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Moderators of fatigue: the complexity of interactions

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MODERATORS OF FATIGUE: THE COMPLEXITY OF INTERACTIONS

by

Keith Gerard Avin

An Abstract

Of a thesis submitted in partial fulfillment
of the requirements for the Doctor of
Philosophy degree in Physical Rehabilitation Science
in the Graduate College of
The University of Iowa

May 2012

Thesis Supervisor: Associate Professor Laura A. Frey Law

ABSTRACT

Fatigue is a difficult phenomenon to study because the response can vary based upon task-specific (i.e. contraction type, intensity, position- vs. load-matching and muscle group/joint region) and subject-specific (i.e. sex and age) variables. Although numerous investigations have provided insight into muscle fatigue, further efforts were needed to better characterize the influence of age, sex, joint/muscle group, contraction type, and task complexity have upon fatigue. The primary purpose of this series of three studies was to identify and characterize the influences of potential moderating variables (i.e., sex, joint, age, contraction type, and task complexity) upon fatigue resistance during voluntary muscle contraction fatigue tasks through both empirical (systematic review and meta-analysis) and experimental methods. In general, women demonstrated either the same or better fatigue resistance than men (men never better), the sex advantage was joint specific not systematic, old men were more fatigue resistant than young men, task complexity was not an influential factor and fatigue differences were more readily apparent under isometric conditions. The inclusion of empirical and experimental methods helped clarify the driving factors of localized muscle fatigue. This in turn will better direct future study design and power for mechanistic, training and performance response studies.

Abstract Approved: ____________________________________
Thesis Supervisor

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Title and Department

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Date

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Graduate College
The University of Iowa
Iowa City, Iowa

CERTIFICATE OF APPROVAL

PH.D. THESIS

This is to certify that the Ph.D. thesis of

Keith Gerard Avin

has been approved by the Examining Committee
for the thesis requirement for the Doctor of Philosophy
degree in Physical Rehabilitation Science at the May 2012 graduation.

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Richard K. Shields

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To my family for all of their love and support.

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ABSTRACT

Fatigue is a difficult phenomenon to study because the response can vary based upon task-specific (i.e. contraction type, intensity, position- vs. load-matching and muscle group/joint region) and subject-specific (i.e. sex and age) variables. Although numerous investigations have provided insight into muscle fatigue, further efforts were needed to better characterize the influence of age, sex, joint/muscle group, contraction type, and task complexity have upon fatigue. The primary purpose of this series of three studies was to identify and characterize the influences of potential moderating variables (i.e., sex, joint, age, contraction type, and task complexity) upon fatigue resistance during voluntary muscle contraction fatigue tasks through both empirical (systematic review and meta-analysis) and experimental methods. In general, women demonstrated either the same or better fatigue resistance than men (men never better), the sex advantage was joint specific not systematic, old men were more fatigue resistant than young men, task complexity was not an influential factor and fatigue differences were more readily apparent under isometric conditions. The inclusion of empirical and experimental methods helped clarify the driving factors of localized muscle fatigue. This in turn will better direct future study design and power for mechanistic, training and performance response studies.

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CHAPTER 1

MODERATORS OF FATIGUE

Introduction

Fatigue encompasses a number of facets, affording many disciplines the ability to investigate its influence upon performance, injury, and quality of life. While research efforts investigating fatigue are an exciting and challenging field, the interdisciplinary nature sometimes lends to confusion as to what fatigue is and what is being measured. Fatigue may be described at a perceptual level as a feeling of tiredness (David *et al.*, 1990); at the physiological level as decrement in performance (reduction in force) (Bigland-Ritchie & Woods, 1984); or at the cognitive level as a decreased ability to concentrate (Barak & Achiron, 2006). The diverse nature of fatigue is attributed to the multiple contributing pathways; from the initial electrical response in the cortex of the central nervous system transmitted through the spinal cord to the peripheral muscle via the neuromuscular junction. Although it is understood these fatigue perspectives are not independent of one another, the nature of the current investigations assess localized muscle fatigue from the performance standpoint. In this context muscle fatigue has been defined as "any exercise-induced reduction in the ability to exert muscle force or power, regardless of whether or not the task can be sustained," (Bigland-Ritchie & Woods 1984); the "failure to maintain the required or expected force," (Edwards, 1981); and the "failure to continue working at a given exercise intensity" (Booth & Thomason, 1991).

The development of localized muscle fatigue depends on several factors, such as variation in muscle fiber type (Burke *et al.,* 1973), motor unit distribution/activation (Bigland-Ritchie & Woods, 1984), neural activation (Clark *et al.,* 2005), absolute force/muscle cross-sectional area (Hunter & Enoka, 2001), and/or task dependency (Enoka, 1992). The concept of fatigue task dependency identifies the manner in which fatigue occurs is specific to the context under which it was measured. The nature of task dependency may be extended to include various task-specific variables, such as: contraction type, intensity, position- vs. load-matching (i.e. maintaining a target angle or target force), and muscle group/joint region. To further the complex nature of fatigue, subject-specific variables such as sex and age may influence performance (see Figure 1-1). Although there are numerous investigations of muscle fatigue, efforts to fully describe the various influences of each factor on fatigue remain lacking. Therefore the aims of this series of projects are to better characterize localized muscle fatigue, focussing on the influences of age, sex, joint/muscle group, contraction type, and task complexity from both empirical (systematic review and meta-analysis) and experimental means.

Significance

The ability to successfully complete a task over a period of time for work, health, sport, and/or daily living, is dependent upon the proper integration of neural, contractile and metabolic systems. Interestingly, how these systems respond are highly dependent upon the context in which they are tested (task dependency) (Enoka, 1992). It is not clear how the integration of these systems differs within (i.e. joint/muscle group) or between (i.e. age, sex) persons. Accordingly, to fully understand fatigue processes proper characterization of fatigue moderators must first be performed. Proper characterization of fatigue moderators will in turn direct future studies with a mechanistic focus, modeling of human capabilities, and direct therapeutic prescription. Therapeutic exercise prescription should be administered with the same understanding of a dose-response relationship as aspirin, per se. Therefore, irrespective of mechanism, fully characterizing fatigue capabilities by sex, age and joint will clarify how to properly dose. In particular, if the elbow demonstrates different fatigue properties than the knee; men differently than women; and old differently than young; one global exercise prescription may be incorrect. While specific instances of deficiencies can be identified for all cohorts, this lack of knowledge may be particularly troubling for older adults whose quality of life and independence may be influenced. Therefore, it is important to first globally characterize fatigue by their moderators.

Fatigue Moderators

Contraction Intensity

One of the earliest clearly-identified moderators of fatigue is contraction intensity, which was first modeled by Rhomert more than 50 years ago (Rhomert, 1960). Studied under isometric conditions, there is a non-linear decay in maximum endurance time (MET) with increased task intensities; where MET is the duration a given contraction level can be sustained. This relationship has been utilized for decades in the ergonomics arena as the primary predictor of work performance as it relates to muscle fatigue. Over the years, various similar models have been published (Monod & Scherrer, 1965; Hagberg, 1981; Huijgens, 1981; Sato *et al.,* 1984; Manenica, 1986; Sjogaard, 1986; Kahn & Monod, 1989; Mathiassen & Ahsberg, 1999; Rose *et al.*, 2000; Garg *et al.*, 2002) with variations in the underlying model (power versus exponential curves) and joint-specific nature of the relationship. In a recent manuscript, we aggregated 197 publications resulting in a total of 369 data points to model this exponential decay in MET with increased contraction intensity (see Figure 1-2) (Frey Law & Avin, 2010). We demonstrated that the steady pattern of decay across such a large number of studies with varying subject pools supports a power relationship between intensity and fatigue resistance (i.e. MET).

Joint-Differences in Fatigue

Although fatigue resistance has been well-described at the single muscle and clearly differs between fiber types (Burke *et al.* 1973), less attention has been given to whether fatigue varies systematically between muscle groups or joint regions. Prior studies that have attempted to investigate between-joint differences were limited by small subject pools, small number of female subjects, along with contrasting and inconclusive results (Alizadehkhaiyat *et al.,* 2007; Clarkson *et al.,* 1980; Nagle *et al,* 1988; Ohashi, 1993; Petrofsky *et al.,* 1976; Smolander *et al.,* 1998; Urbanski *et al.,* 1999; Zattara-Hartmann *et al.,* 1995). In our recent meta-analysis, we determined that the decay in MET significantly varied between joint regions (Frey Law & Avin, 2010), where the ankle and trunk muscles were most fatigue resistant and the shoulder muscles were the most fatigable, with knee, elbow and hand/wrist falling within the two extremes (see Figure 1-3).

Several factors may partially contribute to these between-joint differences, such as variations in muscle mass and intramuscular pressure (and subsequent reduced blood flow) (Hicks *et al.,* 2001), muscle or fascicle length (Mademli & Arampatzis, 2008), activation strategies and descending motor drive (Seki & Narusawa, 1996), muscle fiber type (Burke *et al.,* 1973), and/or muscle temperature (Petrofsky & Laymon, 2005). For example, it has been suggested that larger muscle mass may result in reduced fatigue-resistance during sustained isometric contractions (Hunter & Enoka, 2001; Hicks *et al.,* 2001). However, this is not consistently observed as reduced endurance was associated with higher handgrip peak force, but not reduced forearm blood flow (Thompson *et al.,* 2007), and the relatively small rotator cuff muscles of the shoulder fatigued more rapidly than the larger knee extensors (Frey Law & Avin, 2010). Similarly, while muscle fiber-type likely differs somewhat between these joint regions, the proportionate differences are not large in humans for most muscles throughout the body (Burke, 1973). Thus, while we have advanced our understanding of how joint region influences fatigue resistance, we cannot fully explain why these differences exist.

Sex-Differences

Several authors have referred to females as being more fatigue resistant than males for a variety of tasks, including: isometric force-matching (Hunter & Enoka, 2001; Hunter *et al.*, 2002), isometric position-matching (Hunter *et al.*, 2002), and isometric contractions with intermittent rests (Russ *et al.*, 2002). Many factors have been considered to explain observed sex differences in fatigue resistance, including muscle mass differences (i.e., peak torque) (Hunter *et al.*, 2004; Hunter & Enoka, 2001), hormonal influences (Hicks *et al.*, 2001), muscle activation strategies (Hunter *et al.*, 2004; Ohashi, 1993) and/or noxious afferent feedback (Hunter, 2009b). However others have reported no sex differences in fatigue resistance with isometric force-matching tasks (Gamet & Maton, 1989; Ulmer *et al.*, 1989). In a recent review, Hunter *et al.,* (2009b) suggests that fatigue resistance can vary by sex and context (i.e. contraction mode, contraction intensity, position- versus load-matching tasks, age, and muscle group). Thus, stating that a sex difference exists is an over simplification.

Sex-Joint Interactions

In particular, a review of several fatigue studies suggests there are differences in the sex effect between elbow flexor and ankle dorsiflexor muscles, where females are more fatigue-resistant at the elbow but not at the ankle (Hunter *et al.*, 2009b). However, this comparison has never been directly assessed in the same cohort of individuals. Thus, these apparent sex differences between muscle groups could simply be due to cohort or methodological variance. Thus, it is not clear whether a female advantage is systemic as suggested by several of the mechanisms proposed to explain observed sex-differences (Hicks *et al.*, 2001) or joint specific, as we know fatigue-resistance can vary between joints (Frey Law & Avin, 2010). The intention of project one is to add clarity to the sex-joint interaction of fatigue resistance.

Age – Related Differences

Older adults are generally thought to be more fatigue resistant than their younger counterparts for a given relative intensity task (Lanza *et al.*, 2004). While overwhelming majorities have found the older adult to be more fatigue resistant, it is commonly observed under isometric conditions (Bazzucchi *et al.*, 2005; Bilodeau *et al.*, 2001; Huang *et al.*, 2007; Hunter *et al.*, 2004; Hunter *et al.*, 2005; Petrofsky & Lind, 1975; Yassierli *et al.*, 2007; Yoon *et al.*, 2008). Under dynamic conditions the results are not quite as clear with varying results. A number of hypotheses have been proposed to explain an age-contraction type interaction, such as: contractile slowing, impaired peripheral blood flow, impaired central drive, substrate utilization efficiency, and task complexity, but to date no clear mechanism has been identified (Allman & Rice, 2001; Hunter, 2009a; Lanza *et al.*, 2004, Tevald *et al.*, 2010). Therefore the purpose of projects two and three will be to examine several underlying factors which may explain an age-contraction type interaction.

Age – Contraction Type Interactions

Several studies have assessed differences in muscle fatigue resistance between young and old adults for isometric and isokinetic contractions with contrasting outcomes. Isometric tasks clearly identify the old adult is more fatigue resistant. However, for isokinetic tasks old adults have been more fatigue resistance (Lanza *et al.*, 2004; Rawson, 2009); less fatigue resistant (Lindstrom, 2006) and no difference (Callahan *et al.*, 2009). A small number of studies performed two different contraction types (isometric and isokinetic) within a study protocol, but with little resolution (see Table 1-1). In three of the four isometric studies older adults were significantly more fatigue resistant with varying effect sizes from medium to large. While for isokinetic tasks three of the four studies found no significant difference, with one study demonstrating a large and significant effect size. It is clearly demonstrated that older adults are more fatigue resistant under sustained isometric conditions, but less clarity exists under isokinetic conditions.

Muscle perfusion is thought to be a mediating factor that underlies the loss of an age-related advantage under dynamic conditions. Attenuated blood flow to the periphery may explain an age-contraction type interaction because under isometric conditions reduced perfusion may lead to lower intramuscular pressure, and less comparative ischemia resulting in greater fatigue resistance. However, during dynamic activity reduced perfusion would theoretically lead to greater fatigue (Hunter, 2009a). Whether muscle perfusion is a contributing factor to the differences observed between isometric and isokinetic contractions may be clarified using intermittent isometric contractions.

Intermittent isometric and isokinetic contractions share similar characteristics of muscle reperfusion, replenishment of oxygenated blood, and removal of metabolic wastes. If muscle perfusion explains an age-contraction type interaction, then intermittent muscle contractions would assumingly display a pattern similar to isokinetic contractions. However, if muscle perfusion does not explain this disparity then intermittent and sustained isometric contractions should behave similarly.

Despite the number of available muscle fatigue studies, these data have not been systematically compiled in an attempt to better estimate a “true” effect size of fatigue resistance. To date, only small scale reviews have provided insights in subsets of the research available, to ascertain age-related differences in muscle fatigue properties (Kent-Braun, 2009; Allman & Rice, 2002). Therefore, the second project was directed towards identifying 1- if an interaction between age and contraction type exists and 2- whether intermittent isometric fatigue resistance behaves similar to sustained isometric or isokinetic contractions.

Age - Task Complexity Interactions

To date, a conclusive outcome has not been reached regarding age-related contraction type dependent fatigue resistance. However it does appear there may be a loss of an age-related fatigue resistance advantage under isokinetic conditions (no difference between old and young). While a number of theories have been proposed on such identifies task complexity as a contributory factor (Lanza *et al.*, 2004). It is proposed that the demands placed upon the central nervous system (CNS) are relative to the demands of the task (i.e. simple task has low demands, complex task has high demands). However, older adults undergo adaptations (i.e. reduced cortical excitability, reduced cortex size, impaired cognitive function) that may impair their ability to optimally respond to an increasingly complex task (Drag & Bieliauskas, 2010). Age-related differences in task complexity have been explored primarily within dual-task paradigms (Brown et al., 1999; Maylor & Wing, 1996; Stelmach *et al.*, 1990). These studies have found that tasks of increased complexity are of greater detriment to the older adult (vs. young adult) because motor performance requires greater cognitive resources in old age (Woollacott & Shumway-Cook, 2002). However this information is gleamed from dual task design and has not been demonstrated in isolated tasks of varying complexity.

In short-duration non-fatiguing tasks, force variation in a force-matching task is clearly negatively impacted by task complexity in the older adult. The older adult demonstrates less variance for a simple task (sustained isometric) compared to the young adult. However, under a complex task (sinusoidal isometric) the results are reversed with the younger adult demonstrating less variance (Figure 1-4) (Vaillancourt & Newell, 2002; Sosnoff & Newell, 2008). The relevance of torque variance (i.e. force fluctuations) is greater variance has been hypothesized to lead to greater fatigue (less fatigue resistance) (Hunter *et al.*, 2004). To date, experiments have not been extended to determine how task complexity influences localized muscle fatigue resistance. It is theorized that the older adult may have greater difficulty processing more complex tasks and lead to greater declines in fatigue resistance; this may explain the difference between isometric (simple) and isokinetic (complex) contractions.

Purpose

The primary purpose of this series of three studies is to identify and characterize the influences of potential moderating variables (i.e., sex, joint, age, contraction type, and task complexity) upon fatigue resistance during voluntary muscle contraction fatigue tasks. The long-term goal of these efforts is to be better able to predict the development of fatigue. This information may benefit the planning and implementation of rehabilitation and therapeutic interventions as well as the development of accurate models for injury prevention.

Specific Aims & Hypotheses

To achieve this purpose, three specific aims will be addressed.

Specific Aim 1: To determine whether sex-differences in localized muscle fatigue resistance are systemic (across joints) or specific to joint regions.

Hypothesis 1: Females will demonstrate greater fatigue resistance at both the elbow (flexor muscles) and ankle (dorsiflexor muscles) joints, indicating that a sex-advantage is systemic in nature.

Rationale: Females have consistently demonstrated a fatigue resistance advantage, particularly at the elbow. While this advantage is typically demonstrated under isometric conditions at the elbow (primarily flexor muscles), with less consistent findings observed at other joints, it is one of the most commonly studied joint regions, providing a model to better understand fatigue behavior. Thus, we propose observed joint-dependent sex-differences are likely a result of differences in cohorts and/or study methodologies and not evidence for regional sex-differences as opposed to widespread, systemic differences. This information is needed to help us better understand the degree to which sex differences exist and the potential underlying mechanisms that may explain them.

Specific Aim 2: To determine whether localized muscle fatigue resistance differs between young (18-45 years) and old (>55 years) adults, considering contraction-type (sustained isometric, intermittent isometric, and isokinetic).

Hypothesis 2: Older adults will demonstrate greater fatigue resistance (i.e. significant effect size) for sustained isometric contractions, but not for intermittent isometric or isokinetic contractions (i.e., smaller or insignificant effect sizes).

Rationale: Numerous studies have demonstrated enhanced endurance times for older adults when performing a relative intensity sustained isometric task (i.e., the typical approach to standardize tasks across individuals) (Bazzucchi *et al.*, 2005; Bilodeau *et al.*, 2001; Huang *et al.*, 2007; Hunter *et al.*, 2004; Hunter *et al.*, 2005; Petrofsky & Lind, 1975; Yassierli *et al.*, 2007; Yoon *et al.*, 2008). Conversely, some investigators have observed no differences in fatigue resistance with age, particularly those involving dynamic contractions (Callahan *et al.*, 2009; Johnson, 1982; Mademli *et al.*, 2008). One theory proposed to explain the difference in age-related fatigue between static and dynamic contractions is that of muscle perfusion (Hunter, 2009a). Accordingly, this provides the rationale for our hypothesis that the older adult will be more fatigue resistant for isometric contractions, with the most limited muscle perfusion, but no difference will be exhibited for intermittent isometric and isokinetic contractions, where muscle perfusion is less restricted. The similarity between intermittent and isokinetic contractions is based upon rest allowance, while the contraction types are different, they both afford reduced muscle ischemia and filtration of particulates.

Specific Aim 3: To determine if contraction-specific differences in age-related fatigue resistance are influenced by the complexity of the task.

Hypothesis 3: Age-related differences in fatigue are dependent upon task complexity. Older adults will demonstrate greater fatigue resistance than young adults for the simple isometric task, but less fatigue resistance for complex (sinusoidal isometric and isokinetic) tasks.

<u>Rationale:</u> Older adults have demonstrated a greater decrement than young adults in performance of increasingly complex tasks both in dual task and isolated non-fatiguing task paradigms (Brown *et al.*, 1999; Maylor & Wing, 1996; Sosnoff and Newell, 2008; Stelmach *et al.*, 1990; Vaillancourt & Newell., 2003). This evidence suggests an interaction between task performance and task complexity. Applying these same principles to localized muscle fatigue tasks would suggest that the underlying physiologic adaptations to aging will not be hindered by the complexity for the simple tasks (i.e., older adults will demonstrate greater fatigue resistance under isometric (simple) conditions). Whereas when cognitive demands escalate, a greater reserve of cognitive resources may negate the physiologic fatigue advantage and therefore no net advantage is observed.

Table 1-1. Effect sizes from studies performing isometric and isokinetic contraction types in the same cohort.

Author, Year	Isometric effect size (p-value)	Isokinetic effect size (p-value)
Callahan et al., 2009	1.16 (0.002)	0.085 (0.816)
Johnson, 1982	0.322 (0.365)	-0.31 (0.387)
Lanze et al., 2004	0.54 (0.242)	1.72 (0.002)
Mademli et al., 2008	1.2 (0.005)	0.31 (0.421)

∗ (+ older better fatigue resistance; - young more fatigue resistant) and p-value for significance of effect size.

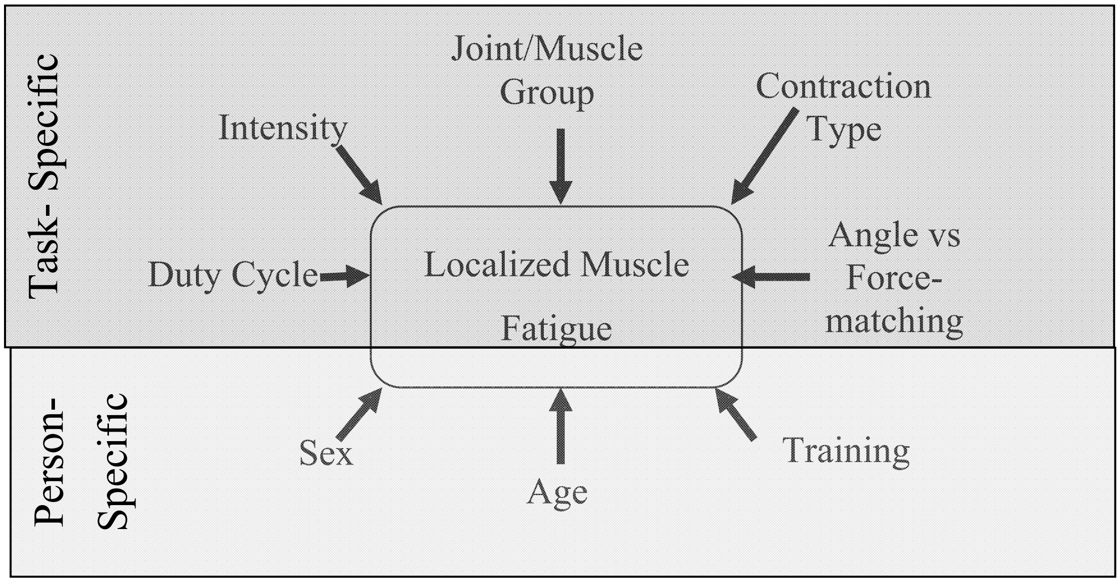


Figure 1-1. Schematic of moderating factors of fatigue.

