor neurons from the motor cortex.

Neuromuscular Fatigue and Cognitive Function

Older adults had more false starts overall and women had more lapses than men overall. Lapses (RT > 500ms) on the PVT are associated with subjective ratings of fatigue and decline in energy [47,68]. In the present study, this could indicate that women felt more fatigued or less energetic in general. Alternatively, there is some evidence for a sex difference in the speed-accuracy tradeoff. Women are typically slower but more accurate than men during cognitive tasks [120,121]. Additionally, Blatter et al. [122], examined sex and age differences in PVT performance and demonstrated that women were less

likely to have false starts and maintained accuracy better than men suggesting that women prioritize accuracy whereas men prioritize speed. In the present study, women may have experienced lapses because they were trying to be accurate, whereas men were focusing on speed. The speed-accuracy trade-off may also explain why older adults had more false starts in general. With age, there is a reduction in the speed with which cognitive functions can be executed [123]. In the present study, older adults may have sacrificed accuracy and prioritized speed to counteract the age-related decline in speed of cognitive function. Despite these differences between groups, neuromuscular fatigue did not affect the number of false starts or lapses during the cognitive function task.

Reaction time during the cognitive task increased after neuromuscular fatigue, but only in the young group (Young Adults ~9% slower vs. Older Adults ~1% faster). After NMF, subjective ratings of fatigue were higher, but this was not different among groups. Results from the present study indicate that while all participants felt more fatigued after the NMF task, NMF had a negative effect on cognitive function (reaction time) only in the young group. This could suggest that the cognitive function of young adults is negatively affected by acute bouts of exercise but older adults' cognitive function is not affected.

Changes in reaction time with NMF, in the present study, may be attributed to multiple factors including: use of TMS and/or varying effects of an acute bout of exercise. First, TMS itself may have an effect on reaction time. In a study examining choice reaction time and TMS, results suggested that TMS can delay choice reaction time without increasing errors [124]. Additionally, a study looking at TMS and voluntary movement found that the optimal site to delay voluntary movement corresponded to the

optimal site for eliciting a MEP [125]. These studies, in conjunction with results from the present study suggest that TMS itself could impact reaction time on a cognitive task. However, RT was increased only in young adults in the present study, which makes it unlikely that TMS was the cause of our observed differences.

Several studies have examined the effect of an acute exercise bout on cognitive function [126–129] in young and middle aged adults with conflicting findings; both a shortening and lengthening of simple reaction time have been reported. Differences in previous findings could be due to: arousal level achieved with exercise and/or exercise duration. The cue-utilization theory posits that moderate increases in arousal lead to a narrowing of attention onto relevant cues, resulting in better performance; whereas, high levels of arousal may cause an over narrowing of attention, resulting in poorer performance [130]. Moderate exercise has been shown to increase arousal level [131]. There is a possibility that in the present study younger adults became either: 1) over aroused by the NMF task leading to a slowing of reaction time or (2) the task was not intense enough to sufficiently arouse younger adults also leading to a slowing of reaction time; whereas older adults became moderately aroused leading to faster reaction time.

Further, in younger adults, studies indicate that exercise duration affects the effect of acute exercise on cognitive function [128]. When exercise lasts 20 minutes or more, both complex [132] and simple reaction time performance improves [133]. The fatigue protocol in the current study was 16 minutes long and may not have been long enough for the young adults to experience a positive effect of exercise on cognitive function. Additionally, there is some evidence to suggest that if the cognitive task is not challenging enough, a positive effect of exercise on cognitive function will not be seen [128,131]. It is possible that

in the present study the cognitive task was not challenging enough for the young adults whereas in the older adults the cognitive task was sufficiently challenging thus we saw a positive effect of exercise on reaction time in the older adults.

Older adults typically have lower levels of neurotransmitters, specifically dopamine [134] and when dopamine is administered to healthy older adults, there are enhancements in both cognitive [135] and motor functions [136]. A presumed increase in dopamine levels with exercise, in the present study, may have acted to improve cognitive and motor function in the older adults, leading to faster reaction times. Further research is warranted to determine the mechanisms behind differences in cognitive function between young and older adults with neuromuscular fatigue.

Limitations

There is high intra-individual and inter-subject variability in MEP amplitude. Location and orientation of the coil can affect MEP amplitude [73]. In the present study, once the optimal site for TMS was found, location of this site, as well as an outline of the coil, was marked on a wig cap and the same researcher applied the stimulation each time to minimize movement of the TMS coil. Further, MEP variability decreases with increasing contraction intensity [73] and participants were contracting to 50% during these recordings, which should help to minimize variability . Lastly, MEP was normalized to M_{Max} which should account for potential differences in MEP amplitude that are due to the size of the muscle or neuromuscular transmission that are not related to cortical excitability itself. The low number of older men in the study may have impacted the results related to sex differences. Additional work with equal samples sizes across groups is warranted.

Conclusions

Results from the present study suggest that a neuromuscular fatigue task may affect cognitive function in young but not older adults. Significant decreases in MVC force were observed in all groups, suggesting that neuromuscular fatigue was present and not different among groups. Measures of neuromuscular function (slowed HRT, smaller M_{Max}) and cortical function (increased CSP) significantly changed, suggesting that changes in force production with neuromuscular fatigue in the present study were due to several factors, including: slowing of neuromuscular propagation, reuptake of Ca^{2+}, and an increase in cortical inhibition. Neuromuscular fatigue increased self-reports of fatigue but only affected cognitive function (increased reaction time) in young adults. Factors such as level of force and amount of neuromuscular fatigue induced could have influenced performance on the cognitive task. More research on the mechanisms behind age-related differences in cognitive function in response to neuromuscular fatigue is needed.

Bridge

Chapters II and III examined the interactions of neuromuscular fatigue, mental fatigue, cognitive function, and neuromuscular function. In chapter IV, functional consequences of mental fatigue are explored.