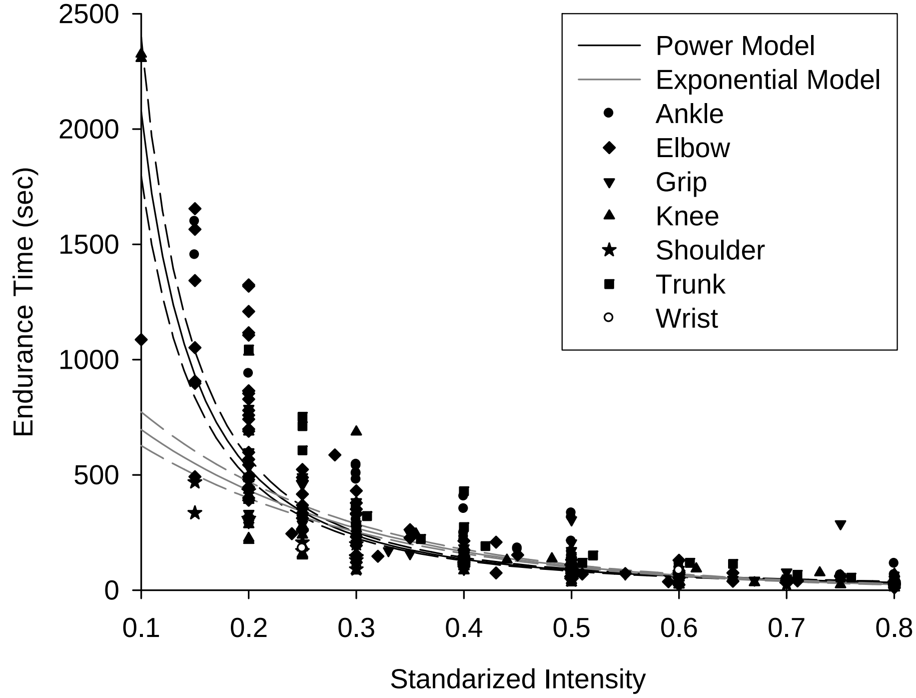


Figure 1-2. The nonlinear decay in endurance time (fatigue) with increasing intensity (workload) during sustained isometric tasks follows a power function.

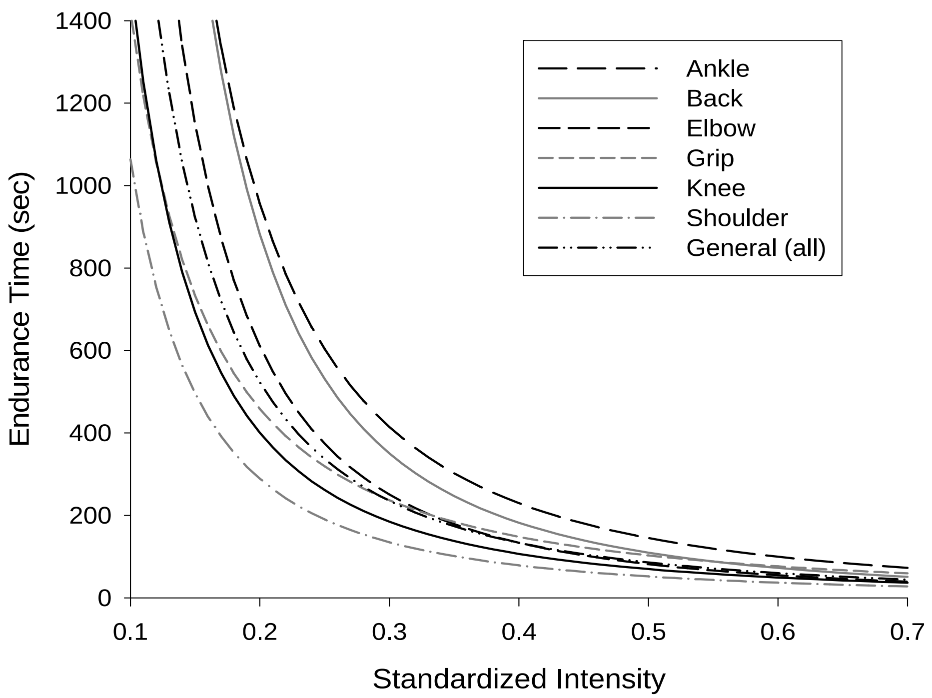


Figure 1-3. Joint-specific power fatigue models are plotted to demonstrate relative differences in fatigue resistance (endurance time, ET) as a function of contraction intensity: ankle (solid, dashed); trunk (solid, gray); grip (short-dash, gray); elbow (long-dash, black); knee (solid, black); shoulder (dash-dot, gray). The general model is also shown (dash-dot-dot, black). Note, greater fatigue-resistance is predicted by longer ETs at a given intensity (e.g. ankle versus shoulder).

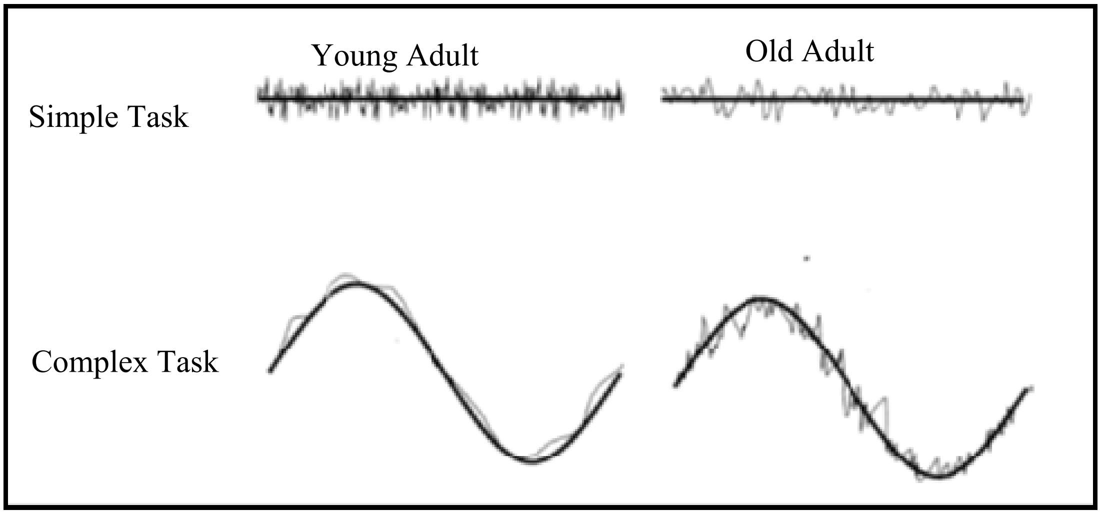


Figure 1-4. Schematic of common findings in old vs young force-matching paradigms where olds adults are less variable for the simple task, but more variable for the complex task as compared to young adults (Adapted from (Yates 1988)).

CHAPTER 2

SEX DIFFERENCES IN FATIGUE RESISTANCE ARE MUSCLE GROUP DEPENDENT

Introduction

Females have demonstrated greater fatigue resistance for a variety of tasks, including: isometric force-matching (Hunter *et al.*, 2001; Hunter *et al.*, 2002) isometric position-matching (Hunter *et al.*, 2002), and isometric contractions with intermittent rests (Russ *et al.*, 2002). Several factors have been considered to explain observed differences in fatigue resistance, ranging from muscle mass differences to hormonal influences (Hicks 2001). However others have reported no sex differences in fatigue resistance with isometric force-matching tasks (Gamet & Maton, 1989; Ulmer *et al.*, 1989). In a recent review, Hunter (2009b) suggests sex differences in muscle fatigue can be influenced by task specificity; encompassing contraction mode, contraction intensity, position- versus load-matching tasks, cognitive load, age, and muscle group (Hunter *et al.*, 2009b). Thus, the statement that females are more fatigue resistant than males for relative intensity tasks is clearly an over simplification.

In particular, a review of several fatigue studies suggests there are differences in the sex effect between elbow flexor and ankle dorsiflexor muscles (Hunter *et al.*, 2009b). However, this comparison has never been directly assessed in the same cohort of individuals. Thus, these apparent sex differences between muscle groups could simply be due to cohort or methodological variance. Other potential mediating factors may include: peak torque (Hunter *et al.*, 2004, Hunter *et al.*, 2001), muscle activation strategies (Hunter *et al.*, 2004, Ohashi 1993), and/or noxious afferent feedback (Hunter *et al.*, 2009b). Whether these factors contribute to sex differences or vary between muscle groups is not clear.

Thus, the primary purpose of this study was to examine sex differences in fatigue resistance at two distinct muscle groups, the elbow flexors and the ankle dorsiflexors; considering several potential contributors to fatigue. These factors included: peak torque, self-reported activity level, muscle activation strategy, perceived pain, perceived exertion, and rate of increase for pain and exertion. This finding may help to better elucidate the underlying mechanisms contributing to sex differences in fatigue resistance. For example, if fatigue differences are indeed muscle group specific, local (e.g. muscle mass) rather than systemic (e.g. hormonal milieu) mechanisms are likely to be responsible for this phenomenon. This information may be used to better discern whether sex differences are widespread or localized phenomena. An improved understanding of factors influencing fatigue may be useful for mathematical fatigue modeling applications as well as impact optimal training and performance in sport, exercise, and rehabilitation applications.

Methods

Subjects

Thirty-two (16 male, 16 female) recreationally-active young adults participated in this study (see Table 2-1 for subject demographics). All subjects were classified as healthy with no major medical history, including: cardiovascular disease, asthma, diabetes, elbow or ankle major joint trauma, neuromuscular disease or chronic pain conditions. Subjects who were college- or professional-level athletes were excluded due to their unique level of training. Prior to participation all subjects provided written, informed consent. The study procedures were approved by the University of Iowa Institutional Review Board. All participants were reimbursed for their time.

Experimental Procedures

Subjects performed isometric force-matching fatigue tasks at 50% maximal voluntary isometric contraction (MVIC) for both elbow flexion and ankle dorsiflexion during one visit. The order of testing was block-randomized by sex to minimize any fatigue effects. A 20 min rest was provided between the two fatigue tasks, during which time participants completed the activity questionnaire.

Fatigue Task

The fatigue task for each muscle group started with a 5-minute warm-up on a stationary bike, followed by assessing maximum torque generating capability using a Biodex Isokinetic Dynamometer System 3 (Biodex Medical Systems, New York). Maximum torque was operationally defined as the maximum of three MVIC trials separated by 1 minute rests. The fatigue task was then performed using the isokinetic dynamometer at 50% MVIC until volitional failure with visual and verbal feedback. Failure was operationally defined as the inability to maintain torque within 10% of the target level for five seconds or falling below the target level three times within a 30 second window. For the elbow flexion fatigue task, subjects were seated, with the forearm positioned at 60° of elbow flexion, and the shoulder flexed approximately 30°. For the ankle dorsiflexion fatigue task, subjects were tested in a seated position with the knee flexed approximately 90° and the ankle positioned at 20°of plantarflexion.

Perceptual ratings

Participants were asked to verbally rate their pain and exertion throughout and immediately following the fatigue tasks using the Borg Category Ratio 0-10 numeric rating scale (Borg CR10)(Borg, 1998). A written script, modified from Borg (1998), was read to each participant to ensure consistent instructions for scale use. The peak values were extracted for further analysis. The mean rate of change for pain and exertion were calculated using linear regression techniques for each individual subject (i.e., slope of each rating vs. time relationship). Immediately following the fatigue protocol for both the ankle and elbow, participants completed the McGill Pain Questionnaire – short form (SF MPQ). The SF MPQ is comprised of 3 subscales, providing both qualitative and quantitative pain assessments. Participants rated their pain using 15-adjective verbal descriptors, a 10 cm horizontal visual analog scale (VAS), and a 6-point evaluative scale.

Demographic Data

Height (cm) and weight (kg) were measured using calibrated scales to document subject demographics. Activity levels were assessed using the International Physical Activity Questionnaire (IPAQ), a self-report measure of activities performed in the past 7 days (Craig *et al.*, 2003. Assessments include estimates of leisure; domestic and gardening; work; and transportation related physical activities. Calculated algorithms based upon activity levels classify the participant as low, moderate or high physical activity (Craig *et al.*, 2003).

Muscle activity

Muscle activity was measured using 4 channels of surface muscle electromography (EMG, Delsys Bagnoli, Boston, MA), band pass filtered from 20 – 450 Hz. For the elbow, EMG electrodes were attached to the skin over the biceps brachii, brachioradialis, triceps brachii, and upper trapezius muscles. For the ankle, EMG electrodes were attached to the skin over the tibialis anterior, medial and lateral gastrocnemius and soleus muscles. The skin was prepared with 70% alcohol wipes and electrodes were adhered using medical-grade adhesive tapes. The EMG signals are pre-amplified peripherally at the electrode (10 times) and again prior to analog-to-digital conversion (1000 times) to maximize signal quality.

Data Analysis

All torque and EMG signals were collected using custom Labview (National Instruments) software at 1000 Hz. Torque signals were low-pass filtered at 10 Hz. Absolute and normalized (by body mass) peak torque values were used in the analyses. Times to fatigue were determined from the torque tracings offline, and corroborated with stop-watch results collected during each fatigue trial. The EMG data were rectified, filtered using a moving average with a 200ms window and standardized by their respective maximum EMG values. EMG data were averaged across each successive 5% time interval from 0 to 100% endurance time for each muscle.

Statistical Analysis

Summary statistics were calculated for endurance time, peak torque, peak torque normalized by body mass, peak pain and exertion, mean rate of change for pain and exertion, surface EMG, and demographic data. Data are reported as mean ± standard error of the mean (SEM) within the text and figures. Independent and paired t-tests were used to compare endurance time and peak torque between sexes for each muscle group, and secondarily between the two muscle groups. Repeated measures analysis of variance (ANOVA) was used to compare EMG amplitude between sexes and between muscle groups at 25, 50, and 75% of task duration, with follow-up paired t-tests as appropriate. Effect sizes (Cohen's d) were calculated for between-joint and between-sex differences. Large effect sizes were operationally defined as d values of 1.0 or greater. Correlation analyses assessed the relationships between endurance time and the following variables: peak torque, normalized peak torque (peak torque/body mass), peak pain, peak exertion, rate of pain increase, rate of exertion increase for each muscle group separated by sex. Stepwise, linear regression techniques were utilized to model endurance time for each muscle group as a function of sex, peak torque, rate of pain or exertion, and activity level.

All statistical analyses were performed using SPSS (v16.0, Chicago, IL), with alpha set at 0.05.

Results

Subjects

Subject demographics are provided in Table 2-1. Men were heavier and taller than women but age and activity levels were not significantly different. Self-reported activity levels were predominantly in the moderate (n = 15) and high activity (n= 15) levels, with only 1 in the low range, based on normative data for the IPAQ (Craig *et al.*, 2003). One subject's IPAQ data was excluded as the survey was not completed correctly.

Endurance Time

Females (112.3 ± 6.2 sec) were significantly more resistant to fatigue than males (80.3 ± 5.8 sec) for elbow flexion (p=0.001; see Figure 2-1). Conversely, no significant difference (p=0.45) in endurance time occurred between females (140.6 ± 10.7 sec) and males (129.2 ± 10.5 sec) for the ankle dorsiflexion task. The corresponding effect sizes (Cohen's d) for the observed sex-difference were large for the elbow flexors but small for the ankle dorsiflexors (Table 2-2). Comparing endurance times between muscle groups revealed that ankle dorsiflexion was more resistant to fatigue than elbow flexion for both females (Δ 28.3 s; p= 0.021) and males (Δ 48.9 s; p< 0.001). The corresponding effect sizes for the ankle to elbow muscle group differences were 0.85 and 1.49 for females and males, respectively.

Peak Torque

Males exhibited greater peak torque (p < 0.0001) than females (Figure 2-1B) at both the ankle (45.0 ± 1.7 Nm vs. 30.1 ± 1.0 Nm, respectively) and the elbow (75.7 ± 3.1 Nm vs. 34.4 ± 2.2 Nm, respectively). Similar differences were observed for normalized peak torque (Figure 2-1C) for males and females, respectively at the ankle (0.58 ± 0.02

Nm/kg vs. 0.51 ± 0.01 Nm/kg) and the elbow (0.97 ± 0.03 Nm/kg vs. 0.58 ± 0.03 Nm/kg). The corresponding effect sizes for peak torque sex differences were large for both muscle groups (Table 2-2). Peak torque and normalized peak torque were significantly related to endurance time at the elbow (Figure 2-2A and 2-C), but not at the ankle (Figure 2-2B and D).

Peak torque and normalized peak torque were significantly greater for the elbow flexors than the ankle dorsiflexors for males ($p< 0.0001$) but did not reach significance ($p > 0.06$) in females. Accordingly, the effect sizes for the between-joint peak torque differences were large for males (3.16) but only medium for females (0.65).

Muscle Activity

EMG data was incomplete due to data collection complications during the ankle (n=4) and elbow (n=6) fatigue tasks, thus sample sizes were reduced for the muscle activity analyses. Using the ANOVA, mean EMG increased significantly over time during the 50% fatigue tasks for both muscle groups and sexes ($p < 0.0001$; Figure 2-3). Muscle activity did not vary between males and females ($p = 0.13$). However, EMG was significantly higher at the elbow than the ankle overall ($p = 0.001$), and increased at a greater rate than the ankle ($p = 0.04$). Follow-up paired t-tests at 25, 50 and 75% of total endurance time were further analyzed to determine if one muscle group was consistently greater. These tests revealed elbow muscle activity was significantly greater than ankle muscle activity at each relative time point assessed: 25% ($p = 0.012$), 50% ($p = 0.003$), and 75% ($p = 0.001$) of endurance time.

Perceived Pain and Exertion

Both males and females reported similar peak pain and exertion ratings across both muscle groups (Figure 2-4A and C, $p > 0.15$). The absolute time of each fatigue task did not appear to influence peak perceptual ratings, as females were able to sustain the elbow task longer than males with no significant difference in peak ratings. The ankle fatigue task was reported to be significantly more painful than the elbow task across all subjects (Figure 2-4A, $p = 0.016$), but did not achieve significance when considering only male ($p = 0.08$) or female ($p = 0.09$) subjects separately. Peak exertion did not vary between muscle groups (Figure 2-4B, $p = 0.24$). The mean pain increase per minute did not vary between sexes or muscle groups (Figure 2-4B and D, $p > 0.65$). However men reported significantly faster increases in perceived exertion at the elbow ($p = 0.002$) than females; resulting in a significant overall difference between muscle groups ($p = 0.003$). The most frequently identified qualitative pain descriptors on the SF MPQ immediately post-fatigue for both tasks were “cramping,” “aching,” and “tiring/exhausting”.

No pain measures (peak or rate of change) resulted in significant correlations with endurance time.. In males, both ankle and elbow endurance times were related to exertion rate of change ($r = -0.81$ and -0.82, respectively). While in females, only ankle endurance time was correlated to exertion rate of change ($r = -0.67$). Peak exertion did not significantly correlate with any endurance time variables.

Predicting Endurance Time

For the elbow, only sex was a significant predictor in the model to predict endurance time (considering peak torque, sex, and self-reported activity) using stepwise linear regression techniques ($R^2 = 0.30$). Once sex was accounted for, peak torque did not add any additional predictive information, but these two variables were collinear ($r = 0.89$). Thus, either variable provided essentially equivalent information (i.e., see Figure 2-2A). For the ankle, no linear regression model achieved significance, using peak torque, sex, and self-reported activity levels as possible predictors.

Discussion

The most notable findings of this study are: 1) the large sex differences in fatigue associated with sustained isometric contractions at the elbow were not observed at the ankle; 2) peak torque was a good predictor of fatigue-resistance only at the elbow; 3) muscle activation strategies differed between muscle groups, but not between sexes; 4) no sex differences were exhibited for peak pain or exertion ratings across both muscle groups; and 5) the ankle fatigue task was reported to be significantly more painful than the elbow task across all subjects.

The observed endurance times for both ankle dorsiflexion and elbow flexion are consistent with other published values (Hansen, 1967; Lowery *et al.*, 2002; Ohashi, 1993), suggesting our study population was not substantially different from other populations investigated. The observed sex differences for the elbow flexors (effect size, d = 1.4) are largely in accordance with previous findings at the elbow, with a median effect size of 0.8 from previous studies (range -0.7 to 3.9) (Calder *et al.*, 2008; Dimitrova *et al.*, 2009; Gamet & Maton, 1993; Hunter *et al.*, 2004; Hunter & Enoka, 2001; Hunter *et al.*, 2003; Hunter *et al.*, 2002; Yoon *et al.*, 2007). At the ankle, the median effect size was 0.1, (range -1.1 to 3.1) (Houtman *et al.*, 2001; Houtman *et al.*, 2003; Hunter *et al.*, 2008; Melbech & Johansen, 1973; *Ng et al.*, 2000; Shahidi & Mathieu, 1995), similar to that observed here (d=0.3). Thus, females consistently are significantly more resistant to fatigue than males for elbow flexors, but not for ankle dorsiflexors. Few other muscle groups have been systematically studied for sex differences, but the limited evidence available suggests sex differences may not be readily predictable, as shoulder abduction was not different between men and women, whereas trunk flexion was more fatigue-resistant in females(Yassierli *et al.*, 2007).

Historically, assessment of isometric endurance between men and women has been performed at single, not multiple muscle groups. Underlying differences in protocols and/or laboratory settings confounds the ability to conclusively evaluate regional versus systemic sex differences in fatigue-resistance. A limited number of studies include two-muscle group protocols, but typically had very small sample sizes and/or no representation of women. The current study demonstrates that sex differences in fatigue development during a sustained isometric force task are regional and muscle group dependent. Thus, the regional differences suggested in a recent review (Hunter *et al.*, 2009b) are further substantiated by our findings.

In studies that have observed fatigue sex differences, the most commonly postulated explanatory mechanisms can be parceled into: muscle mass / perfusion, neuromuscular activation, and substrate utilization. Hicks, *et al*., (2001) suggests that larger massed muscles may result in greater intramuscular pressure and blood flow occlusion at a given contraction intensity, resulting in more rapid fatigue when compared to smaller muscles. As peak torque is roughly proportional to muscle mass (via cross-sectional area), endurance time has been noted to decrease linearly (Hunter *et al.*, 2006) or exponentially (Thompson *et al.*, 2007) with increasing peak torque. However, in the current study, females were weaker than males for both muscle groups; yet only the elbow yielded a significant sex-difference in endurance time. In addition, peak torque explained 30% of the variance in endurance time at the elbow, but only 3% at the ankle. These findings suggests muscle mass may be one contribution to fatigue differences, but cannot fully account for variations in endurance time between men and women, particularly across bodily regions.

Additional vascular mechanisms, such as vascular reactivity and vasoconstriction, are not uniform throughout the body (Proctor & Newcomer, 2006); thus could influence muscle perfusion during a sustained fatiguing contraction. Clearly, the lower extremities are chronically exposed to elevated hydrostatic pressures in upright postures, suggesting upper and lower limbs may differentially respond to changes in intramuscular pressure. Sex differences have been documented in vasodilatation (Parker *et al.*, 2008); capillary fluid filtration (Lindenberger & Lanne, 2007); and blood flow during sustained (Thompson *et al.*, 2007) and brief maximal (Hunter *et al*, 2009b) contractions. However, blood flow and vascular conductance were not able to explain sex differences in fatigue using an intermittent contraction endurance task (Hunter *et al*, 2009b). Thus, it is not yet clear whether differential limb vascular response can potentially explain a portion of the regional fatigue sex differences observed between the elbow and the ankle.

Neuromuscular activation strategies, assessed via comparison of EMG amplitudes, were similar to previous studies with a gradual increase in activation over time during a submaximal isometric task (Fuglevand *et al.*, 1993; Hunter *et al.*, 2008). Unfortunately few, if any, studies have compared EMG activation between men and women at more than one muscle group. Consistent with previous sustained isometric tasks, that did not strength-match women, no sex differences in activation strategy were evident at the elbow (Hunter & Enoka, 2001; Hunter *et al.*, 2006). However, when matched for strength, conflicting results have been observed. For example, at the elbow women display a reduced rate of activation despite similar endurance times as men (Hunter *et al.*, 2004); whereas at the ankle, no sex differences in activation strategy or endurance time were observed (Hatzikotoulas *et al.*, 2004). Although not strength-matched, we also observed no difference in ankle activation strategy between men and women. However, both males and females consistently displayed greater EMG activity at the elbow compared to the ankle, suggesting activation strategies may vary more between muscle groups than between sexes. Thus, muscle activation does not appear to play a key mechanistic role in explaining the fatigue sex differences observed only at the elbow.

Another possible neuromuscular activation component which could result in apparent sex differences in fatigue is central activation. If women do not maximally activate during the MVIC testing, i.e. interpolated twitch techniques, then their relative-intensity target workload will be less than expected. A recent meta-analysis modeled endurance times as a function of task intensity for sustained isometric contractions at several joints (Frey Law & Avin, 2010). Using these models, the current 30 sec difference in endurance time observed between men and women at the elbow would require a difference in central activation of 14-16% between the sexes (e.g. 100% vs. 84 –

86%). It has been suggested that women are less able to achieve full central activation, similar to that seen in children (Dotan & Falk, 2010), although the available data is inconsistent. Central activation ratios did not significantly differ between men and women for the elbow flexors (≤ 4%) (17) or the ankle dorsiflexors (≤ 1%) (26) prior to or following a fatiguing task. Thus it is unlikely voluntary activation sufficiently explains the difference in endurance time observed for the elbow flexors.

Substrate utilization has been suggested as another mechanism that may contribute to differences in fatigue between men and women (Hicks *et al.*, 2001). Men may preferentially rely on glycolytic pathways (Russ *et al.*, 2005), whereas women may preferentially use oxidative processes for energy metabolism (Venable *et al.*, 2005). While this may contribute to sex differences in fatigue, particularly when evaluating fatigue-resistance across a range of relative intensities, it is not clear how differences in substrate utilization may help explain the sex differences observed at a single intensity at the elbow but not the ankle. It may reflect differential motor-unit activation between men and women or possibly differences in daily functional use of these two muscle groups (e.g. training) between the sexes (e.g. walking versus lifting and carrying). Future studies are warranted to specifically assess the effect of daily use patterns on fatigue sex differences.

Variations in endurance time across bodily regions may be readily explained by differences in muscle composition. Elbow flexors (biceps brachii) are predominantly composed of type II fibers (~61 ± 5% type II) (MacDougall *et al.*, 1984) whereas the ankle dorsiflexors (tibialis anterior) are composed of primarily type I fibers (~77 ± 7% type I) (Jaworowski *et al.*, 2002). These reported compositions mirror our observed endurance times, with the ankle dorsiflexors being more fatigue resistant than the elbow flexors overall. However, muscle composition has not been shown to significantly differ between men and women (Miller *et al.*, 1993). Thus, while muscle fiber composition may be the leading explanation for the fatigue differences between muscle-groups, it is less clear how muscle composition contributes to the sex differences observed predominantly for one muscle group. As previously mentioned, it may be that in muscle groups with greater type II fibers, women are better able to sustain contractions due to their preferential use of oxidative metabolism and activation of type I fibers. However, the relationship between muscle composition and fatigue resistance is complex and may vary by task intensity. Endurance times of the elbow flexor and extensor groups did not differ at 40% MVIC, but differed by more than 600% at 10% MVIC, despite similar compositions (Fallentin & Jorgensen, 1992).

Differential excitation between men and women of group III and IV afferents during fatigue may lead to differences in muscle activation and/or endurance time (Hunter, 2009). However, in this study neither rate of pain increase or peak pain varied between sexes. This differs somewhat from studies demonstrating sex differences in elicited pain response following isometric exercise (Hoeger Bement *et al.*, 2008; Koltyn *et al.*, 2001). Only the rate of exertion was significantly related to endurance time suggesting that nociceptive input was not a primary mechanism explaining the observed localized sex differences. Group III and IV afferents include a wide variety of afferent input, including nociceptive signals in response to changes in metabolite concentration. Thus afferent signals uniquely contributing to perceived exertion may be important.

Several study limitations warrant discussion as they may impact further interpretation. The lack of significant sex-difference in endurance time at the ankle may be a result that our study was underpowered to detect that level of effect size (0.3). Power analysis estimates indicate 178 subjects per group would be needed to detect this small effect size as significant ($p \leq 0.05$, $\beta = 0.2$). A small effect size would put into question the clinical relevance even if statistical significance was present with a sufficient sample size. A second potential limitation is that no methods such as interpolated twitch were employed to measure the degree of muscle activation during the MVIC, therefore we could not quantify if men and women were able to similarly fully activate their elbow flexor or ankle dorsiflexor muscle groups. Third, we caution against the extension of these results to additional muscle groups or tasks. Future studies are needed to better define whether sex differences in fatigue can be generalized across neighboring joints and/or extremities and to examine whether these muscle-dependent sex differences also occur with position-matching tasks in addition to force-matching tasks.

These results may have implications in rehabilitation and sport, as well as ergonomics. Regardless of whether the goal is to restore function or improve performance, exercise prescription may be erroneously based on inappropriate dose-response relationship assumptions that the body fatigues uniformly between sexes and muscle groups. This information may be most directly applicable to the post-surgical patient where isometric contractions are a frequent intervention. In addition, it may be valuable for the advancement of mathematical fatigue models, used increasingly in ergonomic applications. To this end, accurate models will require more information highlighting the multifaceted influences on fatigue.

In summary, this study demonstrated that sex differences in fatigue resistance are not necessarily uniform and systemic, but can vary by region suggesting strong localized influences. Women were significantly more fatigue-resistant for the elbow flexors but not the ankle dorsiflexors during sustained isometric contractions. Further, peak torque was associated with endurance time at the elbow but not the ankle. Thus, factors which may contribute to fatigue-resistance for one muscle group (e.g. sex, peak torque) may not be critical for another. Future studies are needed to better delineate additional underlying mechanisms that may contribute to this phenomenon.

Table 2-1. Mean (SEM) subject demographic information by sex.

	N	Height (cm)	Weight (kg)	Age (yr)	IPAQ (MET*hr)
Male	16	177.8* (1.8)	78.5* (2.1)	24.4 (1.4)	57.7 (11.1)
Female	16	164.6* (1.8)	59.4* (1.9)	23.0 (0.5)	38.1 (10.9)

IPAQ = International Physical Activity Questionnaire, total score
* Significant differences between sexes ($p < 0.05$).

Table 2-2. Effect sizes (Cohen's d) for endurance time and peak torque

Muscle Group	Endurance Time	Peak Torque	Peak Torque/ Body Mass
Elbow Flexors	1.38	- 3.95	- 2.90
Ankle Dorsiflexors	0.28	- 2.75	- 1.01

Note: Effect sizes represent female to male (F:M) ratios.

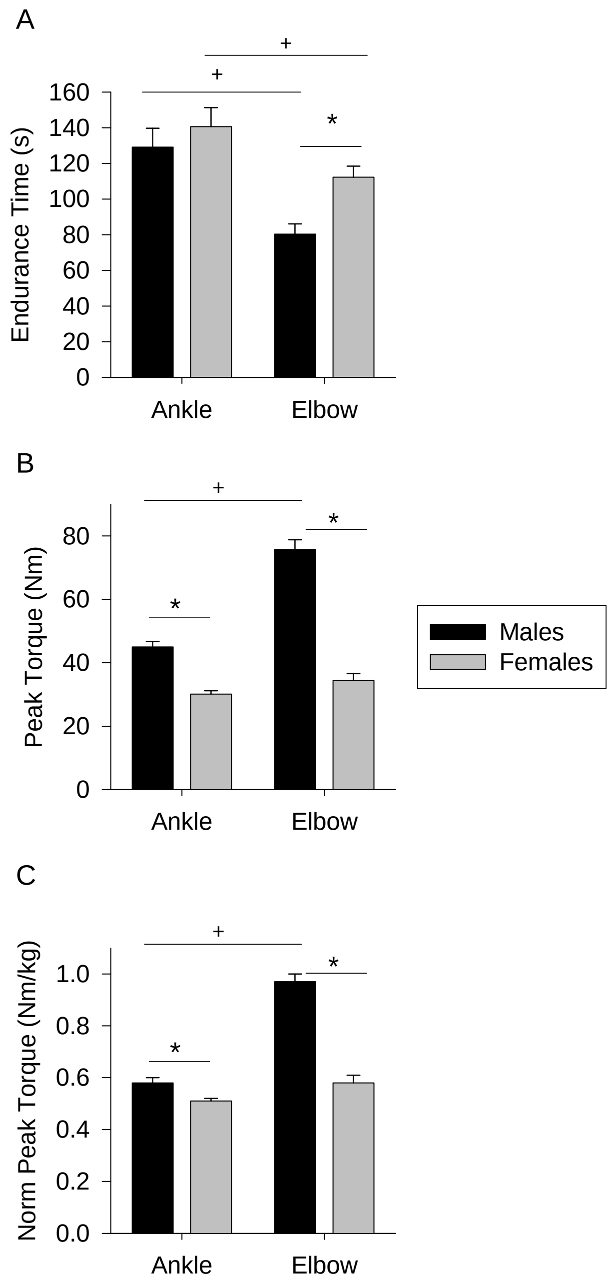


Figure 2-1. Mean (SEM) endurance time (A); peak torque (B); and normalized peak torque (C) for the ankle and elbow muscle groups by sex. * Significant difference between sexes ($p < 0.05$). † Significant difference between muscle groups ($p < 0.05$).

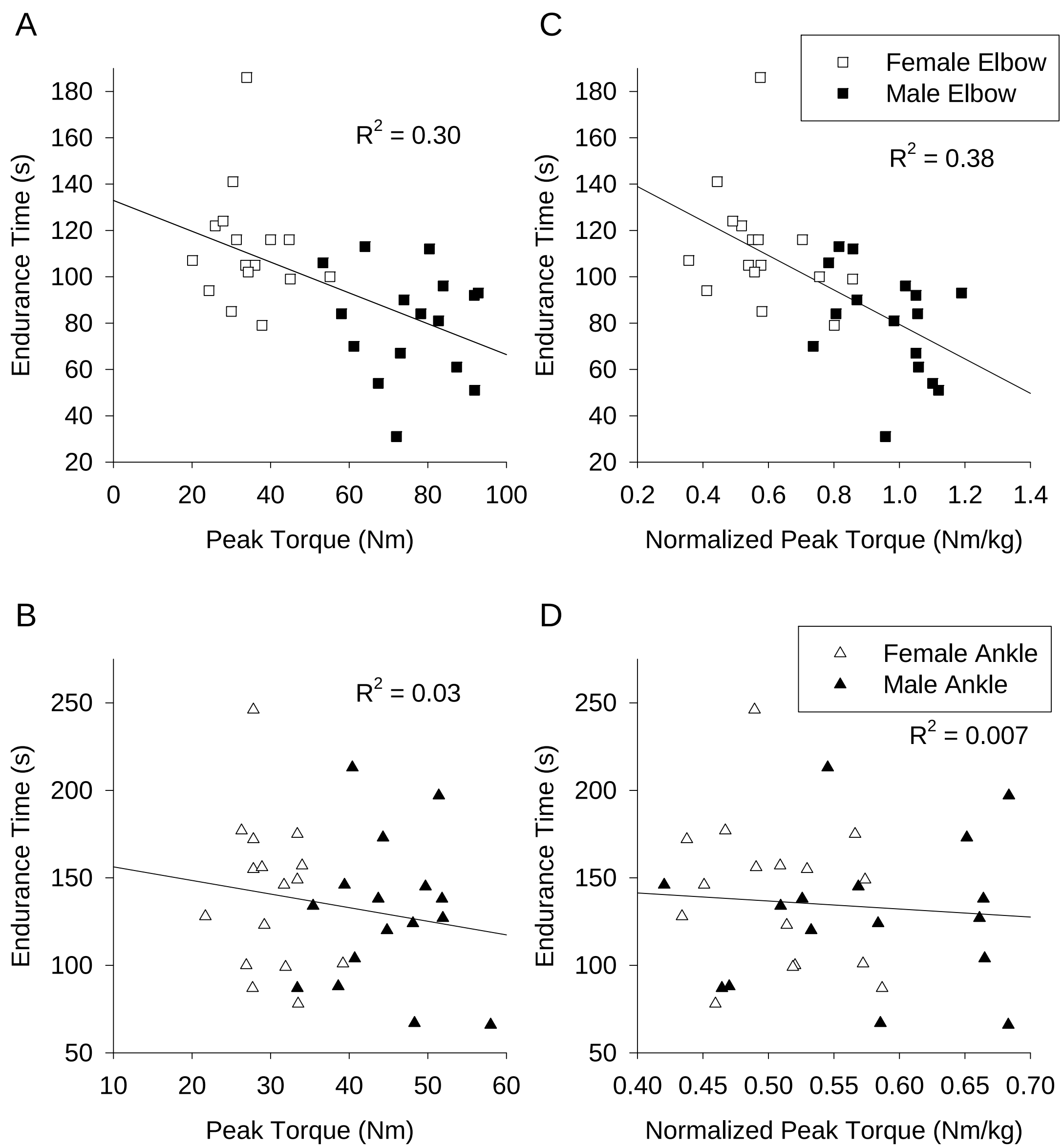


Figure 2-2. The relationship between endurance time and peak torque for the elbow (A) and ankle (B); and between endurance time and peak torque normalized by body mass for the elbow (C) and ankle (D).

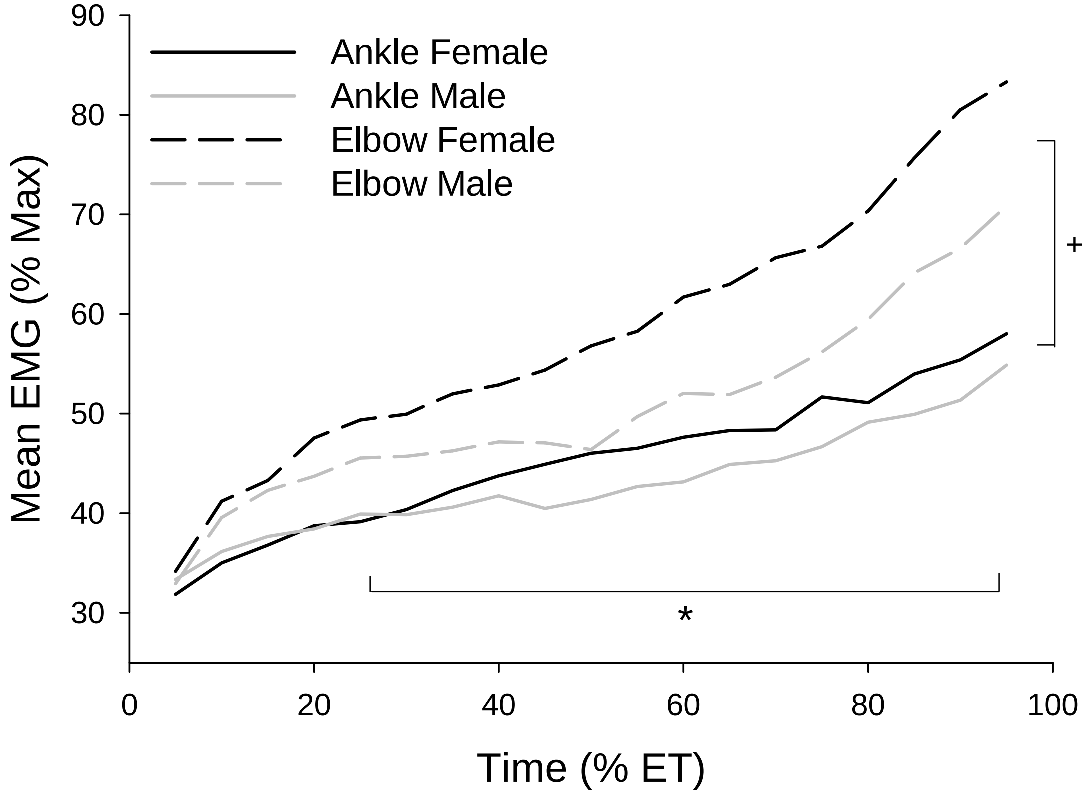


Figure 2-3. Mean EMG for ankle and elbow muscle groups by sex. * Significant difference over time for both muscle groups ($p < 0.0001$). † Significant difference between muscle groups ($p < 0.05$).

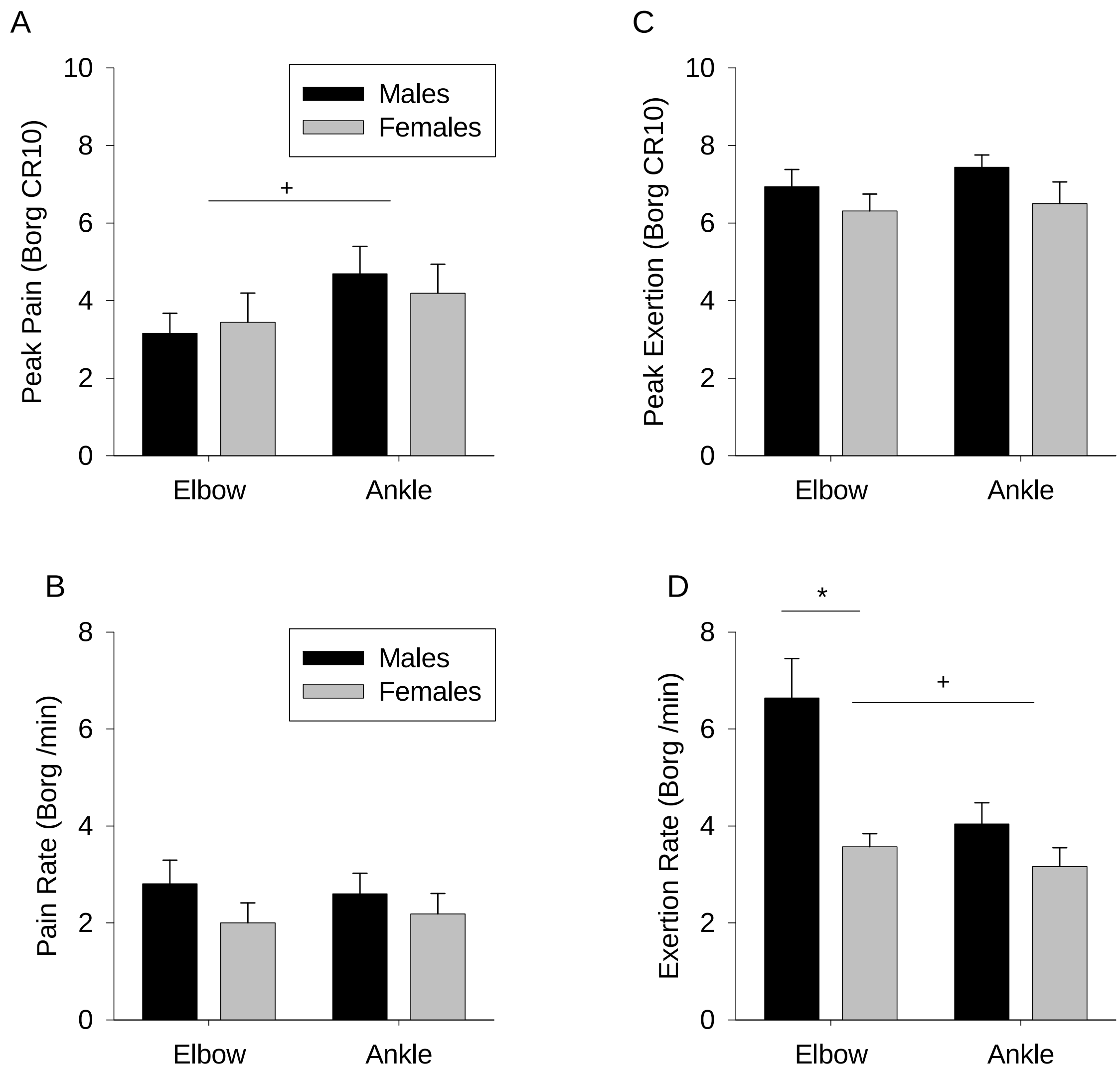


Figure 2-4. Mean (SEM) peak pain (A), rate of pain increase per minute (B), peak exertion (C), and rate of exertion increase per minute (D) for ankle and elbow muscle groups and sex. *Significant difference between sexes ($p < 0.05$). †Significant difference between muscle groups ($p < 0.05$).

CHAPTER 3

AGE-RELATED DIFFERENCES IN MUSCLE FATIGUE VARY BY CONTRACTION TYPE. A META-ANALYSIS

Introduction

While it is well recognized that sarcopenic changes in the aging adult result in diminished muscle mass and subsequent loss of strength (Larsson & Karlsson, 1978; Lexell, 1995), it is less clear how aging impacts muscle fatigue properties. A greater understanding of muscle fatigue capabilities across the lifespan may influence clinical decision-making and impact therapeutic exercise prescription.

Although the older adult may be commonly perceived as fatiguing more readily, muscle fatigue resistance may actually improve with age (Kent-Braun, 2009). Perceptions of fatigue may be reported as a "feeling of tiredness" or "lack of energy" (St Clair Gibson, 2003); which can be distinct from muscle fatigue, defined as, "any exercise-induced reduction in the ability to exert muscle force or power, regardless of whether or not the task can be sustained" (Bigland-Ritchie & Woods, 1984). Several studies have been performed to assess differences in muscle fatigue resistance in young versus old adults. However, to date, these data have not been systematically compiled to determine whether old adults indeed have consistently greater muscle endurance than young adults and which factors may influence these age-related differences.