CHAPTER IV

THE EFFECT OF MENTAL FATIGUE ON POSTURAL STABILITY

Amanda Morris contributed to the concept of the studies, recruited subjects, collected data, performed data analysis, and prepared the initial manuscript. Dr. Anita Christie contributed to the concept of the study, provided editorial support, and critically reviewed and revised the manuscript.

Introduction

Fatigue is a multidimensional concept that has both physical and psychological components. Mental fatigue is a psychophysiological state that occurs after or during prolonged periods of cognitive activity [4] that is characterized by self-reported feelings of tiredness, lack of motivation, and decreased cognitive performance [37,38]. Mental fatigue is linked to several negative outcomes including: the development of physical fatigue, decreases in physical and cognitive performance, and an inability to properly allocate attention [5,8].

Several studies have reported that women experience significantly more mental and physical fatigue than men [40–42]. Moreover, older adults, especially older women, also report higher levels of fatigue than young adults [41]. In older adults, self-reported fatigue is associated with earlier onset of disability, slower gait speed, and increased hospitalization risk [36,43]. Despite these important associations, little is known about the direct impact of a current state of mental fatigue on physical function.

In addition to having increased incidence of fatigue, women are at increased risk of falls, as older women have worse balance control than men [137] and 70.5% of non-fatal

fall injuries occur in women [138]. The ability to properly allocate attentional resources is important for postural stability [23]. A series of studies examining the effect of attention on postural stability indicate that older adults are at higher risk of falls when fewer attentional resources are available [23]. In a study examining causes of falls in older women specifically, it was determined that 35% of reported falls were due to lapses in attention [139]. Taken together, these results suggest that the reduction in attentional resources that occurs with mental fatigue may compromise physical functions such as balance control [8,21]. Such compromised function may be more pronounced in older women, who report higher levels of fatigue, and demonstrate worse balance control than men [40,42]. However, currently little is known about the impact of mental fatigue on balance control in older women.

In healthy young and older adults, muscle responses to postural perturbations occur within 70-110 ms [140]; any delays in onset of muscle activity could result in instability [140]. When compared with young, older adults often have a larger center of pressure displacement in response to postural perturbations, which could be attributed to delayed muscle activation times [24,141,142]. Further, Rankin et al. [142] found a decrease in muscle activity in response to postural perturbation when a simultaneous cognitive task was performed. These results suggest that cognitive function may impact muscle activity. However, it is unknown if mental fatigue, a state that results in decreased cognitive function, impacts muscle activity.

The purpose of this study was to examine the effect of a mentally fatiguing task on postural responses to perturbation in young and older women. Postural responses to unexpected perturbations in the posterior direction were characterized by center of

pressure (COP) displacement and corrective peak velocity, and by electromyography (EMG) of the medial gastrocnemius. It was hypothesized that the mentally fatiguing task would result in larger COP displacement and faster COP velocity than the control condition in all groups, with older women showing augmented responses compared to young women. It was further hypothesized that mental fatigue would result in a reduction in EMG amplitude and no change in EMG onset in all groups, with older women having a greater reduction in amplitude compared to young women.

Methods

Sixteen young women (22.4 ± 0.93 years) and 16 older women (72.6 ± 1.63) years participated in this study. Participants were healthy and free from any chronic disease, illness, condition, or medication that could impact balance. Exclusion criteria included: a positive screen for cognitive impairment, history of illness associated with fatigue (e.g. chronic fatigue syndrome, multiple sclerosis), history of cognitive deficiencies (e.g. memory loss, difficulty concentrating), poor sleep habits, history of neurological impairment, history of musculoskeletal impairments, use of alcohol or central nervous system depressant pharmacological agents within 12 hours of performing tasks, or active substance abuse. All participants provided written informed consent and were asked to complete a brief medical history report, Pittsburgh Sleep Quality Index, Multidimensional Fatigue Index, and the Mini-Cog cognitive screening test.

Testing was divided into two sessions involving postural perturbations; one session with mental fatigue and the other without (control condition). The order of the protocols across the two visits was randomized across participants. First, participants had

a practice session of 20 total perturbations (5 forward, 15 backward; randomized), then performed either the mental fatigue task or the control task for 20 minutes with 5 perturbations (1 forward, 4 backward; randomized) at 1 minute (beginning) and 18 minutes (end). Forward perturbations were used to prevent anticipation of the direction of plate movement. Only responses to the backwards perturbations were analyzed.

Questionnaires

The Pittsburgh Sleep Quality Index (PSQI) was used to measure the sleep patterns and quality of sleep in seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, sleep medication use, and daytime dysfunction. The participants self-rated these aspects of sleep quality on a 0 to 3 scale, where 3 is negative. A total score, summed across all questions, of 5 or greater indicates a poor sleeper [44].

The Multidimensional Fatigue Inventory (MFI) is a 20 item, self-report instrument that measures fatigue in the following domains: general fatigue, physical fatigue, mental fatigue, motivation, and activity. Participants responded to each item on a scale of 1 to 7 and the total score was summed across all items. A higher total score corresponds to greater acute levels of fatigue.

Postural Perturbations

Custom built, hydraulically activated, dual force plates (University of Oregon Institute of Neuroscience, Eugene, OR) that translated forward and backward were used for postural perturbations. Participants were asked to stand barefoot, with arms at the sides, and one foot on each plate. A safety harness anchored to the ceiling was used to

prevent falls. Translations were set at 30 cm/s for 15 cm [142]. This speed was chosen to result in a postural perturbation that did not cause participants to take a step [142].

Force data was sampled at 1000 Hz with a 16-bit A/D converter (NI USB-6251, National Instruments, Austin, TX), then low pass filtered at 10 Hz in MATLAB (MathWorks Inc., Natick, MA, USA). Center of pressure (COP) (Figure 1) was calculated using the equation [143]:

$$Total\ COP = LCOP_{A/P} \times LF_z \div (LF_z + RF_z) + RCOP_{A/P} \times RF_z \div (LF_z + RF_z)$$

where L = left; R = right; F_Z = force in the z direction; $COP_{A/P}$ = center of pressure in the anterior-posterior direction.