Muscle fatigue can vary greatly within- and between-individuals due to the complex nature of fatigue. That is, muscle fatigue capabilities can vary between contraction types (isometric vs. isokinetic) (Hunter, 2009a), joints and/or muscle groups (Frey Law & Avin 2010), task intensities (Bazzucchi *et al.*, 2005), and position- versus force-matching paradigms (Hunter *et al.*, 2005). In addition, muscle fatigue may differ between men and women (Hunter *et al.*, 2004) and/or with physical activity status (Laforest *et al.*, 1990). These factors may also have the potential to influence age-related muscle fatigue properties. To date, only small scale reviews have provided insights to subsets of the research available, to ascertain age-related differences in muscle fatigue properties (Kent-Braun, 2009; Allman & Rice, 2002).

Despite the number of studies on muscle fatigue available, our understanding of age-related changes in fatigue remains incomplete. Properly identifying capabilities in the older adult may impact dose-response relationships and modify therapeutic exercise interventions. Thus, the purpose of this study was to characterize differences in muscle fatigue between young and old adults, using systematic, meta-analysis techniques to compile the available literature. Effect sizes were used to assess the degree to which young or old adults were more fatigable considering all data, as well as pre-planned subgroupings based on contraction type, sex, joint region, task intensity, and physical activity levels, when possible.

Methods

Database Review

A two-stage systematic review of the literature was used to identify studies on muscle fatigue including both old and young adults. Stage one involved searches of the following databases: PubMed (1948 – 06/28/2010), the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1937 – 06/28/2010), Pedro (1929 – 06/28/2010), EBSCOhost: ERIC (1966 - 06/28/10), EBSCOhost: Sportsdiscus (1800 - 06/28/10), and The Cochrane Library (1993 – 06/28/2010). A total of 11 search terms/keyword combinations were used to elicit relevant articles, including: endurance, fatigue, aging adult, older adult, intermittent fatigue, isokinetic fatigue, and isometric fatigue. For example, a search performed in Pubmed (accessed 10/5/2009) using aging and fatigue yielded 600 related articles. The inclusion/exclusion criteria (see below) were employed to include studies providing young versus old adult muscle fatigue data. Stage two involved reviewing bibliographies of studies meeting the inclusion criteria of stage one to find additional relevant fatigue studies. All abstracts were first screened for studies that reported the performance of a relative-intensity fatigue task, including young and old adult cohorts. These studies were then retrieved full text and reviewed by both authors to ensure agreement on inclusion/exclusion criteria and all entered data were reviewed twice against the original articles to decrease the likelihood of transcription errors.

Inclusion and Exclusion Criteria

The following criteria were used for study inclusion: healthy, human subjects; young cohort mean age between 18-45 years and mean older cohort age ≥ 55 years; sustained isometric, intermittent isometric, isokinetic and/or isotonic tasks using relative intensities based on maximum voluntary contraction (%MVC); outcome measures of either time to task failure (i.e., endurance time) or reduction in peak torque (i.e., fatigue index, see below); single-joint involvement (per fatigue task); and published in English. Studies were excluded that used: electrical stimulation to elicit fatigue; simultaneous multi-joint testing, functional tasks that did not assess torque as percent of maximum or used body/limb weight as the primary resistance (e.g. Sorensen Test). In addition if variance information, e.g., standard deviation (SD), was not reported or unattainable from the authors, studies were excluded. Inclusion/exclusion criteria did not account for athletic training status or level of physical activity, but when reported, this information was utilized.

Quality assessment of included studies did not require the traditional approaches used for meta-analyses to assess interventions, such as blinded investigators, placebo-controls, or random-assignment. Rather, the powerful statistical application of meta-analysis was used with observational studies to systematically compile the data available to better distinguish fatigue capabilities in the older versus younger adult, considering several possible moderating variables.

Outcome Variables

To characterize differences in muscle fatigue between two groups, protocols typically utilize relative-intensity tasks (% maximal voluntary contraction) to standardize task demands between individuals. Muscle fatigue properties are indirectly assessed either by the time duration a relative-intensity task can be sustained (i.e., endurance time) or the percent of baseline peak force remaining following the performance of a task for a pre-set duration. Most studies reported only one of these two outcome variables, but occasionally those involving intermittent tasks reported both. When this occurred, only the percent change in peak force was used in the meta-analysis as this was the preferred outcome variable reported for intermittent tasks. Greater muscle fatigue is observed as shorter endurance times or lower percent of baseline torque values. Endurance time is usually reported as the total duration a relative intensity task can be maintained until the target muscle torque falls to 5 to 10% below target levels. Only acute muscle fatigue was assessed in this study, i.e., these immediate or short-term outcomes, rather than long-duration decrements in force-producing capability associated with low frequency fatigue. Relevant endurance or fatigue data reported only in graphic form were extracted using pixel analysis (Adobe Photoshop, San Jose, CA) to determine the respective numerical values. Mean and standard deviations (SD) for young and old cohorts were recorded for each pair of data.

Moderating Variables

Additional study information was recorded for analysis, including sample size, sex, mean age for each cohort (young, old), standardized task intensity (from 1 to 100% maximum), contraction type (sustained isometric, intermittent isometric, and isokinetic), joint-region tested (e.g., ankle, back, elbow), joint angle, torque direction (e.g. flexion or extension), and physical activity level (when reported). When outcome measures were not reported separately by sex, and were unavailable following attempts to contact the corresponding authors, the data was coded simply as “mixed sex.” Contractions were classified as one of three types: two static (isometric with (sustained) or without (intermittent) rest intervals) and one dynamic (isokinetic). Task intensity was categorized as low (≤33% max), moderate (34-66% max), or high (≥67% max), regardless of contraction type. Given the varying methods for quantifying physical activity, data was dichotomized to active or inactive when available.

When necessary the data for multiple age-cohorts (e.g. for 20 – 29 and 30 – 39 years) were combined using weighted means and pooled standard deviations (Higgins & Green, 2010). When multiple task intensities (e.g. 30% or 50% maximum) or joint regions (e.g. ankle and elbow) were reported in a single manuscript, data for each fatigue task were included (in separate rows) rather than combining into a single mean or selecting only one task per study. We chose this strategy to minimize any potential self-selection bias or miss potential effects due to joint or intensity factors. While this approach allows for multiple measures that are not fully independent, particularly for observational studies it is in fact challenging to determine whether independence is assured across publications (by the same authors). That is, the same subject population may be recruited for studies reported in multiple separate publications.

Statistical Analyses

Effect size (ES) is the standardized mean difference between two populations (i.e. young versus old). Hedge’s g was chosen as the best effect size estimate, due to its correction for slight overestimations that may occur with small samples (Borenstein, 2009). Mean effect sizes (and associated variances) across studies were calculated (Comprehensive Meta-Analysis, Biostat, Englewood, NJ) using a mixed-effects model determined a priori (random and fixed effects). A random-model approach was chosen under the guise of generalizing results among the older population and inherent inequality of effect sizes across studies. A fixed subgroup analysis assumes results will generalize to the specific variables of interest such as contraction type (e.g. sustained isometric, intermittent isometric, isokinetic), intensity, etc. Results are presented such that positive ES values indicate older adults are more resistant to fatigue, whereas negative values indicate young adults are more resistant to fatigue. Analyses were stratified into three levels (see Figure 3-1), with pre-planned subgrouping categories. A specific subgroup was only included in comparisons if it included data from a minimum of three, separate published studies, thus the final set of subgroups was determined by the data available.

The level I analysis determined a single composite effect size for old versus young fatigue resistance including all data points with no subgroups. Level II analyses included subgrouping by single individual categories to the extent sufficient data was available: sex, contraction type, intensity, joint tested, and activity level. Level III analyses involved further subgrouping the contraction types from Level II when sufficient data were available, e.g. comparing intensity levels, sex, or joints within each contraction type (e.g., interaction or moderated effects). Level III subgroupings were only considered when sufficient data were available (i.e. ≥ 3 independent studies).

The goal of a meta-analysis is to not only compute summary effect sizes, but also to determine the extent of variation present in the true effect size (i.e., heterogeneity), suggesting whether additional moderating variables are involved. Heterogeneity was quantified via the I^2 index and the *Q* test (Borenstein, 2009). A significant *Q* statistic indicates only the presence of heterogeneity among the data included, whereas the I^2 index is better able to quantify the magnitude of the heterogeneity (Higgins & Thompson, 2002). We operationally defined the magnitude of heterogeneity as low ($I^2 \leq 33\%$), moderate ($34\% \leq I^2 < 67\%$), and high ($I^2 \geq 67\%$) based on previous suggestion (Higgins & Thompson, 2003). Heterogeneity estimates were evaluated at each level of analysis.

Results are reported as mean summary effect sizes for each subgroup analysis (±SE; p-value). A more stringent alpha level than conventionally used ($\alpha \leq 0.01$) was chosen to minimize both type I and II errors (Garamszegi, 2006). Observational studies are less likely to be adversely affected by publication bias than interventional studies, as identifying a fatigue advantage in either direction would be deemed a valuable scientific contribution. Further, several studies were investigating other aspects of muscle fatigue such that the data relevant to this meta-analysis were not necessarily the primary outcomes (accordingly lack of age-related fatigue differences would not influence likelihood of publication). Therefore, our analyses were not further extended for publication bias within or between studies.

Results

Database Review

Initial search strategies (stages 1 and 2) resulted in 3,457 potential studies (after duplicates removed), with 46 meeting all inclusion criteria (see Figure 3-1). Several studies reported on more than one joint/muscle group, contraction type, or task intensity for a total of 78 young versus old adult fatigue comparisons (i.e., individual effect sizes) to analyze. The numbers of data points per subgroup comparison are detailed in Table 3-1.

Level I Overall Age Effect

The level I analysis, using all 78 individual effect sizes, revealed that older adults were significantly more resistant to acute muscle fatigue (greater muscle endurance) than young adults, with a medium mean effect size of 0.49 (95% Confidence Interval 0.35-0.63). See Figures 3-2 to 3-4 for the forest plots showing each individual effect size by contraction type and Figure 3-5 for the effect sizes for each analysis level. Note that one isotonic effect size was included in the overall analysis, but was not extended to a separate contraction-type subgroup due to a lack of comparative studies.

Level II Subgroups

Contraction Type: Older adults demonstrated greater muscle fatigue resistance (i.e. more endurant) for both sustained (Figure 3-2) and intermittent (Figure 3-3) isometric contractions, but the intermittent tasks showed the greatest age-related advantage compared to sustained tasks (ES = 0.82 versus 0.52, $p = 0.009$; Figure 3-5). However, for dynamic contractions no age-related difference in muscle fatigue was observed (ES = 0.05, Figure 3-4).

Sex: Older adults were more fatigue-resistant than younger adults for both males and females. This age-related advantage, however, was greater for males than females ($p=0.009$) when not accounting for any additional moderating factors (see Figure 3-5).

Joint: Older adults were significantly more fatigue resistant than young adults across all joint-region subgroups assessed (i.e. ankle, elbow, hand/grip, and knee had sufficient data available). However, these effect sizes differed between each joint ($p < 0.008$), with the exception of the ankle versus the hand/grip ($p=0.42$) regions. The largest effect size was observed at the elbow and the smallest at the knee, when not accounting for any additional factors (Figure 3-5). However, the elbow joint tasks were comprised solely of static contraction protocols, whereas the knee included both isometric and isokinetic testing (see further Level III subgrouping below).

Intensity: Older adults were more resistant to fatigue across all intensity levels (low, moderate, and high, Figure 3-5). Although effect sizes decreased with increasing intensity, i.e., the fatigue advantage with advancing age decreased at higher intensities, none of the differences achieved significance ($p>0.067$) (Figure 3-5).

Physical activity: Older adults were more resistant to fatigue across active and inactive cohorts, with the difference in effect sizes between subgroups just beyond significance ($p = 0.063$).

Level III Subgroups

Contraction Type by Intensity: While task intensity moderated the age-related fatigue advantage overall (Level II above), this effect was lost or reversed when controlling for contraction type (Figure 3-5). For sustained isometric contractions older adults remained more fatigue-resistant than young adults across all intensities (low, moderate, and high) with no significant difference exhibited between intensity subgroups ($p \geq 0.07$). Conversely, for intermittent isometric contractions, no significant age-differences occurred for moderate intensities; whereas a large effect size was observed for high intensities (insufficient low intensity intermittent data available). Although this demonstrates opposing influences of intensity on intermittent tasks than observed with the sustained isometric tasks (or overall in level II), only three of the 16 intermittent tasks were performed at a moderate intensity.

Contraction Type by Sex: While sex was a significant moderator of the age-related endurance advantage in the Level II analyses, sex was not a significant moderator when considering each contraction type separately. The older adult remained more fatigue-resistance in both men and women for sustained and intermittent isometric tasks, but this time did not differ between sexes ($p > 0.17$, see Figure 3-5). Further, no age-related advantage was observed in either men or women (effect sizes not significantly different than zero) for the isokinetic contractions.

Contraction Type by Joint: Similarly, further subgrouping contraction type by joint region slightly altered the findings from the previous level II analyses. Within sustained isometric contractions, the older adult was again more fatigue resistant across the joints considered (elbow, hand/grip, and knee joint regions, with ankle just surpassing our stringent critical value). However, only the elbow continued to result in significantly larger effect sizes than the remaining joints, with the knee now exhibiting similar effect sizes as the hand and ankle (Figure 3-5). For intermittent isometric contractions, the ankle (only subgroup possible) demonstrated significant age-related advantages in muscle fatigue. During isokinetic contractions, neither the ankle nor the knee (the only joints with sufficient data) demonstrated any age-related advantage (or disadvantage) in fatigue resistance ($p \geq 0.06$). Overall, joint region had only mild moderating influences on the fatigue differences observed between young versus old adults, when controlling for contraction type.

Contraction Type x Physical Activity: Physical activity did not substantially alter the previous contraction-type subgroups (Figure 3-5). Older adults were significantly more fatigue resistant across each combination of sustained and intermittent isometric contraction types and activity levels except for the inactive, sustained isometric group which was likely underpowered ($p=0.07$, $n=4$, ES=0.38). The age-related fatigue advantage did not differ significantly between the active and inactive groups for isometric or intermittent tasks ($p > 0.40$).

Heterogeneity

Overall, the heterogeneity was categorized as low to moderate for all levels of the meta-analysis (see Table 3-1). The proportion of subgroups categorized with low heterogeneity increased from 28.6% for level II analyses to 60.9% for level III analyses. The increased proportion of low heterogeneity with additional subgroup analyses suggests that several moderators identified in this analysis (e.g., contraction type, joint, and intensity) contributed to variations in age-related fatigue resistance. Although the level III heterogeneity increased at the ankle for both sustained and isokinetic contractions, the limited number of data points (four and three, respectively) demonstrated the difficulty in attaining a consistent summary effect size. Additional data is needed to fully characterize age-related fatigue differences.

Discussion

This is the first study to systematically compile fatigue outcomes data to characterize age-related differences in muscle fatigue considering several potential moderating variables: contraction type, intensity, sex, joint region, and activity level. The primary finding of this meta-analysis was that muscle fatigue is enhanced with age for relative intensity tasks when additional intrinsic and extrinsic factors are not considered (level I analysis). This age-related advantage in fatigue resistance occurred for both sustained and intermittent isometric contractions, but is lost for isokinetic contractions.

Improved fatigue resistance with advancing age is consistent with several reported changes in muscle properties with aging. A preferential atrophy of type II fibers (Larsson & Karlsson, 1978; Lexell *et al.*, 1988) and preferential loss of fast motor units (Lexell, 1995) have been observed with advancing age, and sarcopenia. These changes would result in a greater proportion of type I or slow, oxidative fibers, which may account for greater fatigue-resistance during relative intensity tasks (i.e. tasks standardized to maximum strength). However, this adaptation did not prove beneficial under all conditions (i.e. dynamic tasks).

Level II and III analyses revealed older adults were more endurant than young adults for sustained and intermittent isometric (static) contractions, but not for isokinetic (dynamic) contractions. This result is somewhat surprising as we anticipated the intermittent isometric contractions to behave similarly to isokinetic tasks, as greater muscle reperfusion, replenishment of oxygenated blood, and removal of metabolic wastes might be facilitated under both conditions. To the contrary, the intermittent tasks resulted in the greatest age-related fatigue advantage, whereas isokinetic tasks showed no age-related differences. Thus, the inclusion of rest intervals, and accordingly muscle reperfusion, does not appear to be the key variable, but rather the contraction type itself appears to be of importance in age-related endurance changes. One explanation may be that the proportional shift towards type I fibers and the slowing of both contraction and relaxation times that occurs with aging may cause a leftward shift in the force-frequency curve (Allman & Rice, 2004) and a left- and downward shift in the force-velocity curve (Raj *et al.*, 2010). Thus, while the muscle fibers are slower, and rely on greater oxidative energy sources, they may be less able to maintain power (i.e. force times velocity) over time. These adaptations may enable the older adult to be more fatigue resistant for isometric contractions (slower, oxidative fibers), but not during dynamic contractions where impaired power generation would be expected to have its greatest impact.

Anecdotal perceptions of muscle fatigue increasing with advancing age are in opposition to the controlled research findings of greater fatigue resistance with aging. This may be partially explained by the differences observed between static and dynamic tasks, as many functional tasks (e.g. sit to stand, ambulation, etc) require dynamic rather than static contractions. However, even with dynamic tasks, the older adults are not disadvantaged; thus this potential discrepancy may be further attributed to differences between absolute and relative intensity conditions. Functional tasks require absolute loads (e.g. stair climbing) that are not proportional to peak strength. As the older adult weakens with age (Larsson & Karlsson, 1978; Lexell, 1995), functional tasks can require a greater percentage of maximal capacity and thus, tasks are performed at a higher relative intensity (Hortobagyi *et al.*, 2003). Fatigue occurs more rapidly with increasing task intensity; maximum endurance time decreases nonlinearly with increasing task intensity (Frey Law & Avin, 2010). Thus, while fatigue-resistance may improve with age for a relative intensity (e.g. 50% of max) task that is standardized between individuals, the increased relative workload for a functional task may offset any age advantage. That is, if a given task requires 40% of maximum strength for a young adult, but 60% for an older adult, the apparent task endurance may be less for the older adult, even if underlying muscle fatigue resistance is greater with age.

Interpretation of the remaining potential moderators (sex, physical activity, intensity and joint) associated with age-related differences in muscle fatigue was somewhat challenging given the incomplete data available for each possible subgrouping. No significant differences between men and women were consistently observed in these meta-analyses, once contraction type was controlled for, which is in agreement to conclusions drawn from several individual studies (Aniansson *et al.*, 1978; Ditor & Hicks, 2000; Kent-Braun *et al.*, 2002), but in opposition to others (Hunter *et al.*, 2004).

Current comparisons did not assess whether sex-differences in muscle fatigue occurred, but rather if age-differences varied by sex. Lastly, greater physical activity did not influence the age-related fatigue advantage. However these findings are based on smaller subgroup samples, with heterogeneous definitions of active versus inactive individuals, thus may reflect less stability in effect size estimates.

While the current meta-analysis is able to identify differences across contraction types between young and old adult muscle fatigue properties, there are several limitations that should be acknowledged. Several subgrouping comparisons in levels II and III for joint, intensity and contraction type were not performed due to a lack of data available. The majority of intermittent isometric and isokinetic protocols were performed at intensities of 50% MVC or higher (most at 100%), limiting the interpretation intensity has upon fatigue differences with aging for these contraction types. Intermittent tasks were further limited by the disproportionate number of comparisons including males (8 males vs. 4 females) and limited joint regions that have been tested (ankle = 9, all others combined = 7). Physical activity data was simply classified as active versus sedentary, which may miss subtle influences of varying levels of physical activity. Lastly, we included studies with cohorts aged 55+ years, thus a relatively "young" older adult minimum age criterion. Secondary analyses demonstrated no significant difference in effect size estimates if we had used only studies with adults over 60 years as our age minimum criterion.

These findings suggest the need for future studies to explicitly report fatigue data by sex and provide physical activity information for both young and old adult cohorts when possible. Additional fatigue studies involving isokinetic and intermittent tasks using the upper extremities and/or lower intensities would help to minimize the potential bias and interactions present between muscle group, intensity, and contraction type, as observed here. In particular, it is not clear why this age-related advantage is lost during dynamic contractions, which would benefit from research considering potential influences such as: task complexity, passive tissue contributions, and/or muscle power. Finally, while these findings provide us greater insight into age-related changes in muscle fatigue properties, additional research is needed to clarify the magnitude and impact of this potential benefit, and whether it can be further altered by therapeutic interventions.

Despite the abundance of acute muscle fatigue research, few studies have attempted to compile all the available data on age-related differences in fatigue resistance. This meta-analysis supports that aging results in a general muscle fatigue resistance advantage, but is particularly dependent on contraction type. Dynamic tasks, specifically isokinetic tasks were not found to exhibit any advantage (or disadvantage) in muscle fatigue for old versus young adults. The underlying mechanisms for these findings remain somewhat unclear, but may be due to a greater loss of muscle power with aging. Ultimately these age-related fatigue differences may help offset the deleterious effects of sarcopenia and loss of muscle strength. In light of a reduction in strength, therapeutic interventions may target muscle fatigue resistance to impact functional capabilities in the older adult.

Table 3-1. Summary of heterogeneity statistics for each subgroup analysis.