Total displacement of COP was calculated by subtracting the maximum anterior excursion from the maximum posterior excursion using a custom written MATLAB program (MathWorks Inc., Natick, MA, USA).

Velocity of COP displacement (Figure 4.1) was calculated by taking the first time derivative of COP displacement, using the equation:

$$V_{COP} = \frac{ds}{dt}$$

where s = center of pressure displacement and t=time.

Peak velocity was considered as the maximum velocity attained during corrective center of pressure motion. Corrective COP was the COP displacement in response to backward plate movement. Peak COP velocity was automatically detected with a custom written MATLAB program, and manually verified for each trial.

Total displacement of COP and peak COP velocity in response to backward perturbations were averaged across the 4 trials at each time point and used to assess postural stability.

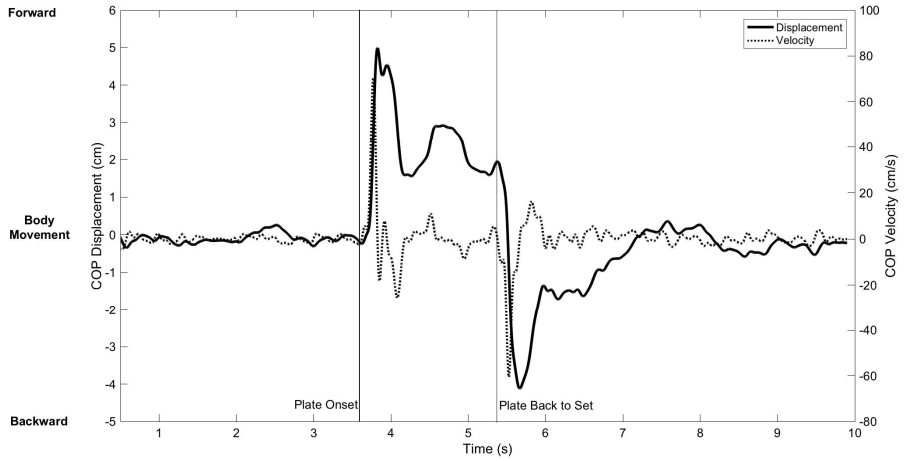

Figure 4.1. Representative center of pressure (COP) displacement and velocity profiles in response to a backward platform perturbation.

Mental Fatigue Task

To induce mental fatigue, participants were asked to perform the psychomotor vigilance task (PVT) for 20 minutes (Biotechnology HPC Software Applications Institute, MathWorks Inc., Natick, MA, USA). The PVT is an objective, valid measure for assessing behavioral alertness and vigilant attention [144]. Lapses in reaction time (reaction time > 500 ms) during this task are associated with subjective measures of fatigue and decline in energy [144,145]. When performed for 20 minutes or more, reaction time increases and accuracy decreases indicating a decrease in vigilant attention and presence of mental fatigue [48,50].

A 24" computer monitor was placed at eye level, three feet in front of the participant and participants held a wireless mouse in a comfortable position in their dominant hand. When a red number appeared on the screen, participants were asked to click the left button on the mouse as soon as the number appeared. Reaction time was

displayed for 500 ms, then cleared. Time between presentation of each stimulus varied randomly between 2 and 10 seconds. Reaction time was calculated as the time from presentation of stimulus to time of response. Reaction times less than 90 ms were considered false starts and not included in the analyses [145]. Reaction times longer than 500 ms were considered lapses (4).

Before and immediately after the protocol, participants were asked to rate their subjective fatigue. Participants responded to the question "how sleepy do you feel" on a scale of 1 to 10, with 1 representing not at all sleepy and 10 representing very sleepy.

Control Condition

To ensure that any observed changes in postural responses were due to mental fatigue, participants were asked to complete a control trial, on a separate day. Participants stood on the same force platforms as during the mental fatigue day, however, in place of the PVT task, participants were instructed to watch a nature video, with no sound, for 20 minutes. The monitor set up was identical to the mental fatigue trial and the same number of postural perturbations were provided at the same intervals (baseline, beginning and end). Similar to the mental fatigue trial, participants rated their subjective fatigue on a 10-point scale before and immediately after the protocol.

Muscle Activity

Pre-amplified, bipolar Ag-AgCL electrodes (DE-2.1, Delsys Inc., Boston, MA), with an inter-electrode distance of 1 cm, were placed over the muscle belly of the medial gastrocnemius (MG) of the right leg. The signal was amplified and band-pass filtered

(20-450 Hz) and sampled at 1 kHz with a 16 bit A/D converter (NI USB -6251, National Instruments, Austin, TX) and DasyLab software.

Electromyography (EMG) onset and amplitude were assessed as a measure of neural control of postural responses using custom written MATLAB programs (MathWorks Inc., Natick, MA, USA). Onset was considered as the time at which the EMG signal was 3 standard deviations above baseline activity, after the onset of the platform perturbation. Onset time was automatically detected, and manually verified for each trial. Root mean squared (RMS) amplitude was calculated over a window of 500 ms from onset of activity using 50 ms bins to determine peak EMG amplitude.

Statistical Analyses

Descriptive characteristics of participants, including age, height and weight were compared using independent samples t-tests. Responses to the PSQI and the MFI were compared using a 2 factor (age-group, condition) repeated-measures ANOVA. Results were considered significant if $p \leq 0.05$.

The following quantitative variables were obtained: mental fatigue: subjective ratings, PVT reaction time and number of lapses; postural stability: total displacement of center of pressure, and center of pressure velocity in response to perturbations; muscle activity: EMG onset and amplitude. All data are presented as mean $\pm$ standard error. To examine the effect of each protocol on each variable, 3 factor (age group, condition, time) repeated-measures ANOVAs were used. If significance was found post hoc comparisons were made using a Bonferroni correction.

Percent change was calculated for the following variables: EMG amplitude, PVT reaction time, COP displacement and COP velocity. Percent change was calculated using the following equation:

$$\frac{(Post\ Value - Pre\ Value)}{Pre\ Value} \times 100$$

A positive percentage value indicates an increase in: EMG amplitude, PVT reaction time, COP displacement, and COP velocity. A negative percentage value indicates a decrease in: EMG amplitude, PVT reaction time, COP displacement, and COP velocity.

Linear regression was used to determine if there was a significant relationship between the percent change in COP displacement or corrective COP velocity and the percent change in PVT reaction time.

Results

Participant Characteristics

Participant characteristics and scores (mean ± SE) for the Multidimensional Fatigue Inventory (MFI) and the Pittsburgh Sleep Quality Index (PSQI) are presented in Table 4.1. There was no significant difference between groups in height (p=0.43) or weight (p=0.87). Older women were significantly older than young women (p<0.0001). There was no significant interaction of condition and age (p=0.53) on total Multidimensional Fatigue Inventory scores nor was there a significant main effect of age (p=0.22) or condition (p=0.34). There was no significant interaction of age and condition (p=0.14) on PSQI scores, nor was there a significant main effect of age (p=0.71) or condition (p=0.37).

Table 4.1. Participant characteristics

Variable	Young (n=16)		Older (n=16)	
Age	22.40±0.93*		72.60±1.63*	
Height (cm)	164.06±2.29		161.37±1.65	
Weight (kg)	59.66±3.49		60.50±1.78	
	Control	MF	Control	MF
MFI	60.41±1.59	60.00±1.06	59.07±1.39	57.10±1.66
PSQI	5.17±0.57	4.92±0.88	4.20±0.51	5.2±0.79

MFI, Multidimensional Fatigue Index; PSQI, Pittsburgh Sleep Quality Index. Higher scores indicate more fatigue or poorer sleep quality. *indicates a significant difference between age groups ($p<0.001$).

Mental Fatigue Task

Likert ratings of subjective fatigue are shown in figure 4.2. There were no significant interactions of condition by age (p=0.82), time by age (p=0.45), condition by time (p=0.43), or condition by time by age (p=0.87) on Likert ratings of subjective fatigue. These ratings were significantly higher (p=0.001) at the end of the trial than pre-ratings across both conditions (p=0.001). There was also a significant effect of age (p=0.007), with younger women having higher ratings of fatigue than older women, overall.

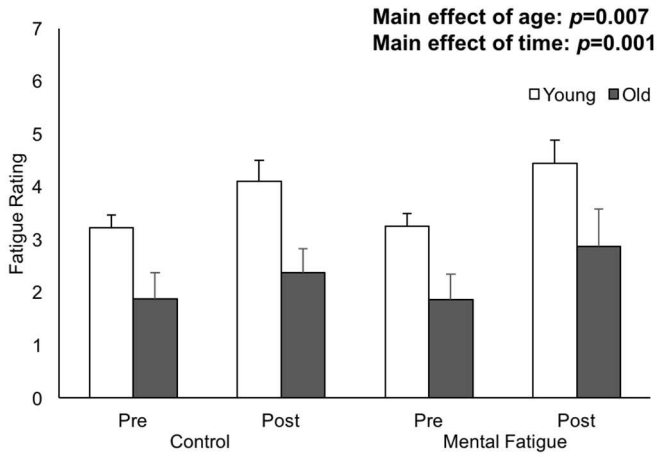

Figure 4.2. Likert Scale rating of fatigue before and after the control and mental fatigue sessions. Higher values indicate greater fatigue. Main effects of age and time were observed, whereas no significant main effect of condition or interactions were found. Data presented as mean ± SE

Reaction time during the mental fatigue task is presented in figure 4.3. There was a significant age by time interaction (p=0.04) on reaction time during the mental fatigue task. significantly slower reaction times than the beginning of the task. At the beginning of the task older women had significantly slower (p=0.002) reaction times than young women but only young women experienced a significant slowing (p=0.001) of reaction time from the beginning of the task to the end of the task. There was no significant main effect of age (p=0.06) on reaction time. However, there was a significant main effect of time (p=0.003), with the end if the task having slower reaction times than the beginning. Additionally, there were no significant differences (p=0.36) between age group in number of lapses (RT > 500 ms) or false starts (p=0.08).

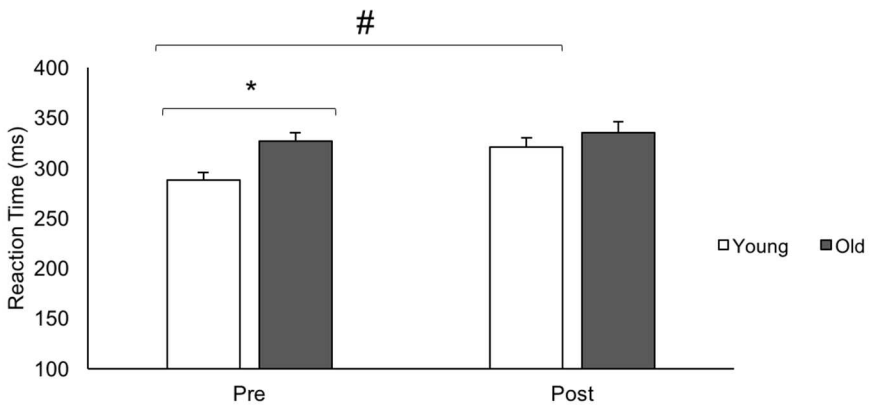

Figure 4.3. Reaction time (RT) during the mental fatigue task. *Older women had significantly slower (p=0.002) RT than young women before mental fatigue. #Younger women had significantly slower (p=0.001) RT after mental fatigue. Data presented as mean ± SE.

Postural Stability

There were no significant interactions of condition by age (p=0.13), time by age (p=0.34), condition by time (p=0.10), or condition by time by age (p=0.46) on anterior-posterior center of pressure displacement (Figure 4.4, left). Older women had significantly larger anterior-posterior COP displacement than young (p=0.001), but there were no significant main effects of condition (p=0.32) or time (p=0.18).