Analysis Level	Subgrouping		n	Q (p-value)	I^2 (%)
Level I	-		77	<0.001	52.0
Level II Contraction	Sustained Isometric	-	45	0.005	38.9
	Intermittent Isometric	-	16	0.652	0.0
	Isokinetic	-	16	0.001	60.4
Level II Sex	Male	-	44	<0.001	50.0
	Female	-	18	0.006	51.8
Level II Intensity	Low	-	14	0.004	57.4
	Moderate	-	25	0.081	29.8
	High	-	38	<0.001	57.1
Level II Joint	Ankle	-	16	0.018	47.7
	Elbow	-	14	0.024	47.7
	Hand/Grip	-	16	0.183	23.9
	Knee	-	22	<0.001	57.5
Level II Activity	Active	-	43	<0.001	46.1
	Inactive	-	11	0.512	0.0
Level III Contraction/Intensity	Sustained Isometric	Low	14	0.004	57.4
		Mod	21	0.036	38.8
		High	10	0.692	0.0
	Intermittent Isometric	Mod	3	0.554	0.0
		High	13	0.582	0.0
Level III Contraction/Sex	Sustained Isometric	Male	29	0.006	44.6
		Female	8	0.236	24.2
	Intermittent Isometric	Male	8	0.449	0.0
		Female	4	0.709	0.0
	Isokinetic	Male	7	0.001	74.3
		Female	6	0.336	12.4
Level III Contraction/Joint	Sustained Isometric	Ankle	4	0.015	71.5
		Elbow	12	0.030	48.4
		Hand	13	0.669	0.0
		Knee	7	0.237	25.2
	Intermittent Isometric	Ankle	9	0.960	0.0
	Isokinetic	Ankle	3	0.002	83.5
		Knee	13	0.031	46.9
Level III Contraction/Activity	Sustained Isometric	Active	30	0.064	29.8
		Inactive	4	0.739	0.0
	Intermittent Isometric	Active	7	0.289	18.5
		Inactive	6	0.750	0.0
	Isokinetic	Active	8	0.004	66.4

n= # of data points per analysis level; p-values are uncorrected for multiple comparisons

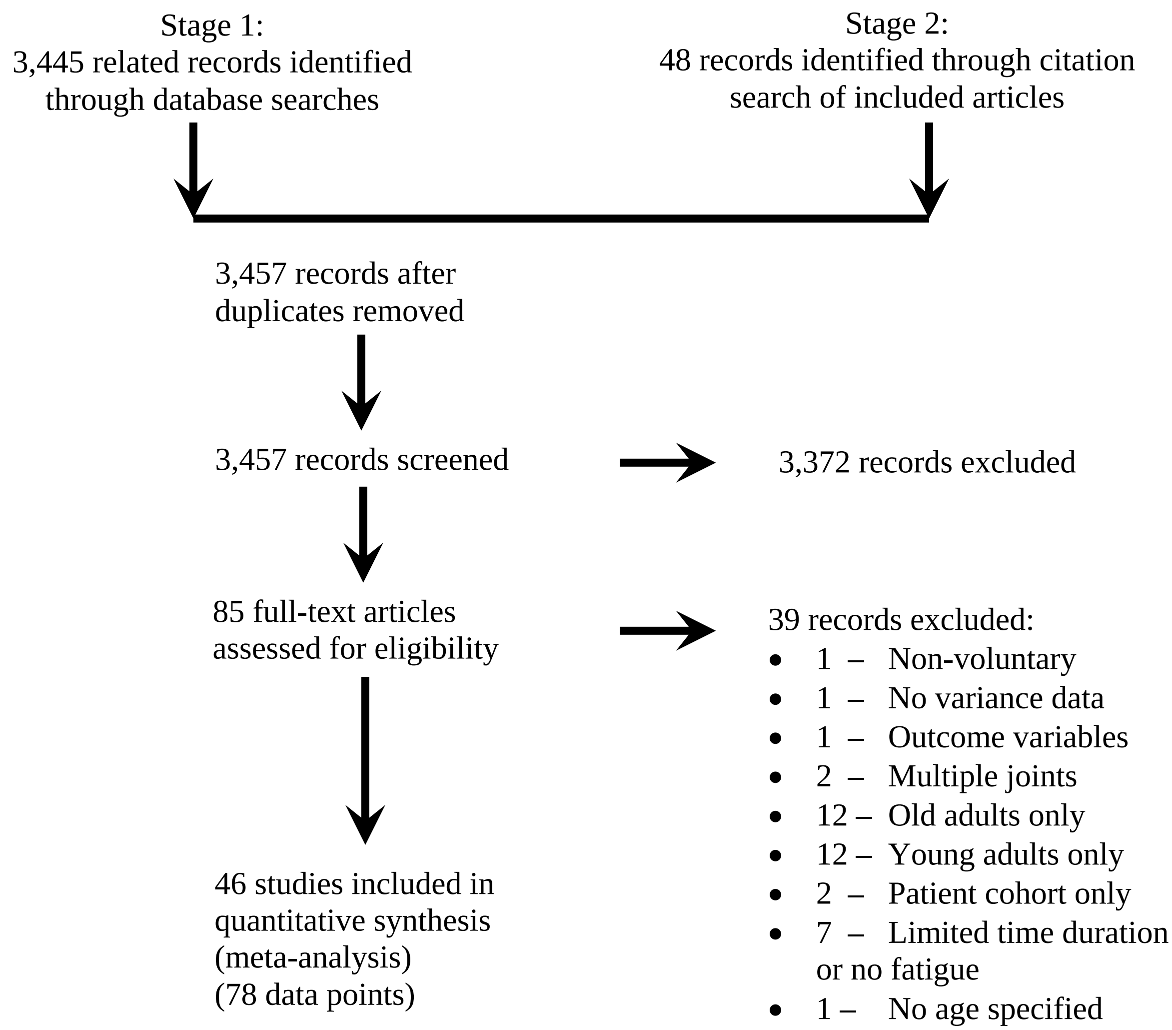


Figure 3-1**.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement flow diagram of the literature search.

Author	Joint	Sex	Activity Level	% max	Hedges' g	SE	p-value
Aniansson, *et al.* 1978	Hand	M	NA	50	0.36	0.35	0.309
Bazzucchi, *et al.* 2005	Elbow	M	Act	30	0.27	0.54	0.620
Bazzucchi, *et al.* 2005	Elbow	M	Act	50	1.72	0.64	0.007
Bazzucchi, *et al.* 2005	Elbow	M	Act	80	1.26	0.59	0.033
Bilodeau, *et al.* 2001	Elbow	MX	Inact	100	0.70	0.43	0.104
Bilodeau, *et al.* 2001	Elbow	MX	NA	35	1.53	0.50	0.002
Chatterjee & Chowdhuri 1991	Hand	M	Inact	40	0.12	0.34	0.719
Christie & Kamen 2009	Ankle	MX	Act	50	-0.68	0.49	0.163
Griffith, *et al.* 2010	Ankle	MX	Act	30	0.64	0.38	0.091
Hara, *et al.* 1998	Hand	MX	Inact	50	0.56	0.49	0.253
Huang, *et al.* 2007	Hand	MX	NA	75	0.89	0.39	0.021
Hunter, *et al.* 2004	Elbow	M	NA	20	1.98	0.49	0.000
Hunter, *et al.* 2004	Elbow	F	NA	20	0.32	0.43	0.465
Hunter, *et al.* 2005	Elbow	M	NA	20	1.42	0.54	0.008
Johnson, 1982	Knee	F	Act	50	0.32	0.36	0.365
Lanza, *et al.* 2005	Ankle	M	Inact	100	0.33	0.48	0.492
Larsson, *et al.* 1978	Knee	M	Act	50	0.42	0.36	0.244
Mademli & Arampatzis 2008	Ankle	M	Act	40	1.40	0.43	0.001
Mademli, *et al.* 2008	Knee	M	Act	25	1.15	0.41	0.005
Momen, *et al.* 2004	Hand	MX	NA	40	0.56	0.49	0.254
Petrofsky, *et al.* 1975	Hand	M	NA	40	0.03	0.27	0.907
Petrofsky & Lind 1975	Hand	F	NA	40	0.72	0.28	0.010
Petrofsky & Laymon 2002	Hand	M	NA	40	1.15	0.40	0.004
Petrofsky & Laymon 2002	Knee	M	NA	40	1.43	0.41	0.001
Petrofsky, *et al.* 2009	Hand	MX	Act	40	0.45	0.36	0.207
Smolander, *et al.* 1998	Hand	M	Act	20	0.18	0.47	0.695
Smolander, *et al.* 1998	Hand	M	Act	40	0.46	0.47	0.333
Smolander, *et al.* 1998	Hand	M	Act	60	0.29	0.47	0.542
Smolander, *et al.* 1998	Knee	M	Act	20	0.30	0.47	0.530
Smolander, *et al.* 1998	Knee	M	Act	40	0.19	0.47	0.682
Smolander, *et al.* 1998	Knee	M	Act	60	0.39	0.47	0.408
Taylor, *et al.* 1991	Hand	M	Act	30	0.28	0.37	0.455

Effect Size (95% CI)

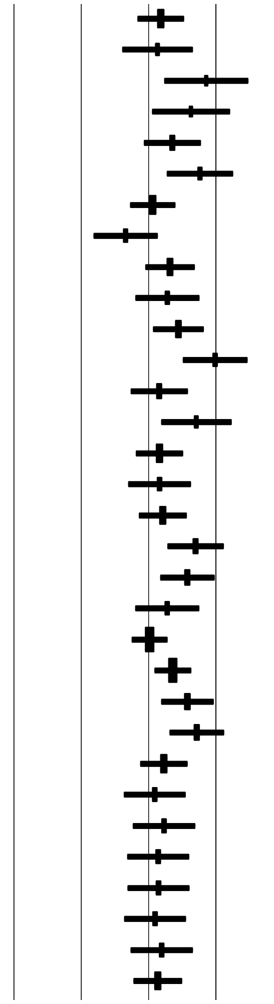


Figure 3-2 Forest plot of individual effect sizes for sustained isometric contractions only, with their corresponding subgrouping categories for sex, joint, task intensity, and physical activity level. Positive effect sizes indicate greater endurance for the older adults, whereas negative effect sizes indicate greater endurance for the younger adults.

Author	Joint	Sex	Activity Level	% max	Hedges' g	SE	p-value
Yassierli, *et al.* 2007	Shld	M	Act	30	0.60	0.29	0.039
Yassierli, *et al.* 2007	Shld	M	Act	50	0.40	0.29	0.165
Yassierli, *et al.* 2007	Shld	M	Act	70	0.21	0.28	0.465
Yassierli, *et al.* 2007	Back	M	Act	30	0.44	0.40	0.272
Yassierli, *et al.* 2007	Back	M	Act	50	0.28	0.40	0.475
Yassierli, *et al.* 2007	Back	M	Act	70	0.12	0.39	0.767
Yassierli, *et al.* 2007	Back	F	Act	30	-0.12	0.39	0.753
Yassierli, *et al.* 2007	Back	F	Act	50	0.15	0.39	0.696
Yassierli, *et al.* 2007	Back	F	Act	70	0.00	0.39	1.000
Yoon, *et al.* 2008	Elbow	M	Act	20	3.17	0.84	0.000
Yoon, *et al.* 2008	Elbow	M	Act	80	0.64	0.55	0.247
Yoon, *et al.* 2008	Elbow	F	Act	20	1.51	0.51	0.003
Yoon, *et al.* 2008	Elbow	F	Act	80	0.44	0.45	0.332
Isometric Summary	(Fixed)				0.53	0.06	0.000

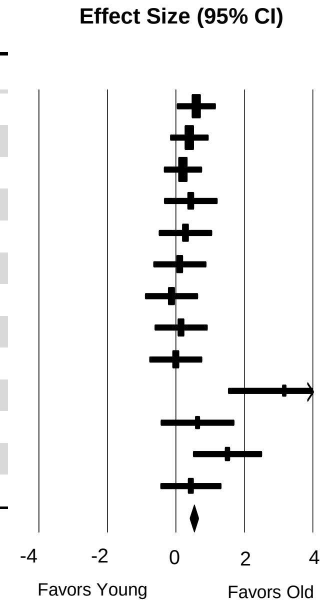


Figure 3-2. (continued) Forest plot of individual effect sizes for sustained isometric contractions only, with their corresponding subgrouping categories for sex, joint, task intensity, and physical activity level. Positive effect sizes indicate greater endurance for the older adults, whereas negative effect sizes indicate greater endurance for the younger adults.

Author	Joint	Sex	Activity Level	% max	Hedges' g	SE	p-value
Allman & Rice 2003	Elbow	M	Act	60	0.24	0.54	0.656
Allman & Rice 2001	Elbow	M	Act	60	0.42	0.51	0.409
Callahan, *et al.* 2009	Knee	MX	Inact	100	1.16	0.38	0.002
Chan, *et al.* 2000	Hand	MX	Act	100	1.36	0.49	0.006
Chung, *et al.* 2007	Ankle	M	NA	100	0.97	0.42	0.020
Ditor & Hicks 2000	Hand	M	Act	100	1.85	0.52	0.000
Ditor & Hicks 2000	Hand	F	Act	100	0.77	0.45	0.085
Kent-Braun, *et al.* 2002	Ankle	M	Inact	100	0.74	0.43	0.082
Kent-Braun, *et al.* 2002	Ankle	F	Inact	100	1.20	0.47	0.010
Lanza, *et al.* 2004	Ankle	M	Act	100	0.54	0.46	0.242
Lanza, *et al* 2007	Ankle	MX	Inact	100	0.90	0.33	0.007
Mademli & Arampatzis 2008	Ankle	M	NA	65	0.94	0.44	0.033
Rubinstein & Kamen 2005	Ankle	F	Act	100	0.86	0.34	0.012
Russ, *et al.* 2008	Ankle	M	Inact	100	0.48	0.49	0.335
Russ, *et al.* 2008	Ankle	F	Inact	100	0.43	0.47	0.361
Stackhouse, *et al.* 2001	Knee	MX	NA	100	0.34	0.34	0.318
Intermittent Isometric Summary	(Fixed)				0.82	0.11	0.000

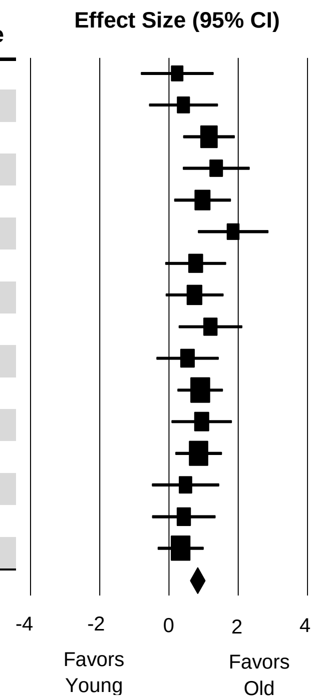


Figure 3-3**.** Forest plot of individual effect sizes for intermittent isometric contractions only, with their corresponding subgrouping categories for sex, joint, task intensity, and physical activity level. Positive effect sizes indicate greater endurance for the older adults, whereas negative effect sizes indicate greater endurance for the younger adults.

Author	Joint	Sex	Activity Level	% max	Hedges' g	SE	p-value
Aniansson, *et al.* 1978	Knee	M	NA	100	0.25	0.35	0.476
Aniansson, *et al.* 1978	Knee	F	NA	100	-0.03	0.33	0.917
Baudry, *et al.* 2007	Ankle	F	NA	100	-0.46	0.35	0.188
Callahan, *et al.* 2009	Knee	MX	Inact	100	0.09	0.36	0.816
Johnson 1982	Knee	F	Act	100	-0.31	0.36	0.387
Laforest, *et al.* 1990	Knee	MX	MX	100	-0.09	0.22	0.686
Lanza, *et al.* 2004	Ankle	M	Act	100	1.72	0.55	0.002
Larsson & Karlsson 1978	Knee	M	Act	100	0.20	0.43	0.644
Lindstrom, *et al.* 1997	Knee	M	Act	100	-0.47	0.43	0.280
Lindstrom, *et al.* 1997	Knee	F	Act	100	0.74	0.49	0.134
Lindstrom, *et al.* 2006	Knee	F	Act	100	0.12	0.47	0.809
Lindstrom, *et al.* 2006	Knee	M	Act	100	-1.13	0.46	0.014
Mademli, *et al.* 2008	Knee	M	Act	50	0.31	0.38	0.421
Muller, *et al.* 2007	Ankle	MX	NA	100	0.55	0.28	0.046
Rawson 2009	Knee	M	NA	100	0.98	0.35	0.005
Schwendner, *et al.* 1997	Knee	F	NA	100	-0.40	0.23	0.085
Isokinetic Summary	(Fixed)				0.05	0.09	0.578

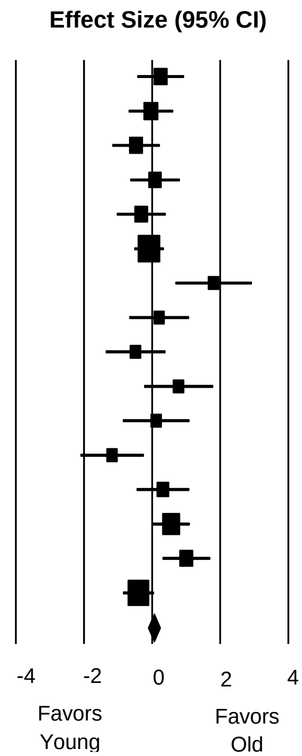


Figure 3-4. Forest plot of individual effect sizes for isokinetic contractions only, with their corresponding subgrouping categories for sex, joint, task intensity, and physical activity level. Positive effect sizes indicate greater endurance for the older adults, whereas negative effect sizes indicate greater endurance for the younger adults.

Level	Subgroupings		Hedges' g	SE	p-value
Level I All	-	-	0.49	0.07	<0.001
Level II Contraction Type	Sustained Isometric	-	0.53	0.06	<0.001
-	Intermittent Isometric	-	0.82	0.10	<0.001
-	Isokinetic	-	0.05	0.08	0.358
Level II Sex	Male	-	0.49	0.06	<0.001
-	Female	-	0.23	0.09	0.005
Level II Intensity	Low	-	0.51	0.11	<0.001
-	Moderate	-	0.50	0.08	<0.001
-	High	-	0.35	0.06	<0.001
Level II Joint	Ankle	-	0.51	0.10	<0.001
-	Elbow	-	0.97	0.14	<0.001
-	Hand/Grip	-	0.55	0.09	<0.001
-	Knee	-	0.20	0.08	0.003
Level II Activity	Active	-	0.39	0.06	<0.001
-	Inactive	-	0.60	0.12	<0.001
Level III Cont/Intensity	Sustained Isometric	Low	0.67	0.11	<0.001
-	-	Mod	0.50	0.08	<0.001
-	-	High	0.41	0.13	0.005
-	Intermittent Isometric	Mod	0.58	0.28	0.128
-	-	High	0.85	0.11	<0.001
Level III Cont/Sex	Sustained Isometric	Male	0.55	0.08	<0.001
-	-	Female	0.40	0.14	0.003
-	Intermittent Isometric	Male	0.78	0.17	<0.001
-	-	Female	0.82	0.21	<0.001
-	Isokinetic	Male	0.26	0.15	0.054
-	-	Female	-0.20	0.14	0.268
Level III Cont/Joint	Sustained Isometric	Ankle	0.51	0.22	0.020
-	-	Elbow	1.08	0.15	<0.001
-	-	Hand	0.44	0.10	<0.001
-	-	Knee	0.61	0.16	<0.001
-	Intermittent Isometric	Ankle	0.81	0.14	<0.001
-	Isokinetic	Ankle	0.37	0.20	0.106
-	-	Knee	-0.02	0.09	0.807
Level III Cont/Activity	Sustained Isometric	Active	0.44	0.08	<0.001
-	-	Inactive	0.38	0.21	0.07
-	Intermittent Isometric	Active	0.86	0.18	<0.001
-	-	Inactive	0.85	0.17	<0.001
-	Isokinetic	Active	0.05	0.15	0.344

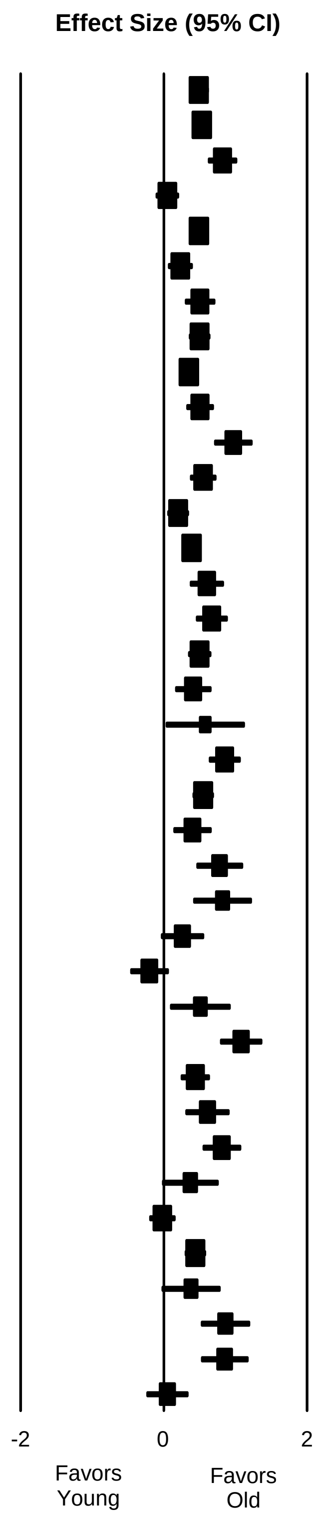


Figure 3-5. Forest plot of summary effect sizes for each subgrouping category (Level I through III). Positive effect sizes indicate greater endurance for the older adults, whereas negative effect sizes indicate greater endurance for the younger adults.

CHAPTER 4

AGE-RELATED FATIGUE RESISTANCE MEDIATED BY TASK COMPLEXITY

Introduction

Anecdotally, older adults may seem to be more fatigable than their younger counterparts; fatiguing with tasks such as stair climbing, rising from a chair and brisk walking. These conclusions may or may not be correct depending upon the conditions in which comparisons are being drawn (i.e. absolute or relative loads). Research suggests that under relative load, static contractions, old adults are more fatigue resistant than young adults. However, this age-related fatigue advantage is believed to be lost under dynamic conditions (Hunter, 2009a; Chapter 3). A number of hypotheses have been proposed to explain this disparity such as: contractile slowing, impaired peripheral blood flow, impaired central drive, substrate utilization efficiency, and task complexity, but to date a clear mechanism has not been identified (Allman & Rice, 2001; Hunter, 2009a; Lanza *et al.*, 2004; Tevald *et al.,* 2010). The lack of mechanism clarity may be in part due to the number of factors that influence the fatigue response. Properly characterizing influential moderators may in turn delineate underlying mechanisms.

It has been hypothesized that the demands placed upon the central nervous system (CNS) are relative to the demands of the task (i.e. simple task = low demand; complex task = high demand) (Lanza *et al.*, 2004). Under this premise it is conceivable that age-related changes within the central nervous system (i.e. decreased cortical excitability (Roos *et al.*, 1997), decreased cortex size (Drag & Bieliauskas, 2010), and impaired cognitive function (Drag & Bieliauskas, 2010) may result in relative increases in task demand and subsequent reduction in performance. Increased task complexity has been proven detrimental (i.e. poorer performance) for the older adult in both dual-task paradigms (Verhaeghen *et al.*, 2003) and short duration (non-fatiguing) motor control tasks (Vaillancourt & Newell, 2003). Yet it is unknown whether increased task complexity is a mediating factor for the loss of an age-related fatigue advantage with isokinetic tasks, which are presumably more complex than isometric tasks.

The ability to perform a motor task is the culmination of multiple central and peripheral processes. One subset of these processes known as executive function, involves the planning, coordinating, sequencing and monitoring of complex goal-directed behavior (Royall *et al.*, 2002).Executive function assessment may include evaluating one or more of the following cognitive abilities: dividing attention, updating and monitoring information, mental set and task switching, response inhibition and visuospatial function (Rucker *et al.*, 2012). Outcomes for these abilities have demonstrated positive associations with motor performance tasks including gait (Watson *et al.*, 2010), falls (Rapport *et al.*, 1998), activities of daily living (Razani *et al.*, 2007) and dual-task performance (Coppin *et al.*, 2006). It is not clear whether executive function plays an important role in the relationship between task complexity and muscle fatigue. If so, this may be an opportunity to improve motor performance (i.e. fatigue) by incorporating cognitive tasks within a rehabilitation protocol.

The primary purpose of this study was to identify if task complexity is an influential factor in the age-related fatigue advantage that is lost under dynamic conditions. It is hypothesized that the older adult will be more fatigue resistant for a simple isometric task but not for a complex isometric task (e.g., a force-matching sine waveform paradigm). Thus indicating that despite similar workloads and task conditions, the complexity of the task influences fatigue resistance. A secondary purpose was to identify the predictive value of executive function upon fatigue resistance. It is hypothesized that reduced executive function will be a significant predictor of poorer fatigue resistance for complex tasks (i.e., sinewave isometric and isokinetic) in older adults. The results of this study will further delineate the role of task complexity on age-related fatigue differences which may have clinical relevance to traditional rehabilitation and fitness training regimens in the older adult.