Center of pressure (COP) velocity is shown in figure 4.4 (right). There was a significant interaction of age and condition (p=0.02); only young women experienced significantly faster COP velocity during the mental fatigue condition versus the control condition. However, there was no significant time by age (p=0.32), condition by time (p=0.27), or condition by time by age (p=0.50) interactions. Older women had significantly faster COP velocity than young women (p=0.02).

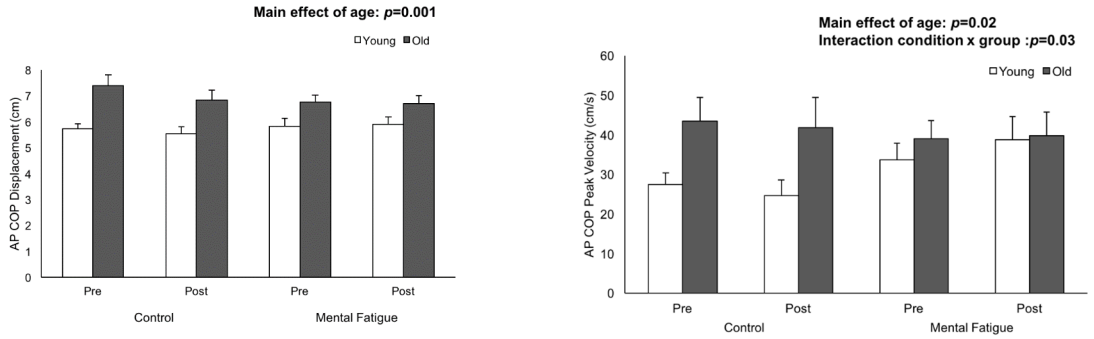

Figure 4.4. Anterior-**posterior center of pressure displacement (AP COP) and velocity.** Presented as mean ± SE. AP COP (Left). Main effect of age was observed, whereas no significant effect of condition, time or any significant interactions were found. AP COP peak velocity (Right). Main effect of age and interaction of condition and age were observed, whereas no significant effect of time or any other significant interactions were found.

Muscle Activity

There was no significant condition by age (p=0.11), time by age (p=0.52), condition by time (p=0.13), or condition by time by age (p=0.31) on medial gastrocnemius (MG) EMG onset times are shown in (Figure 4.5 (left)). There was a significant effect of age group (p=0.03), as older women had significantly slower MG EMG onset times than young women. There was also a significant main effect of time (p=0.03) on MG EMG onset time; MG EMG onset time was significantly longer at the end of the 20 minutes than at the beginning, regardless of condition (control or mental fatigue). Additionally, the mental fatigue condition resulted in significantly longer (p=0.006) MG EMG onset times than the control condition.

There was no significant condition by age (p=0.29) interaction (Figure 4.5, right), nor was there a significant main effect of age (p=0.86) or condition (p=0.89) on percent change in MG EMG amplitude (p=0.86).

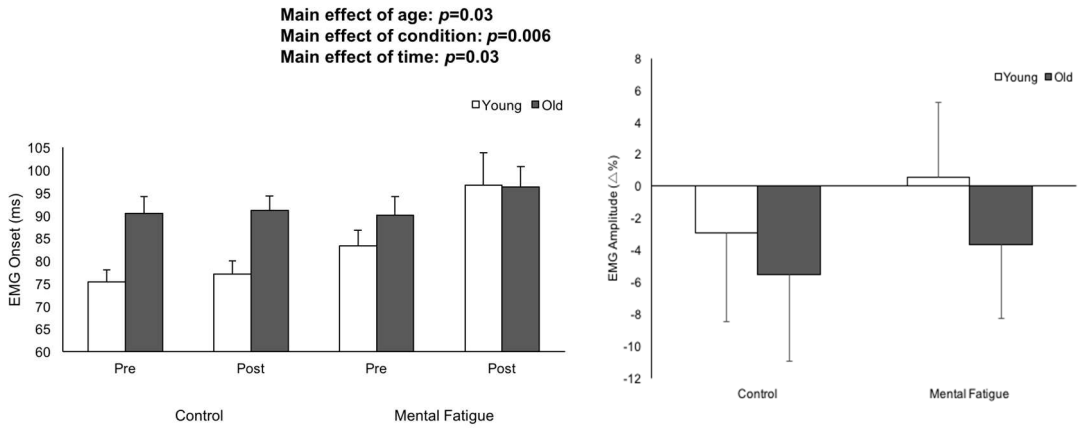

Figure 4.5. Medial gastrocnemius muscle activity. Data presented as mean ± SE. EMG onset time (left). Main effects of age, condition, and time were observed, whereas no significant interactions were found. Percent change in EMG amplitude (right). A main effect of age was observed, whereas no significant main effect of condition or interactions were found.

Relationship Between PVT Reaction Time and Postural Stability

There was no significant relationship between the percent change in COP displacement and PVT reaction time in either age group (Table 4.2). However, the percent change in reaction time during the PVT significantly predicted percent change in COP velocity (r=-0.76, p=0.001) in young women. The magnitude of this effect was large, explaining 58% of the variance in percent change in COP velocity (p=0.001) (Figure 4.6).

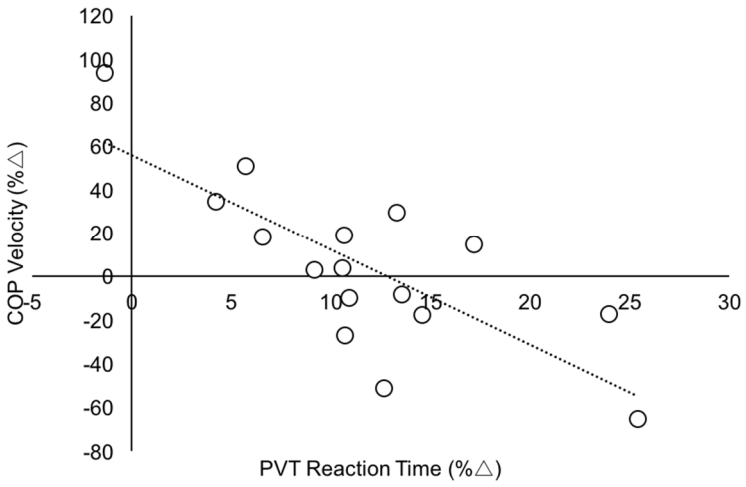

Figure 4.6. Relationship between the percent change in center of pressure (COP) displacement velocity and the percent change in psychomotor vigilance task (PVT) reaction time for young women.

Table 4.2. Relationships between reaction time and center of pressure measurements.

	Group	**r**	***p***
RT %△ vs. COP D%△	**Young**	0.48	0.06
	Older	-0.49	0.13
RT %△ vs. COP V %△	**Young**	-0.76	0.001*
	Older	-0.07	0.82

RT, psychomotor vigilance task reaction time; COP D, center of pressure displacement; COP V, center of pressure velocity. *significant correlation

Discussion

The purpose of this study was to examine the effect of a mentally fatiguing task on postural responses to unexpected perturbations in the sagittal plane in young and older women. This was accomplished by examining postural responses to unexpected perturbations in the posterior direction as characterized by center of pressure (COP)

displacement and corrective velocity as well as electromyography (EMG) of the medial gastrocnemius. Older women had slower reaction time, longer EMG onset times, larger anterior-posterior center of pressure displacement, and faster center of pressure velocity than younger women overall. However, only young women experienced mental fatigue (slower PVT reaction times) and this was accompanied by significantly faster COP velocity during the mental fatigue condition than the control condition. Further, there was a significant relationship between PVT reaction time and COP velocity in young women but not in older women.

Questionnaires

As sleep quality can affect the PVT [50], the PSQI was administered to determine if there were any differences in sleep quality between groups. There was no significant difference between age groups or sexes in sleep ratings, indicating that at baseline, there was no difference between groups in sleep quality. There was also no significant difference in ratings of fatigue on the MFI, suggesting that both age groups had similar levels of subjective fatigue at baseline.

Postural Control in Older Women

Overall, older women had larger AP COP displacement and faster velocity than young women which matches with previous studies examining differences in postural control between ages [146]. In the present study, older women also had slower EMG onset than younger women. Many studies have found similar slowing of the EMG response to postural perturbations in older versus to younger adults [24,140,147]. This could be explained by the many physiological changes that take place with aging, including declines in

sensory system feedback, nerve conduction velocity, motor unit numbers, muscle mass, and central processing abilities [26]. These changes can result in a decline in the ability to produce force and power, as well as an increase in cognitive cost of activity in older adults [31,148,149], all of which would have a negative effect on the ability to maintain balance in response to a postural disturbance. In the present study, the significant delay in EMG onset time in older women might have allowed the center of mass to move closer to the edge of the base of support, resulting in the larger COP displacement observed in older women. Taken together, previous research and results from the present study suggest that older women were less efficient in slowing forward movement of the body in response to the backward perturbations.

Mental Fatigue and Postural Control

Older women had significantly slower PVT reaction times at the beginning of the mental fatigue task versus younger women which can be explained by the reduction in speed with which cognitive functions can be executed in older adults [123]. However, only the younger women experienced a significant slowing in reaction time over 20 minutes of the PVT. There were no differences in errors during the PVT (lapses and false starts) between age groups. Subjective ratings of fatigue (Likert scale) were significantly higher after 20 minutes of both tasks and younger women had significantly higher ratings of fatigue than older women. These results suggest that only younger women experienced mental fatigue. The difference in mental fatigue may be attributed to anxiety and/or arousal. Several studies have examined the influence of fear of falling or a postural threat on postural control and results indicate that fear of falling increases levels of anxiety and

arousal [150–152]. Eason et al.[153] studied the effects of arousal on reaction time and determined that reaction times under "high arousal" were faster than those under "low arousal." In the present study, the postural perturbation may have increased the overall level of arousal in older adults allowing performance on the PVT to be maintained and allowing adults to avoid feeling mentally fatigued.

Center of pressure displacement was not significantly different between conditions (mental fatigue vs. control) nor did it change over time (beginning vs end of each condition), suggesting that mental fatigue did not influence COP displacement. It has been proposed that response to postural perturbations may be controlled largely by brainstem processes. This is because muscular responses to perturbations occur between 70-180 ms, which is longer than reflex latencies (40-50 ms) but shorter than voluntary reaction times (>180 ms) [154]. In a study examining the response to postural perturbations in decerebrated cats, the cats still had appropriately tuned responses thus implying the brainstem and spinal cord have a stronger role than the cortex in generating the automatic response to postural perturbation [155]. In a series of studies examining goal directed postural interactions, participants were instructed to intentionally respond to a predictable perturbation with a step, and were able to inhibit the automatic postural response of the muscle [156]. However, when the velocities of the perturbations were randomized the participants were only able to modify the later part of the response [157]. Taken together, these results imply that response to an unpredictable perturbation, like those used in the current study, are controlled by the automatic postural response and were not significantly impacted by mental fatigue.

Only young women had significantly faster peak AP COP velocity during the mental fatigue condition versus the control condition, suggesting that mental fatigue had an effect on COP velocity in young women. With mental fatigue, young women experienced velocity values that were similar to those of the older women, however it did not affect their ability to recover from the postural perturbation as demonstrated by the lack of significant change in COP displacement. In the control condition young women experienced a 5% slower velocity and a 3.5% decrease in COP displacement, while during the mental fatigue condition their velocity got significantly faster (13%) and their COP displacement increased by 1%, though this was not significant. This could indicate that during the control condition the young women got more efficient at their response to the unexpected perturbation whereas in the mental fatigue condition their efficiency got worse. Additionally, velocity during the mental fatigue condition was 24% faster than during the control condition in young women. In young women only, the degree of change in reaction time was significantly related to the degree of change in peak velocity where longer reaction times resulted in faster velocities. However, the functional significance of this relationship remains unclear.