Methods

Subjects

A total of 69 healthy adults participated in this study, recruited from the local and University community. Participants were recruited specifically for the young adult, 18-35 yrs (n=33) or old adult, >65 yrs (n=36) sub-groupings (see Table 4-1). Exclusion criteria included: history of significant past medical history (i.e. neuromuscular disease, coronary artery disease (myocardial infarction within 1 year), cancer (within last 5 years), diabetes, stroke, hypertension, peripheral vascular disease), non-traumatic osteoporotic fracture, previous history of major injury, trauma and/or surgery in the upper vs. lower extremity (for elbow and ankle testing, respectively), report of pain >4/10 at ankle or elbow (any time during day), pregnancy, recent changes in physical activity level, medications that may influence one's ability to follow instructions, and/or a positive screen for cognitive impairment (<26 on the Montreal Cognitive Assessment). Some participants were eligible for testing at only one joint, ankle (n = 70, 36 F, 34 M) or elbow (n = 67, 34 F, 33 M), due to pain or previous injury. All participants provided written informed consent prior to participation, as approved by the University of Iowa Biomedical Institutional Review Board, and compensated for their time. Subjects participated in three testing sessions, each session lasted 60-90 min. The testing order was performed in a pseudo-randomized order on three separate days with no less than three days between each testing session. All torque signals were digitized and recorded (1000Hz, Labview 8.0 software, National Instruments, Austin, TX) for later offline analyses using Matlab (Mathworks, Natick, MA).

Fatigue Tasks

Fatigue testing was performed at both the ankle (dorsiflexors) and elbow (flexors) joints, as previous studies have demonstrated joint interactions with fatigue moderators (see Chapter 2). Therefore, the two most-commonly studied joints (ankle and elbow) for age-related muscle fatigue were studied to determine consistency of results. All subjects performed a 5-min upper and lower body warm-up on a Schwinn Airdyne bicycle prior to the start of the testing protocol. Unilateral fatigue testing of the dominant ankle dorsiflexors and elbow flexors was performed on a Biodex System 3 (Biodex Medical Systems, New York). The subject was positioned with the corresponding joint center aligned with the dynamometer axis of rotation and properly restrained per standard Biodex testing procedures. Each subject performed one of three voluntary tasks at the ankle and elbow at each visit, in a pseudo-random order.

After the completion of each fatigue task, participants were asked to rate their perceived exertion and pain using the Borg CR-10 (Borg, 1998). In addition, participants were asked to rate how difficult or challenging the task was to perform using a 0 to 10 verbal rating scale. Subjects were instructed to anchor the scale with 0, "no mental effort, extremely easy" to 10, "extreme mental effort, most difficult task possible". Fatigue index (decline in torque producing capability, see specific equations below) was the primary outcome variable for each fatigue task. In addition, the torque variation was assessed as the coefficient of variation (CV) for the two isometric tasks (see below).

Isometric Tasks (simple & complex)

Isometric testing was performed at 110° of ankle plantarflexion and 60° elbow flexion. Prior to the start of the fatigue task 3, 5-sec maximal voluntary isometric contractions (MVICs) were performed in alternating torque directions (30-sec rest). The fatigue tasks were then performed for a fixed time interval of 75-sec at the ankle and 60-sec at the elbow, based on pilot data indicating most individuals can complete the tasks.

Immediately following each isometric fatigue task a 5-sec MVIC was performed. *Simple Isometric Task (Sustained)* - the subject matched a sustained target force (i.e. straight line on the monitor) at 55% of MVIC, which was reassessed at the start of each test session (i.e. the same maximum was not used across multiple testing sessions). *Complex Isometric Task (Sinewave)* - the subject matched a 0.1 Hz sinusoidal target varying from 65% to 45% (mean 55%) of MVIC shown on a computer monitor in real time. For the isometric tasks, the fatigue index was calculated as the relative decay in MVIC following the fatigue protocol:

$$\text{FI (\% decline)} = 100 * (\text{MVIC}_{\text{initial}} - \text{MVIC}_{\text{post fatigue}}) / \text{MVIC}_{\text{initial}}.$$

The coefficient of variation (CV) of the actual torque produced during the fatigue tasks were assessed for 5 ms around the quartile points in time. The CV was calculated as the standard deviation/ mean (σ/μ) for the torque signal (for the isometric tasks only). Given the nature of the sustained and sinewave tasks were different, the quartiles of CV were normalized to the first bin (% of initial). Therefore relative comparisons may be drawn, despite the absolute differences in variability. A greater CV of torque production has been shown to result in greater motor unit activation and subsequently greater fatigue (Hunter *et al.*, 2004). This simple measure of the torque signal may give insight into how a task is coordinated without performing intricate signal processing of electromyographic signals.

Complex Isokinetic Task

Forty maximal isokinetic concentric-concentric contractions were performed at 60°/s through a 40 – 60 degree range of motion: 10° dorsiflexion to 30° plantarflexion for the ankle and 60° to 120° of flexion for the elbow. Under the assumption dynamic tasks are inherently more complex than isometric tasks, no variation in target force was asked of the participants. For the isokinetic task, the fatigue index was calculated as the relative decay in peak torque (PT) from the initial three to the final three contractions of the fatigue protocol:

$$FI\ (\%\ decline) = 100 * (mean\ PT_{rep\#\ 1\text{-}3} - mean\ PT_{rep\#\ 38\text{-}40}) / mean\ PT_{rep\#1\text{-}3}.$$

Neurocognitive Assessments

Three neurocognitive assessments were performed. Cognitive Screen- The Montreal Cognitive Assessment (MOCA) is a freely accessible, multi-lingual 30-item test that has demonstrated good sensitivity (90%) and specificity (87%) for identifying mild cognitive impairment. Participants were excluded if scores < 26 to ensure cognitive impairment was not a confounding factor in performing a simple vs. complex task (Nasreddine *et al.*, 2005). Executive Function- the Trailmaking A and B tests assess visuoperceptual and working memory, respectively. Part A requires the subject to connect a series of consecutively numbered circles, while Part B requires connecting a series of numbered and lettered circles, in an alternating sequence (number to letter) (Sanchez-Cubillo *et al.*, 2009). The ratio of B/A has been shown to be indicative of executive function, specifically set-switching (a component of executive function assessment) while controlling for differences in motor function that can vary with age (Arbuthnott & Frank, 2000). This B/A ratio is the primary dependent variable used as a measure of executive function (see analysis below). Intelligence (g)- The North American Adult Reading Test (NAART) is a 61- item index that estimates verbal intellectual ability (Blair & Spreen, 1989). This index has been shown to be highly reliable (0.88 inter-rater) and highly valid with IQ (0.75 to 0.85). This variable was included to control for differences in underlying intelligence when assessing the relationships between fatigue index and executive function.

Physical Activity Questionnaires

Self-reported physical activity levels were assessed to determine the homogeneity of the two groups (old and young). Unfortunately, there are few questionnaires available which are validated across the lifespan for use in both young and old adults. Accordingly we chose two instruments: 1) a standardized questionnaire that has been used in the older adult population, but validated only in young adult populations and 2) a well-validated instrument for the older adult population that is not commonly used in young adults. *The International Physical Activity Questionnaire (IPAQ)* - is a 27-item self-report measure of physical activity in the previous seven days (Craig *et al.*, 2003). The IPAQ assesses work, leisure, active transportation, and domestic activities, estimating the total activity as a product of the intensity (metabolic equivalents *x* time in minutes per week). The IPAQ is a valid and reliable measure of self-report physical activity, with a median criterion validity of 0.30 relative to accelerometer data and a 3-7 day test-retest reliability of 0.80 assessed in young adults, comparable to many other established instruments (Sallis & Saelens, 2000). While the IPAQ has not been validated in the old adult population, it has been used with old adult populations (Kolbe-Alexander & Lambert, 2006; Tomioka *et al.*, 2011). *The Physical Activity Scale for the Elderly (PASE)*- is a 10-item self-report instrument which assesses physical activity specifically in older persons over a one-week time period (Washburn *et al.*, 1993). Included are the frequency and duration of leisure activities, housework, lawn work/yard care, etc. The assessment demonstrates both construct (0.20) and concurrent (0.64) validity with mean activity level in older adults (Washburn *et al.,* 1999a; Washburn & Ficker, 1999b).

Functional Performance

The relationship between isolated fatigue measures (such as the ones performed in this study) and function are not well understood. Therefore a simple assessment of functional capacity, the 6-minute walk test (6MWT), will be administered. This test was performed on the 1st, 2nd, or 3rd test visit in a pseudo-randomized fashion, but was always be tested on the same day as ankle isokinetic testing. This test evaluates the global response of all systems during a submaximal, self-paced exercise test. The 6MWT was found to be easier to administer and more reflective of activities of daily living, in comparison to other walk tests (Solway *et al.*, 2001). A hallway of 70 ft. was used for the 6MWT, which is an acceptable deviation from the original design (Weiss *et al.*, 2000). The final outcome variable was total feet ambulated in a six-minute time period.

Statistical Analyses

To examine the influence of task complexity on fatigue, three-way (task x age x sex) mixed analysis of variance (ANOVA) were used to compare each independent variable across the two isometric tasks (primary analyses) for each joint separately. The independent variables included fatigue index (primary analysis), coefficient of variation, task exertion and task difficulty (secondary analyses). Univariate ANOVA were performed for peak torque analyses upon confirming there was not a significant difference between the two isometric peak torques. In addition to traditional null hypothesis significance testing (NHST), effect sizes were also determined using Comprehensive Meta-Analysis software (Biostat, Englewood, NJ). Effect sizes account for magnitude of and precision of the estimate as provided by effect size and the 95% confidence interval (Nakagawa & Cuthill, 2007). Hedge's g was chosen to estimate effect size because of the small sample size correction (Borenstein, 2009).

Linear regression and bivariate correlation techniques were performed to investigate whether a relationship existed between executive function and fatigue indices. Linear regression models included the fatigue index for each "complex" test condition as the dependent variable with the following independent variables: age, sex, Trailmaking B/A ratio and NAART.

Results

Subjects

Subject demographics are provided in Table 4-1. There was no difference between young and adults for height and weight; however, younger adults had significantly less body fat. Overall physical activity levels were similar as indicated by the IPAQ-total and PASE-total. Sitting time was significantly greater for older adults per the PASE-sit, but not per the IPAQ-sit. Vigorous activity (IPAQ-vigorous) was greater for younger adults than older adults (not available with the PASE). There was no significant difference between young and old for the 6-MWT time, but the older adult reported greater perceived exertion levels upon completion of the test. The Trailmaking A and B scores were significantly greater for the older adult, but there was no age difference in the measure of executive function, the B/A ratio.

Fatigue Indices

Ankle: In line with the original hypothesis old adults were more fatigue resistant than young adults indicated by the significant main effect of age ($p<0.05$) and medium ESs (see Table 4-2). However, in contrast to the original hypothesis, there was no difference between the simple isometric task and complex isometric tasks ($p = 0.942$) (see Figure 4-1A). Follow-up tests revealed an unanticipated sex difference in fatigue resistance. Old males were more fatigue resistant for both the sustained ($p = 0.044$) and sinewave ($p = 0.014$) isometric tasks with medium and large ES, respectively (see Table 4-3); reinforcing the minimal influence task complexity was as a contributory factor. Contrary to the original hypothesis, no age-difference in fatigue resistance was observed in females for the sustained ($p = 0.387$) and sinewave ($p=0.722$) isometric tasks (see Figure 4-1B) with small ESs. No differences existed between young and old subjects for the isokinetic task fatigue indices ($p = 0.48$) with small ESs (see Table 4-3).

Elbow: None of the main effects were significant, however the age *x* sex interaction was significant ($p<0.05$) (see Figure 4-2A) and the ESs were small to medium (see Table 4-2). Follow-up comparisons resulted in similar sex-dependent findings found at the ankle, which were contrary to the original hypothesis. Old males were more fatigue resistant for the sustained ($p < 0.01$) and sinewave ($p < 0.5$) isometric tasks (see Figure 4-2B) with large ESs (see Table 4-3). These results yet again indicated that complexity was not a primary mediator of fatigue resistance. Contrary to the original hypothesis, females did not differ in their fatigue resistance demonstrated by insignificant differences for the sustained ($p = 0.915$) and sinewave ($p=0.555$) isometric tasks (see Figure 4-2B) and small ESs (see Table 4-3). No differences existed between young and old subjects for the isokinetic task fatigue indices ($p = 0.64$) with a small ES (see Table 4-3). Effect sizes within sex demonstrated young males being more fatigue resistant with a medium ES (ES= -0.5) and small ES for females (ES= 0.03).

Peak Torque

Ankle: Initial analysis confirmed no difference between peak torque assessed prior to each isometric task ($p > 0.4$), therefore a univariate (age *x* sex) ANOVA was performed to compare mean peak torque between cohorts. Greater isometric peak torque was demonstrated in young adults ($p < 0.05$) and male subjects ($p < 0.01$) (see Figure 4-3). Follow-up comparisons resulted in young females being significantly stronger than old females ($p < 0.01$), but no significant difference existed between old and young men ($p > 0.5$) (see Figure 4-3). Effect size calculations included the isokinetic task in addition to the isometric mean peak torque. Large effect sizes were demonstrated for females across all tasks (ES_{range} = - 0.91 to -1.03) tasks, while male ESs were small and insignificant (ES_{range} = - 0.21 to 0.16).

Elbow: Initial analysis confirmed no difference between peak torques assessed prior to each isometric task ($p > 0.4$), therefore a univariate (age *x* sex) ANOVA was performed for the mean elbow peak torque. Young adults ($p < 0.05$) and male subjects ($p < 0.01$) demonstrated greater peak strength (see Figure 4-3). Despite the significant main effects demonstrated above, none of the follow-up comparisons resulted in significant differences in peak torque between old and young men and old and young women ($p > 0.05$). Effect sizes were small to medium for males and females (ES_{range} = - 0.4 to - 0.61; ES_{range} = -0.23 to - 0.34, respectively).

Torque Coefficient of Variation

Ankle: It was initially thought that old adults would be less variable for the simple task, but more variable for the complex task (as compared to young). A four-way (time *x* task *x* age *x* sex) ANOVA of the coefficient of variation (of the torque signal) indicated a significant change over time ($p = 0.05$), greater in young ($p < 0.05$), and a task *x* age *x* sex interaction ($p < 0.05$). Follow-up comparisons were not in-line with the initial hypothesis because old males were significantly less variable across all 4 quartiles of the sustained task only ($p < 0.05$; ES = 0.56 to 1.4) (see Figure 4-4A). There was no significant difference between males for the more complex sinewave task across all 4 quartiles ($p < 0.18$; ES_{range} = 0.08 to - 0.56). Contrary yet again, none of the female comparisons were statistically significantly different except for the final CV quartile for the sinewave task, where young females had greater variation ($p < 0.05$; ES= 0.8) (see Figure 4-5A).

Elbow: A four-way (time *x* task *x* age *x* sex) ANOVA for the coefficient of variation (of the torque signal) increased over time ($p = 0.01$), old were less variable ($p < 0.05$), females were less variable than males ($p < 0.05$) and there was a task *x* time *x* sex interaction ($p < 0.05$). Due to the triple interaction follow-up comparisons were not made simply between young and old, but rather separated by sex. Again results were in opposition of the original hypothesis of old adults being be less variable for the simple task, but more variable for the complex task (as compared to young). Old and young men were not significantly different for either task across all 4 quartiles ($p > 0.12$) with inconsistent ESs (ES_{range} = - 0.06 to 1.0) (see Figure 4-4B). There was not a consistent pattern of simple versus complex variability with females as the young women were intermittently more variable for the elbow sustained task only during the 1st and 3rd quartiles ($p<0.05$; ES=0.82 and 0.83, respectively) (see Figure 4-5B).

Perceived Difficulty

Ankle: A three-way (task *x* age *x* sex) ANOVA for perceived difficulty resulted in significant task differences ($p < 0.01$) and task x age interaction ($p = 0.01$). Follow-up comparisons indicated that old adults perceived the sinewave task as more difficult than young adults ($p < 0.05$; ES= -0.61), with no difference for sustained or isokinetic ($p > 0.5$; ES < 0.15) (see Figure 4-6A).

Elbow: A three-way (task *x* age *x* sex) ANOVA resulted in old adults reporting greater perceived difficulty than young adults ($p = 0.001$). Follow-up comparisons resulted in old adults reporting greater difficulty than young adults with large ESs for the elbow sinewave ($p < 0.01$; ES = 0.97) and isokinetic ($p < 0.01$; ES = 0.83) tasks and medium ES for the sustained task ($p > 0.05$; ES = 0.51) (see Figure 4-6B).

Perceived Exertion

Ankle: A three-way (task *x* age *x* sex) ANOVA for perceived exertion identified a significant difference among the tasks ($p < 0.05$), but not age. Follow-up tests demonstrated exertion ratings were greater for the sinewave than the sustained task ($p < 0.01$; ES= 0.27) (see Figure 4-7A). Although not significant there we a medium ES for old rating greater exertion for the sinewave task ($p > 0.05$; ES = -0.48). None of the other task or age comparisons were significantly different with small ESs ($p > 0.05$; ES_{range} = 0.04 to 0.27).

Elbow: A three-way (task *x* age *x* sex) ANOVA for perceived exertion resulted in no significant differences between ages, tasks or sex for the elbow (see Figure 4-7B). The ESs between task and age were small ($ES_{range} = 0.04$ to 0.38)

Executive Function Regression

None of the linear regression models, controlling for sex and intelligence, found executive function (B/A ratio) to predict the complex task fatigue indices as indicated by the following coefficients of determination (R^2): ankle sinewave ($R^2 = 0.12$), elbow sinewave ($R^2 = 0.05$), ankle isokinetic ($R^2 = 0.07$) and elbow isokinetic ($R^2 = 0.07$). Uncorrected associations between executive function (B/A ratio) and fatigue indices were also insignificant with low R^2 values ranging from 0.06-0.24 ($p > 0.06 – 0.63$). These findings mirror the lack of change for the fatigue index between the sustained and sinewave tasks; further substantiating the lack of a relationship between task complexity and fatigue resistance.

Discussion

The purpose of this study was to identify if task complexity is a mediator of age-related fatigue resistance. We were unable to support our initial hypothesis that the old adult would be more fatigue resistant for simple tasks (sustained isometric contraction), but under presumably more complex conditions (i.e. sinewave), this advantage would be lost. Task complexity did not influence fatigue resistance between the two tasks with otherwise similar workloads, nor explain the loss of an age-related advantage under isokinetic conditions, at the ankle and elbow. It appears the overall amount work is more important than the complexity of the work as it relates to fatigue resistance.

The large effect sizes for age-related differences in fatigue index for males and small effect sizes for females calculated for the isometric tasks were somewhat unexpected. In the previously completed meta-analysis (Chapter 3) old males and females both were more fatigue resistant at the ankle for intermittent isometric tasks with large effect sizes (ES=0.84-86). Further extending the meta-analysis findings, old males were more fatigue resistant under ankle sustained isometric conditions (ES=0.52), females only were not represented in any ankle studies. It was anticipated that females in the current study would follow suit and demonstrate a similar effect size as the overall female isometric ES (ES= 0.52, $p < 0.01$). However, the findings did not support this assumption; instead the current ES mirrored that of the overall (i.e. sustained, intermittent and isokinetic tasks) female ES observed in the meta-analysis (ES=0.23, $p < 0.01$). The precedent of an age-related sex difference is mixed with some authors finding both old males and females being more resistant (Ditor & Hicks, 2000; Kent-Braun *et al.*, 2002; Russ *et al.*, 2008), while another study found males driving the age-effect (Hunter *et al.*, 2004) as observed in this study. Despite some inconsistent results in the literature, it appears that age-related changes in fatigue resistance affect males to a greater extent than females as demonstrated by the current findings, although it may be muscle group/joint dependent.

A loss of strength is thought to be displayed with aging (Goodpaster *et al.,* 2006), however there was no difference in peak torque between old and young males (ankle and elbow). Young females were significant stronger at the ankle with a large ES, where no difference existed at the elbow. Interestingly, there was consistent age-related advantage in males that was not demonstrated in females regardless of differences in peak strength. Differences in energy system utilization during muscle contraction may offer further insight in the dichotomy between peak strength and fatigue resistance in men. Young men commonly rely upon glycolytic pathways while old men rely upon oxidative pathways (Lanza *et al*, 2005). Additionally, the energy cost of muscle contraction has been demonstrated to be lower in the old adult as determined by the ATP/twitch ratio (Tevald *et al.*, 2010). The sustained ability of glycolysis in conjunction with a reduced metabolic contraction cost may allow for the maintenance of peak strength and isokinetic fatigue resistance as demonstrated by no difference between old and young men. While the utilization of oxidative pathways coupled with lower metabolic costs may explain the enhanced fatigue resistance under isometric conditions for old men. Investigations of metabolic efficiency with aging have been extended to males only. However, these differences may not be evident in females given the lack of difference in fatigue resistance and similar reliance upon oxidative pathways (Yassierli *et al.,* 2007).

The age-related fatigue resistance advantage demonstrated by the male subjects may be attributed to the force fluctuations (CV) during the task. An increase in force fluctuations has been associated with in greater motor unit activation and subsequently greater fatigue (higher fatigue index) (Hunter *et al.*, 2004). It was postulated that the old adult would have less fluctuations during the simple isometric task (resulting in less fatigue), but greater fluctuations during the complex isometric task (resulting in greater fatigue). The results of this study corroborated only the simple (sustained) isometric task portion of this hypothesis as old males had less force fluctuations (CV) throughout the entire task (i.e. all 4 quartiles) as compared to young males. The presumably more complex sinewave task did not result in a significant difference CV between old and young men, yet old men were still significantly more fatigue resistant. The relationship between force fluctuations and fatigue were further demonstrated by significant, medium correlations between CV and the fatigue index for the sustained ankle task only (r^2=0.52, $p<0.05$). Young females utilized a strategy of intermittent variability with large effect size increases in force fluctuations for the 1st and 3rd quartiles, but small differences for the 2nd and 4th. It appears the female strategy to complete the task did not influence their overall fatigue response. It is not clear how force fluctuations (CV) would explain a fatigue advantage for the sustained task, but not for sinewave task, nor why it would be limited to the ankle for males only. While CV may play a role, additional theories may provide further insight into the differences currently identified.

It is not clear to what extent the old subjects recruited influenced the current results. There was no difference in peak torque between old and young males; there was not an age-related fatigue advantage in females; and in general no difference in the force fluctuations. Based upon comparisons of normative values for multiple assessments, the old subjects recruited could be considered high functioning. The Trailmaking A and B scores adjusted for age and education were in the 90th percentile, while the young cohort scored in the 80th percentile (Tombaugh, 2004). The 6-MWT was not significantly different between old and young, and the old mean values were greater than normative 95% CI values (adjusted by age and sex) (Steffen *et al.,* 2002). In addition, there were no differences in their overall physical activity levels (old v young). Future work may seek to identify fatigue responses in old adults from a wide spectrum of very active to sedentary. This type of investigation may clarify what type of adaptation is age-related fatigue resistance; a beneficial one to be exploited or adverse one to be avoided. If adverse, the isolated fatigue task may serve as a quick, cost-effective global indicator of maladaptive age-related changes in skeletal muscle.