In older women, the mental fatigue task may have improved postural stability performance. While not significant, older women experienced ~1% smaller COP displacement and 5% slower velocities during the mental fatigue condition versus the control. The "constrained action hypothesis" suggests that consciously trying to control movement actually interferes with automatic control of posture [158]. There is evidence to suggest that performing a sustained cognitive task might direct attention to the cognitive task rather than posture, which would allow less opportunity to consciously control

posture, thus allowing automatic postural processes to occur [146,159,160]. For example, results from Potvin-Desrochers et al. [159], showed that COP area during a continuous dual-task was smaller than control condition (no task) in older adults, demonstrating the ability of older adults to focus attention on cognitive tasks, allowing more automatic postural control. Similar to the current study, Simoneau et al. [146], found that there was a 17% decrease in COP velocity in older adults with the addition of a continuous cognitive task during tandem stance. Additionally, older women in the present study may have been constraining velocity and displacement of COP for safety. A series of studies by Adkin et al. [150,151] and Carpenter et al.[161,162] examined the effect of fear of falling on postural control, and determined that when posture is threatened participants have reduced displacement and velocity of center of mass. Therefore, older women in the present study may have been constraining velocity and displacement of COP for safety. Fear of falling could have also led to higher levels of arousal thus preserving RT performance (as discussed above) while maintaining postural stability (older women had similar COP displacement and velocity in both conditions).

Mental Fatigue and EMG

Both conditions (control and mental fatigue) resulted in slowing of MG EMG onset time by the end of 20 minutes, suggesting that neuromuscular fatigue may have occurred due to prolonged standing in both conditions. Studies examining prolonged standing have demonstrated a reduction in force production [163] and peak twitch force [164], indicating presence of fatigue in the soleus, tibialis anterior, and gastrocnemius. Additionally, neuromuscular fatigue slows both the short and medium latency responses

of reflexes [165] and neuromuscular transmission [78,102,103]. This may explain why onset time, in the present study, slowed over 20 minutes in both conditions.

EMG amplitude was not significantly different between conditions nor was it different between age groups. This suggests that mental fatigue does not influence EMG amplitude. Again, this could be a result of the postural task being mediated by brainstem and spinal cord processes rather than cortical processes. However, overall, EMG onset times were slower in the mental fatigue condition than the control condition. This could suggest that mental fatigue has an effect on EMG onset time. This was most likely driven by the 18% increase in onset time duration in the young women from the control to the mental fatigue condition, whereas older women only experienced a 3% increase. Young women also had a slight, but not significant, increase in EMG amplitude with mental fatigue. This may have been to compensate for the slowing of EMG onset and might help explain why young women had increases in velocity during the mental fatigue condition. There is some evidence that mental fatigue can affect dopamine transmission [4,6,37,70], which, in turn, may increase inhibition in the motor cortex [71,72], leading to suboptimal output and perhaps the slowed EMG onset times we saw in the present study.

Limitations

Backward perturbations allow the center of mass to move farther before reaching edge of the base of support thus providing more time to make postural adjustments, making them less challenging than forward perturbations. Additionally, as mentioned above, it is also possible that responses to postural perturbations from translational platforms are mainly influenced by the brainstem, not cognitive, processes. So, perhaps,

we would not expect to see an effect of mental fatigue on this postural response. A more difficult postural challenge (faster velocity, more forward perturbations, stepping or reaching task) may have allowed us to see more changes in postural responses with mental fatigue. In the present study we chose the speed and direction for safety and to avoid participants from taking a step.

There is a chance that participants in the present study were anticipating the postural disturbances. However, trials of forward and backward perturbations were randomized to prevent anticipation. Randomizing velocity would have helped to further prevent anticipation.

Conclusions

Performance of mental fatigue task, not necessarily the development of mental fatigue, affects neuromuscular activation in young women only, but does not affect the magnitude of postural response to perturbation. EMG amplitude was not affected by mental fatigue. However, EMG onset times were longer in the mental fatigue condition than the control condition. In young women, the degree of change in reaction time was significantly related to the degree of change in peak COP velocity. However, the functional significance of this relationship is not clear and should be explored further. Older women did not experience mental fatigue (lack of change in RT) and did not experience any significant differences in COP displacement or velocity between conditions. It is possible that in older women, a fear of falling increased arousal and performing the sustained attentional task allowed for maintenance of postural stability by preventing conscious control of posture. Further research using more complex postural

tasks, to ensure that voluntary control of posture is occurring, is needed to determine if mental fatigue has an effect on postural control.

CHAPTER V

CONCLUSION

Findings Summary

The overall goal of this dissertation was to determine the interactions between mental and neuromuscular fatigue and the impact of mental fatigue on function and, importantly, to determine age related differences in these interactions. The first two aims of this dissertation focused on the interaction between mental fatigue and neuromuscular fatigue, while the third aim focused on the impact of mental fatigue on postural stability. The last aim focused on age related differences in these interactions and in function.

In the first study, neuromuscular function measures in the tibialis anterior of young and older adults (transcranial magnetic stimulation, electrical stimulation, and force measurements) were investigated before and after mental fatigue (20-minute psychomotor vigilance task). Significant decreases in MVC force were observed only in young women. However, cortical silent period was increased in both young and older groups, suggesting that mental fatigue may cause increased cortical inhibition. Measures of neuromuscular function (contractile properties of the muscle, M_{Max}) did not change, suggesting that changes in force production with mental fatigue are more likely due to supraspinal than peripheral mechanisms. These results suggest that 20 minutes of a mentally fatiguing task may cause a decrease in the ability to produce maximal force in young but not older adults, providing evidence of an interaction between mental fatigue and physical function.

To our knowledge, this study, presented in chapter 2, is the first study using TMS to examine the effects of mental fatigue on neuromuscular function and one of the few

studies examining peripheral measures of neuromuscular function in response to mental fatigue. Further examination of the neuromuscular system at the level of the motor unit may be helpful in identifying additional factors that could have contributed to the decline in force that was observed in the young females. We demonstrated that mental fatigue lengthened cortical silent period in all groups. However, we do not know the mechanism behind this change. Examining changes in neurotransmitter concentrations with a mentally fatiguing task could help elucidate changes that take place at the cortical level that may be influencing the increase in CSP we saw. Further research on physiological mechanisms behind mental fatigue could be helpful in explaining the chronic and debilitating mental fatigue that is often experienced in certain medical conditions such as chronic fatigue syndrome, post poliomyelitis, stroke, and multiple sclerosis [4,166].

The second study examined the effect of neuromuscular fatigue on cognitive function in young and older adults. Measures of cognitive function (reaction time and errors during a 3-minute cognitive task) were taken before and after a 16-minute intermittent isometric contraction of the tibialis anterior in young and older adults. Significant decreases in MVC force were observed in all groups, suggesting that neuromuscular fatigue was present and not different among groups. Measures of neuromuscular function (slowed HRT, smaller M_{Max}) and cortical function (increased CSP) significantly changed, suggesting that changes in force production with neuromuscular fatigue in the present study were due to several factors, including: slowing of neuromuscular propagation, reuptake of Ca^{2+}, and an increase in cortical inhibition. Neuromuscular fatigue increased self-reports of fatigue but only negatively affected cognitive function (increased reaction time) in young adults. These results suggested that

a neuromuscular fatigue task may negatively affect cognitive function in young but not older adults. Providing evidence of an interaction of neuromuscular fatigue on cognitive function.

Many studies have examined the acute effects of exercise on cognitive function in young adults and have shown facilitation of cognitive tasks such as: choice reaction time, simple reaction time, decision making, and concentration [167]. We did not find a facilitating effect of acute exercise on cognitive function in younger adults in the present study. Though not significant, older adults experienced faster reaction times in the cognitive task after neuromuscular fatigue. A presumed increase in dopamine levels or levels of arousal with exercise, in the present study, may have acted to improve cognitive and motor function in the older adults, leading to faster reaction times. Further research is warranted to determine the mechanisms behind differences in cognitive function between young and older adults with neuromuscular fatigue or acute bouts of exercise.

The third study examined the effects of mental fatigue on responses to postural perturbations in the sagittal plane in young and older women. Measures of center of pressure displacement and corrective center of pressure velocity as well as electromyography of the medial gastrocnemius were obtained during a control condition (watching a nature video) and mental fatigue condition (20-minute psychomotor vigilance task). Older women had slower reaction time, longer EMG onset times, larger anterior-posterior center of pressure displacement, and faster center of pressure velocity than younger women overall. However, only young women experienced mental fatigue (slower PVT reaction times) and this was accompanied by significantly faster COP velocity during the mental fatigue condition than the control condition. Further, there was

a significant relationship between PVT reaction time and COP velocity in young women but not in older women, where the degree of change in reaction time was significantly related to the degree of change in peak velocity. These results suggest that mental fatigue affects the efficiency of response (increased COP velocity, EMG onset) but not the response (no change in COP displacement) to postural perturbations in young women only.

When examining the effect of a mentally fatiguing task on postural responses to unexpected perturbations we did not see any functional consequences of mental fatigue (increased displacement of center of pressure). This could be because the postural task that we used was not complex enough to involve voluntary control of movement which is, presumably, what would be affected by mental fatigue. Performance of the mental fatigue task, not necessarily the development of mental fatigue, affects neuromuscular activation in young women only, but does not affect the magnitude of postural response to perturbation. Further research using more complex postural tasks, to ensure that voluntary control of posture is occurring, is needed to determine if mental fatigue has an effect on postural control.

Implications and Future Research

These findings provide evidence to support the concept that fatigue has both physical and psychological components. Our findings suggest that mental fatigue has an influence on neuromuscular function and that neuromuscular fatigue influences cognitive function.

There was a discrepancy in mental fatigue experienced by older adults across studies 1 and 3. Older adults did not experience mental fatigue (lack of significant change in RT) in the postural control study (study 3), but they did in study 1. This difference may be explained by the amount of arousal experienced by the older adults. In study 3, fear of falling could have led to higher levels of arousal thus preserving RT performance (as discussed above). In study 2, the presumed arousal from 16 minutes of isometric dorsiflexor exercise acted to slightly, but not significantly, improve older adults' reaction times during the cognitive task. Previous research also indicates that arousal from exercise facilitates mental and memory processes [168]. Taken together, these results highlight the complex relationship between mental fatigue, arousal, and cognition, in older adults.

Older adults, especially older women, report higher levels of mental and physical fatigue [35,36]. Subjective fatigue ratings are a risk factor for various poor health outcomes in older adults including earlier onset of disability, slower gait speed, and increased risk of hospitalization [35,36]. Since the older adults in the present set of studies were habitually active and did not see any negative effects of mental fatigue on physical function (MVC force, COP displacement), this may suggest that staying active preserves and improves the ability of the neuromuscular response to mental fatigue which has important implications for healthy aging. The role of physical activity in mitigating the impacts of mental fatigue should therefore be studied further.

It has been demonstrated that mental fatigue has a negative effect on performance during cycling [5,10], running [11], knee extension [15], and, in the present study, dorsiflexion force. However, there is still little research on the physiological mechanisms explaining

the impact of mental fatigue on physical function. Our results suggest a potential role of intracortical inhibition, but future research focused on the physiological mechanisms are necessary. Such work will have important implications for healthy aging and medical conditions involving chronic fatigue. This set of studies provides a glimpse into the complex relationships between mental and neuromuscular fatigue and cognitive and neuromuscular function, providing many avenues for future research.

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