A limitation of this study that may account for the lack of a difference in fatigue resistance between the simple and complex isometric tasks could be an insufficient difference in task complexity. Yoon *et al.*, (2009) performed two separate fatigue studies, one involving mental-math tasks of increasing difficulty and the second mental-math of stable, minimal difficulty. Fatigue was experienced to a greater extent during the increasingly stressful session, but no difference during the simple math session. Difficulty was not quantified per se, but rather anxiety measures were assessed via verbal rating scale, cortisol changes and the State Trait Anxiety Index. Although anxiety and complexity are not the same construct, this current study may have been more similar to the complexity of the simple mental-math than the increasingly difficult mental-math task. However, the purpose of this study was not to determine whether a task of extreme difficulty influences fatigue development, but rather to determine if complexity, relative to that expected under isokinetic conditions, could affect fatigue. It is clear that the older adult perceived the complex isometric task as being more difficult with greater ratings of perceived difficulty and exertion. Further the sinewave perceived difficulty ratings were found to be of similar complexity to that of the isokinetic task. Therefore, despite sufficient difficulty, there were no differences in fatigue responses between the two isometric tasks.

A further limitation that may contribute to greater variability in the fatigue response between individuals is the potential for subjects to have achieved differing levels of central activation between age groups. No measures of central activation (i.e. twitch interpolation) were performed to determine if subjects fully activated their elbow flexors or ankle dorsiflexors for either pre- or post-task MVCs. However, numerous studies have demonstrated that both young and old adults are capable to fully activate their muscles, producing similar levels of central activation (Kent-Braun & NG, 1999; Kent-Braun *et al.*, 2002; Russ *et al.*, 2008). Although, that does not preclude the possibility of differences in motivation to fully activate.

In summary, task complexity did not influence fatigue resistance, nor explain the loss of an age-related advantage under isokinetic conditions. Given the lack of cognitive influence, it appears that changes in age-related fatigue resistance may be related to muscle-specific adaptations. Future efforts should be directed towards identifying age-related changes specific to the muscle, substrate utilization, velocity-specific loss of power and the role that maximal versus submaximal intensities play.

Table 4-1. Subject demographic information categorized by age (young and old).

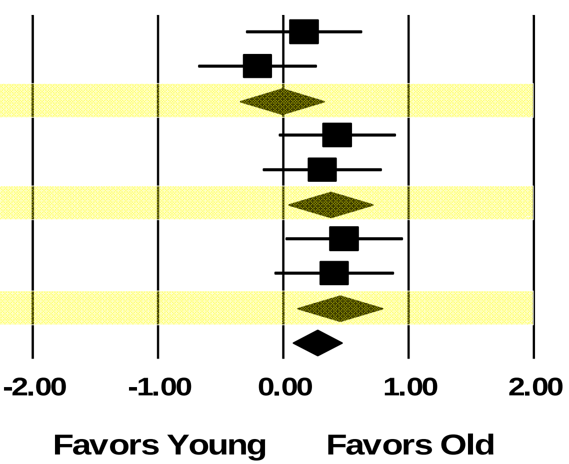
	Young	Old	p-value
Sample size (n)	34	36	
Age (yrs)	24 ± 7	68 ± 2.7	
Height (cm)	172 ± 14	171 ± 11	$p = 0.728$
Weight (kg)	73 ± 16	76 ± 14	$p = 0.323$
Body Fat (%)	21.8 ± 10	30 ± 10	$p < 0.001$
Trail A (s)	18.7 ± 5.8	24.9 ± 7.8	$p < 0.001$
Trail B (s)	37.8 ± 17.5	49.3 ± 18.9	$p < 0.01$
IPAQ-total	5336 ± 5356	5048 ± 4379	$p = 0.803$
IPAQ-sitting	2582 ± 1189	2513 ± 1082	$p = 0.798$
IPAQ-vigorous	181 ± 225	90 ± 138	$p < 0.05$
PASE-total	168 ± 85	162 ± 63	$p = 0.728$
PASE-sit	2.9 ± 1.3	3.5 ± 1	$p < 0.05$
6 MWT (m)	619 ± 94	595 ± 130	$p = 0.373$

Table 4-2. Effect sizes for young and old adults mixed sex grouped by task type (isokinetic, sinewave and sustained).

Young vs. Old All Tasks (effect size)

Study name	Contraction	Joint	Statistics for each study: Hedges's g	Standard error	Lower limit	Upper limit	p-Value
Avin 2012 (MX_K_A)	Isokinetic	Ankle	0.166	0.237	-0.298	0.630	0.484
Avin 2012 (MX_K_E)	Isokinetic	Elbow	-0.205	0.242	-0.680	0.269	0.396
			-0.016	0.169	-0.348	0.316	0.926
Avin 2012 (MX_S_A)	Sine	Ankle	0.431	0.239	-0.038	0.900	0.072
Avin 2012 (MX_S_E)	Sine	Elbow	0.311	0.243	-0.165	0.788	0.200
			0.372	0.171	0.038	0.706	0.029
Avin 2012 (MX_M_A)	Sustained	Ankle	0.485	0.240	0.015	0.956	0.043
Avin 2012 (MX_M_E)	Sustained	Elbow	0.407	0.244	-0.072	0.885	0.096
			0.447	0.171	0.111	0.782	0.009
			0.266	0.098	0.073	0.459	0.007

Hedges's g and 95% CI



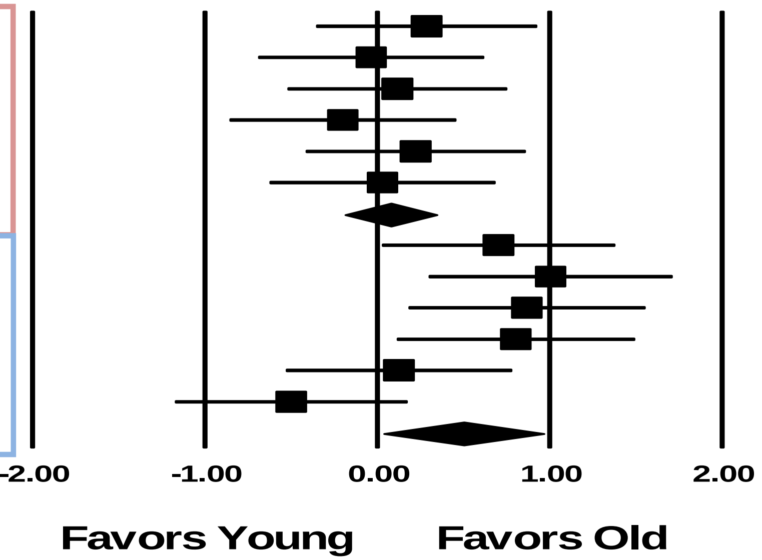
A negative value identifies young adults being more fatigue resistance (fatigued less), while a positive value indicates old adults being more fatigue resistant (fatigued less). The highlighted portion signifies the summary effect size for that grouped task type.

Table 4-3. Effect sizes for young and old adults separated by sex grouped by task type (isokinetic, sinewave and sustained).

Age X Sex All Tasks (effect size)

Sex	Contraction	Joint	Hedges's g	Standard error	Lower limit	Upper limit	p-Value
FEMALE	Sustained	Ankle	0.286	0.328	-0.357	0.928	0.383
FEMALE	Sustained	Elbow	-0.035	0.336	-0.693	0.622	0.916
FEMALE	Sine	Ankle	0.117	0.326	-0.523	0.756	0.721
FEMALE	Sine	Elbow	-0.200	0.336	-0.860	0.459	0.551
FEMALE	Isokinetic	Ankle	0.223	0.327	-0.418	0.864	0.496
FEMALE	Isokinetic	Elbow	0.030	0.335	-0.627	0.688	0.929
FEMALE			0.074	0.135	-0.192	0.339	0.587
MALE	Sustained	Ankle	0.703	0.346	0.025	1.382	0.042
MALE	Sustained	Elbow	1.005	0.362	0.297	1.714	0.005
MALE	Sine	Ankle	0.868	0.352	0.179	1.557	0.014
MALE	Sine	Elbow	0.804	0.354	0.110	1.497	0.023
MALE	Isokinetic	Ankle	0.125	0.336	-0.533	0.784	0.709
MALE	Isokinetic	Elbow	-0.499	0.345	-1.176	0.178	0.148
MALE			0.495	0.236	0.033	0.958	0.036

Hedges's g and 95% CI



A negative value identifies young adults being more fatigue resistance (fatigued less), while a positive value indicates old adults being more fatigue resistant (fatigued less).

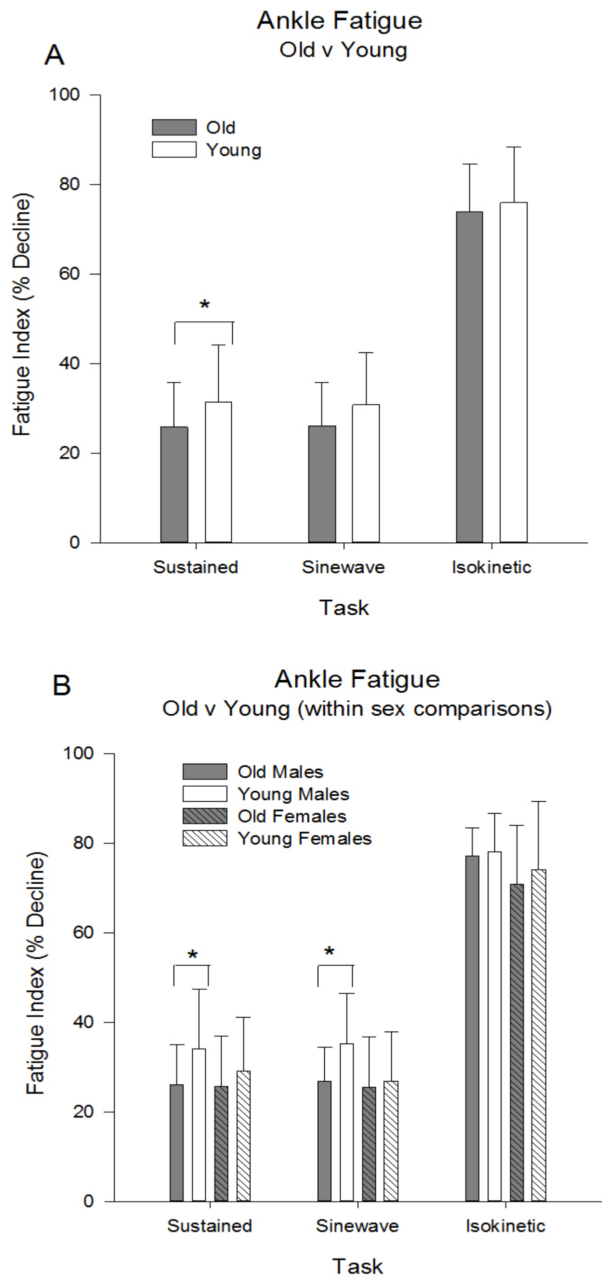


Figure 4- 1 Fatigue indices are depicted at the ankle, where a greater fatigue index (% decline) indicates a greater level of fatigue experienced during the task. Old vs. Young (1A): Old adults (gray) experienced less fatigue than the young adults (white) for the isometric task only.* Within Sex Comparison (1B): Old men (solid gray) experienced less fatigue for the sustained* and sinewave** tasks than the young males (solid white). No differences were found between old women (dashed gray) and young women (dashed white) for any of the 3 tasks performed. (* $p < 0.05$)

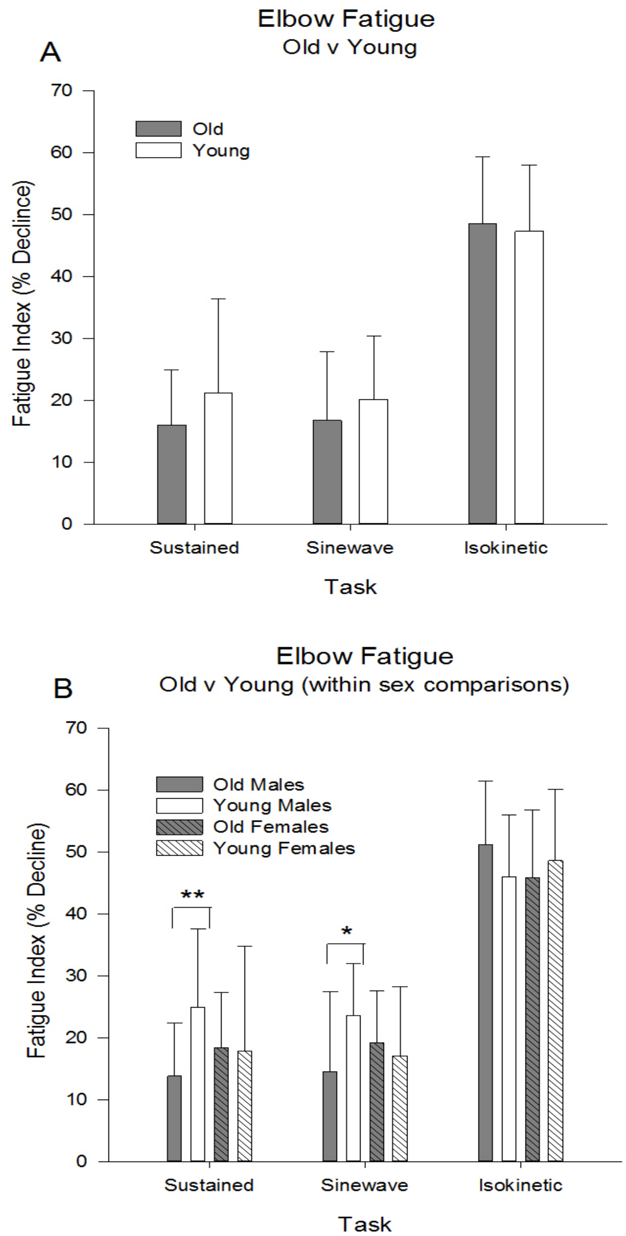


Figure 4- 2 Fatigue indices are depicted at the elbow, where a greater fatigue index (% decline) indicates a greater level of fatigue experienced during the task. <u>Old vs. Young (2A)</u>: There were no significant differences in fatigue resistance between the old adults (gray) and young adults (white) ($p \geq 0.097$). <u>Within Sex Comparison (2B):</u> Old males (solid gray) experienced less fatigue for the sustained** and sinewave* tasks than the young males (solid white). No differences were found between old females (dashed gray) and young females (dashed white). (* $p< 0.05$; ** $p< 0.01$)

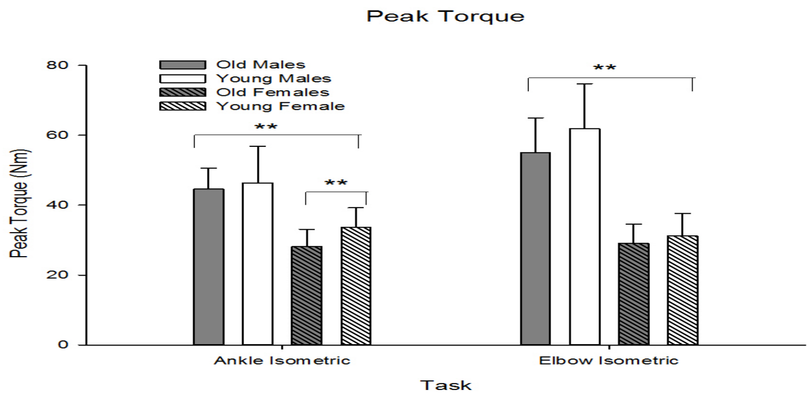


Figure 4- 3 Peak torque for the ankle (left) and elbow (right) are depicted for old men (solid gray) vs young men (solid white) and old women (dashed gray) vs young women (dashed white) for mean isometric torque. Ankle: Young adults* and males ** demonstrated greater strength, while young females were stronger than old females**. Elbow: Young adults* and males ** demonstrated greater strength, while no differences existed with sex groups. (* $p < 0.05$; ** $p < 0.01$)

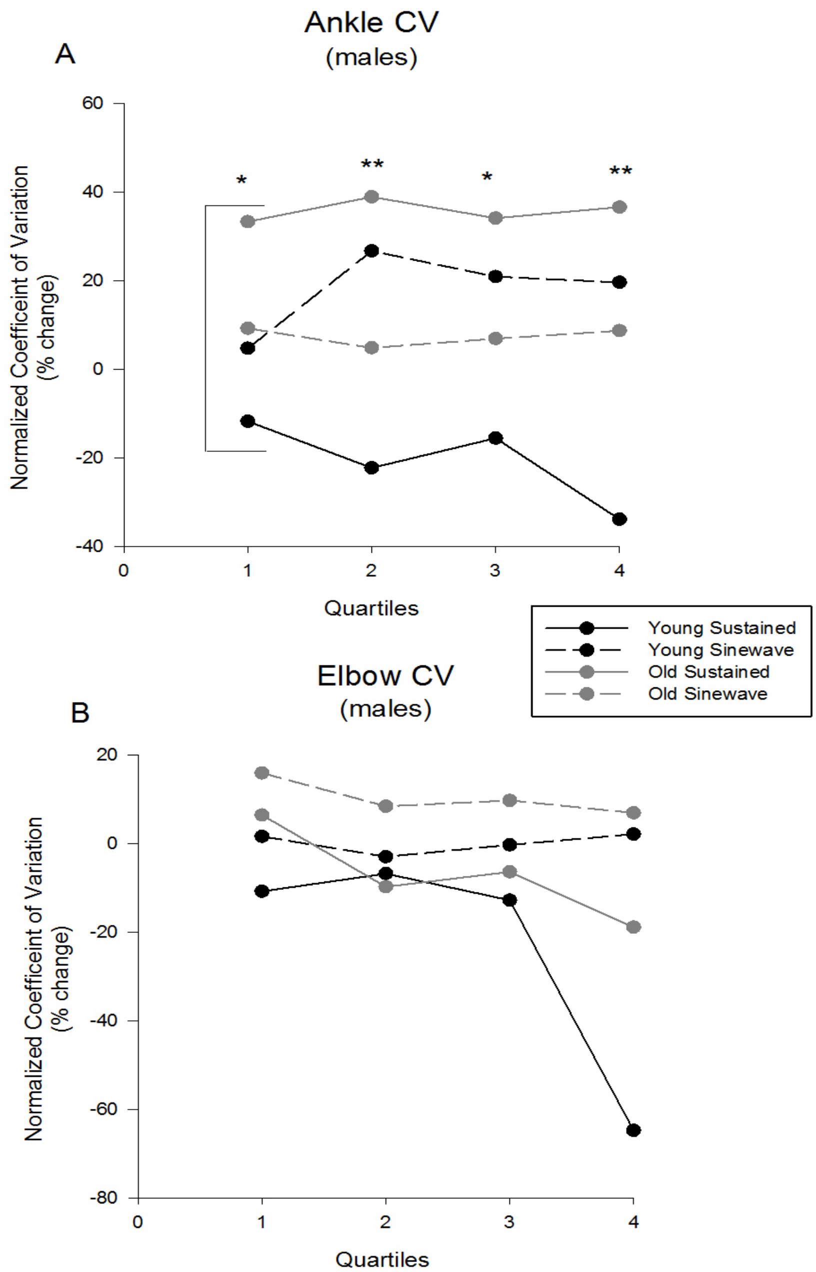


Figure 4- 4. (Males) Coefficient of variation (CV) of the torque signal for old (gray) and young (black) men for the sustained (solid line) and sinewave (dashed line) tasks. The positive direction indicates less variability, while the negative direction indicates more variability. Ankle (4A): Old men were less variable for the sustained task at all quartiles than young men.* ** Elbow (4B): No differences were demonstrated for any quartile for either task. (* $p < 0.05$; ** $p < 0.01$)

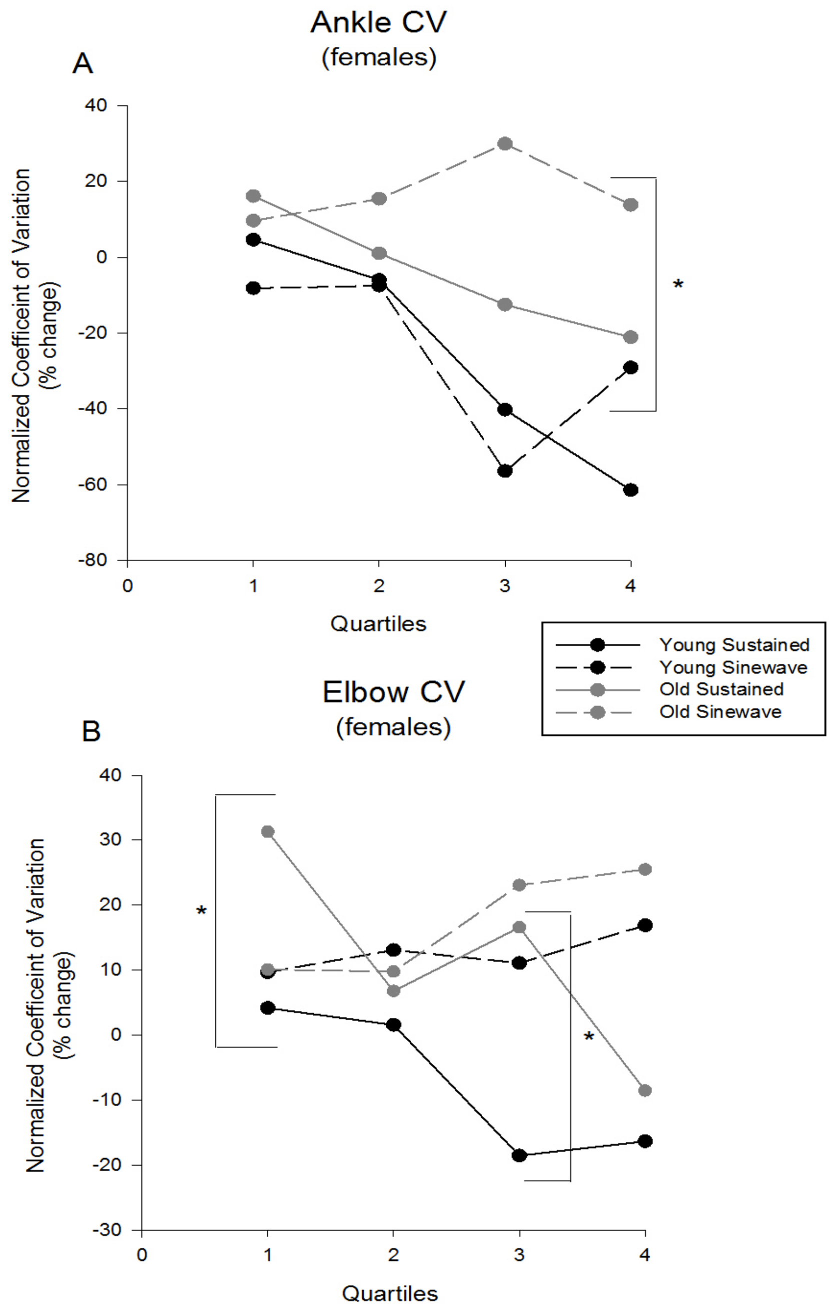


Figure 4- 5. (Females)Coefficient of variation (CV) of the torque signal for old (gray) and young (black) females for the sustained (solid line) and sinewave (dashed line) tasks. The positive direction indicates less variability, while the negative direction indicates more variability. Ankle (5A): Old men were less variable for the sustained task at all quartiles than young men.* ** Elbow (5B): No differences were demonstrated for any quartile for either task. (* p< 0.05; ** p< 0.01)

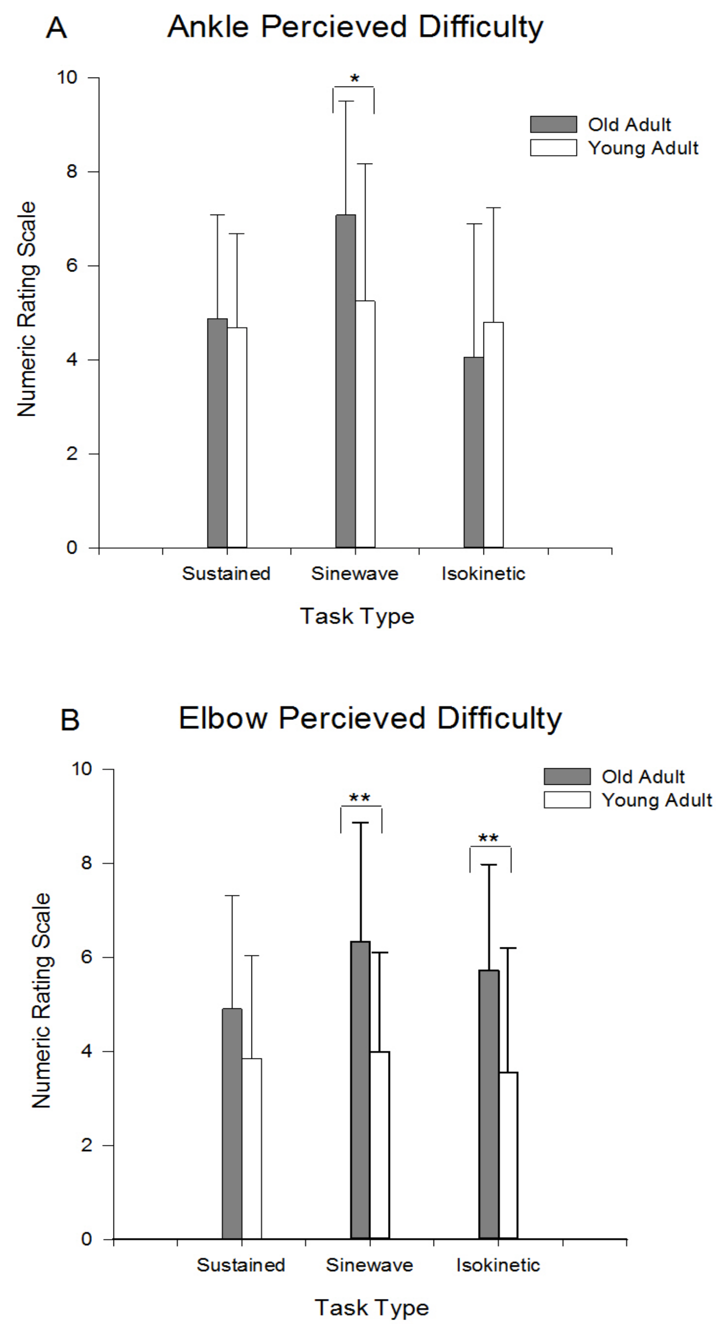


Figure 4- 6 Perceived ratings of difficulty between old (gray) and young (white) adults. Ankle (6A): Old adults reported the task as being more difficult for the sinewave task only*. Elbow (6B): Old adults reported the task as being more difficult for the sinewave** and isokinetic tasks**. (* $p < 0.05$; ** $p < 0.01$)

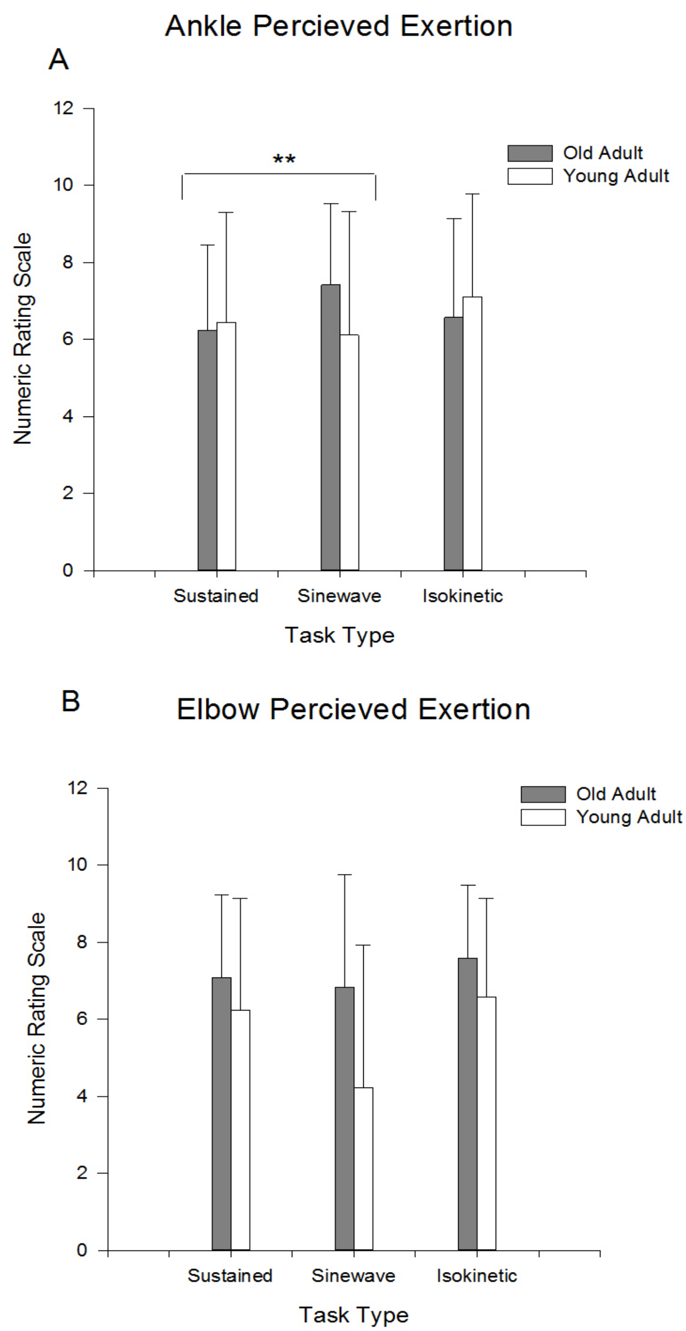


Figure 4- 7 Perceived ratings of exertion across all 3 tasks for old adults (gray) and young adults (white). Ankle (7A): Exertion ratings not different between age groups, but the sinewave task had greater exertion levels than the sustained task**. Elbow (7B): None of the main effects or interactions were significant. (* $p < 0.05$; ** $p < 0.01$)

CHAPTER 5

CONCLUSIONS

Summary

Fatigue is a difficult phenomenon to study due to the multiple contributing pathways; from the cortex of the central nervous system to the skeletal muscle in the peripheral nervous system. Contextually, muscle fatigue was defined as "any exercise-induced reduction in the ability to exert muscle force or power, regardless of whether or not the task can be sustained," (Bigland-Ritchie & Woods, 1984). The concept of fatigue is complicated by the response being dependent upon both constraints of the task and subject-specific traits. Although numerous investigations have provided insight into muscle fatigue, further efforts were needed to better characterize the influence of age, sex, joint/muscle group, contraction type, and task complexity.

The need for clarity was substantiated by developing incorrect hypotheses for all three studies. Although somewhat disappointing, being uniformly incorrect further exemplified the need to characterize the complex interplay among task- and subject-specific variables. This series of studies focused on five main moderators and their interactions: sex, joint/ muscle group, age, contraction type and task complexity. It is clear that several potential moderating variables and their interactions influenced muscle fatigue development as suggested by the updated conceptual model in Figure 5-1. Overall, these studies confirmed several variables influence fatigue, while highlighting their complex interplay.

In general, old adults were more fatigue resistant than young adults under isometric conditions regardless of the task type (sustained, intermittent and/or complex), while no differences existed during isokinetic tasks. This was substantiated by medium to large ESs for the isometric tasks in both the meta-analysis and experimental study. However, the age-related advantage appears to be mediated by sex, with men driving the apparent advantage. Old men (as compared to young men) were consistently more fatigue resistant (see Table 5-1). A female age-related advantage was anticipated in Chapter 4, based upon the Chapter 3 meta-analysis. Large ESs were demonstrated for ankle intermittent isometric tasks similarly in women and men (ES= 0.86, $p < 0.01$; ES=0.84, $p < 0.01$, respectively). However ESs were to the contrary among women in Chapter 4, small and insignificant (ES= 0.12-23) (see Table 5-2). It is apparent that old males are more fatigue resistant than young males. It is not clear whether females demonstrate a contraction type specificity (i.e. sustained vs. intermittent) or if the age-related changes simply affect males more than females.

Fatigue resistance was not a uniform phenomenon among young men and women. In Chapter 2 women were more fatigue resistant at the elbow with no difference at the ankle; where in Chapter 4 there was no difference at the elbow, but more fatigue resistant at the ankle. It is not clear what drove the apparent sex-difference in fatigue resistance between the two experimental studies for young males and females performing an isometric task. Regardless, the sex-advantage was consistent for both studies with females being more fatigue resistant for a joint/muscle group, but was not universally more fatigue resistant (i.e. both joints) as previously postulated. The dependence upon muscle group was demonstrated in review, where there is typically no difference in the lower extremities, and a female advantage in the upper extremities (Hunter, 2009b). There may be underlying factors that were not fully recognized (i.e. additional moderators), but may have influenced fatigue resistance. For example, overall physical activity was quantified (via IPAQ), but the type of training was not qualified (strength vs. endurance training). An effect among training types has previously been shown to influence fatigue resistance, but in males only (Clarkson *et al.*, 1980). It is not clear how training influences females, nor the impact it may have upon different muscle groups. It is possible that a recruitment bias for type of training performed (endurance vs. strength) occurred, but wasn't accounted for. This may help explain the discrepancy in fatigue resistance between Chapters 2 and 4 among females at the ankle and elbow.

These series of projects sought to clarify the influence of five fatigue moderators through both empirical (systematic review and meta-analysis) and experimental methods. In general, women demonstrated either the same or better fatigue resistance than men (men never better), old men were more fatigue resistant than young men, the complexity of the task is not an influential factor and fatigue differences are readily apparent under isometric conditions. This information serves to better direct future study design and power for mechanistic, training and performance response studies. Ignoring the influence of these variables could make drawing conclusions not only quite difficult, but possibly incorrect.

Conclusions

The goal of fatigue-related research is to determine what happens (magnitude of response), how it happens (under what conditions) and why it happens (specific mechanisms). The difficulty lies in the fact that muscle fatigue is complex, made up of a multitude of processes and interactions. The current studies afforded insight into how age, sex, muscle group, contraction type and task type (complexity) influence fatigue resistance. A greater understanding of the contextual variables of fatigue will aid in understanding the following: underlying mechanisms, ideal age-related responses, ideal sex-related responses and training responses.

Future Directions

An age-related fatigue advantage could be thought of as either an adaptation ready to be exploited to improve function (i.e. last longer performing a task) or as a sign of maladaptive aging. It's conceivable that an isometric fatigue task could be used as a clinical marker of aging. The isometric fatigue task may be able to identify muscle-related changes that are not captured by peak strength (as indicated by no difference in

Chapter 4) and may only be recognized in high-cost laboratory assessments. A cross-sectional study of isometric fatigue resistance may be performed in addition to muscle composition, molecular signaling pathways (Akt-mTOR and RhoA-SRF), sarcopenic genetic panels and substrate utilization. If relationships are recognized the isometric task may offer valuable insight into the level of sarcopenic changes. Although the proposed study may seem all inclusive, an interdisciplinary approach will allow for further insight into the what, how and why fatigue occurs given the multitude of inputs.

In Chapters 2 and 4 a sex-difference in fatigue resistance was demonstrated with young females being the same or better than young males. It is not clear whether a more endurant response (i.e. female behavior) or less endurant response (male behavior) is desired. The difficulty lies in the lack of associations between isolated fatigue tasks and functional tasks/performance. It is not clear if isolated fatigue task are unique responses that do not resemble daily performance or if they are truly applicable. In addition, it is not known how modifiable the responses with various protocols. They type of training stimulus that is routinely performed has been shown to influence fatigue resistance endurance-trained athletes having greater fatigue resistance than power-trained athletes for an isolated fatigue task (Kroll *et al.*, 1980). This study was limited to men so it is not clear to what extent females are influenced, aged adults are influenced, and how much training is required for a desired response. It was not further explored with a training protocol how a power-trained athlete would respond to a fatigue task. A study with young male and female subjects who primary strength train vs. endurance train would give further insight into this interaction. This cross-sectional study could be further extended by looking at an endurance training protocol in those who are power- and endurance-trained. The fatigue response may be more specific to the type of training more so than the sex of the person. into account, the type of activity is not (strength training vs. endurance).

The cost-benefit relationship and adequate power are two questions that researchers must commonly answer in study design. Sample size is often based upon previous studies with similar intent and their ability to detect a significant difference. The sample sizes used in the current experimental studies were similar to those previously published (Ditor & Hicks 2000; Kent-Braun *et al.*, 2002; Russ *et al.*, 2008). The difficulty lies in identifying if the sample size is appropriate. A novel approach to build upon the already completed meta-analysis, is to perform an evidence-based sample size calculation (Sutton *et al.*, 2007). This calculation involves performing Markov Chain Monte Carlo simulation modeling to determine appropriate sample size estimations. This simulation may provide insight, based upon the currently available data, as to what studies would be beneficial and impactful.

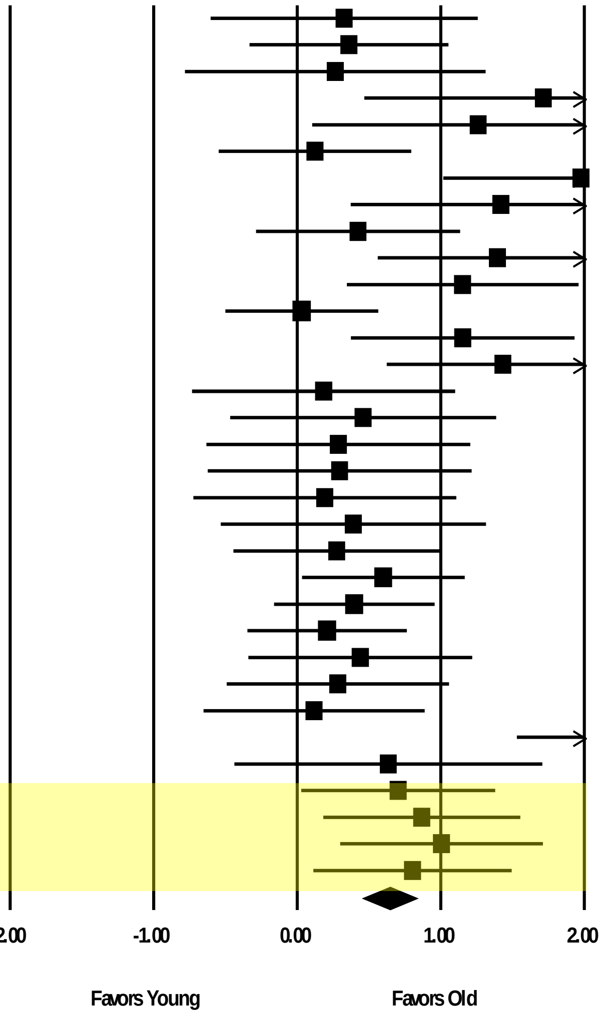
A final study direction may involve identifying the impact multiple test velocities have upon age-related fatigue resistance. The meta-analysis and the task complexity study found no difference between the two age groups for isokinetic tasks (60-180 º /s). Age-related changes within the muscle (i.e. fiber type transformation) may lead to a greater loss of power, particularly at higher velocities. A recent study by Callahan & Kent-Braun, (2011) found old women to be more fatigue resistant than young women at the knee under isometric conditions (ES = 1.1, $p < 0.05$), no difference for an intermediate velocity (ES = 0.46), and young females significantly more fatigue resistant with a large effect size (ES = 1.3, $p < 0.01$) for a high velocity isokinetic conditions (i.e. 270 º /s). Further studies warrant the inclusion of multiple velocities to fully understand the nature of isokinetic fatigue and loss of power with age.

Table 5-1. Effect size calculations for males only from Chapter 3 meta-analysis and Chapter 4 experimental results during isometric tasks only.

Male Isometric (effect size)

Study name	Contraction	Joint	Hedges's g	Standard error	Lower limit	Upper limit	p-Value
Lanza, IR 2005	Isometric	Ankle	0.328	0.476	-0.606	1.261	0.492
Aniansson, A 1978 (C)	Isometric	Hand	0.361	0.355	-0.334	1.056	0.309
Bazzucchi, I 2005 (A)	Isometric	Elbow	0.265	0.536	-0.785	1.315	0.620
Bazzucchi, I 2005 (B)	Isometric	Elbow	1.715	0.638	0.465	2.965	0.007
Bazzucchi, I 2005 (C)	Isometric	Elbow	1.261	0.592	0.101	2.421	0.033
Chatterjee, S 1991	Isometric	Hand	0.124	0.344	-0.550	0.798	0.719
Hunter, S 2004 (A)	Isometric	Elbow	1.978	0.491	1.015	2.940	0.000
Hunter, S 2005	Isometric	Elbow	1.419	0.535	0.370	2.468	0.008
Larsson, L 1978 (A)	Isometric	Knee	0.424	0.364	-0.290	1.137	0.244
Mademli, L 2008a	Isometric	Ankle	1.396	0.427	0.558	2.233	0.001
Mademli, L 2008c (B)	Isometric	Knee	1.152	0.413	0.343	1.962	0.005
Petrofsky & Lind, 1975	Isometric	Hand	0.032	0.273	-0.504	0.568	0.907
Petrofsky, J 2002 (A)	Isometric	Hand	1.153	0.399	0.371	1.935	0.004
Petrofsky, J 2002 (B)	Isometric	Knee	1.433	0.415	0.620	2.246	0.001
Smolander, J 1998 (A)	Isometric	Hand	0.184	0.469	-0.735	1.103	0.695
Smolander, J 1998 (B)	Isometric	Hand	0.459	0.474	-0.470	1.389	0.333
Smolander, J 1998 (C)	Isometric	Hand	0.287	0.470	-0.635	1.209	0.542
Smolander, J 1998 (D)	Isometric	Knee	0.296	0.470	-0.626	1.218	0.530
Smolander, J 1998 (E)	Isometric	Knee	0.192	0.469	-0.727	1.111	0.682
Smolander, J 1998 (F)	Isometric	Knee	0.391	0.473	-0.535	1.317	0.408
Taylor, JA 1991	Isometric	Hand	0.276	0.369	-0.447	0.998	0.455
Yassierli, 2007 (A)	Isometric	Shld	0.599	0.290	0.030	1.169	0.039
Yassierli, 2007 (B)	Isometric	Shld	0.398	0.287	-0.164	0.960	0.165
Yassierli, 2007 (C)	Isometric	Shld	0.208	0.285	-0.350	0.766	0.465
Yassierli, 2007 (D)	Isometric	Back	0.439	0.399	-0.344	1.221	0.272
Yassierli, 2007 (E)	Isometric	Back	0.283	0.396	-0.494	1.060	0.475
Yassierli, 2007 (F)	Isometric	Back	0.117	0.395	-0.656	0.890	0.767
Yoon, T 2008 (A)	Isometric	Elbow	3.170	0.838	1.527	4.813	0.000
Yoon, T 2008 (B)	Isometric	Elbow	0.635	0.548	-0.440	1.710	0.247
Avin 2012 (MM_A)	Sustained	Ankle	0.703	0.346	0.025	1.382	0.042
Avin 2012 (SM_A)	Sine	Ankle	0.868	0.352	0.179	1.557	0.014
Avin 2012 (MM_E)	Sustained	Elbow	1.005	0.362	0.297	1.714	0.005
Avin 2012 (SM_E)	Sine	Elbow	0.804	0.354	0.110	1.497	0.023
			0.639	0.092	0.459	0.819	0.000

Hedges's g and 95% CI



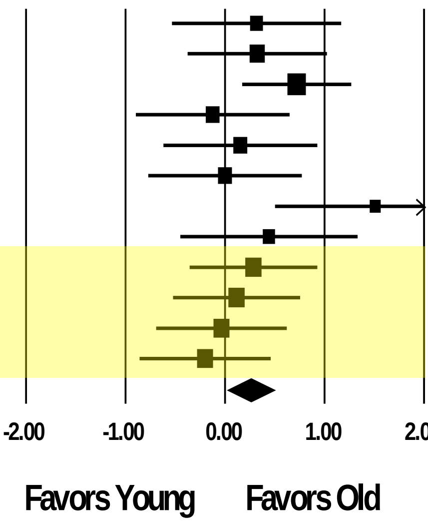
Negative values identify young males as being more fatigue resistant (fatigue less), while positive values identify old males as being more fatigue resistant (fatigued less).

Table 5-2. Effect size calculations for females only from Chapter 3 meta-analysis and Chapter 4 experimental results during isometric tasks only

Female Isometric (effect size)

Study name	Contraction	Joint	Hedges's g	Standard error	Lower limit	Upper limit	p-Value
Hunter, S 2004 (B)	Isometric	Elbow	0.317	0.434	-0.534	1.168	0.465
Johnson, T 1982 (A)	Isometric	Knee	0.324	0.358	-0.377	1.025	0.365
Petrofsky, J 1975	Isometric	Hand	0.720	0.280	0.172	1.269	0.010
Yassierli, 2007 (G)	Isometric	Back	-0.124	0.395	-0.897	0.649	0.753
Yassierli, 2007 (H)	Isometric	Back	0.154	0.395	-0.619	0.928	0.696
Yassierli, 2007 (I)	Isometric	Back	0.000	0.394	-0.773	0.773	1.000
Yoon, T 2008 (C)	Isometric	Elbow	1.510	0.515	0.501	2.519	0.003
Yoon, T 2008 (D)	Isometric	Elbow	0.441	0.455	-0.451	1.333	0.332
Avin 2012 (MF_A)	Sustained	Ankle	0.286	0.328	-0.357	0.928	0.383
Avin 2012 (SF_A)	Sine	Ankle	0.117	0.326	-0.523	0.756	0.721
Avin 2012 (MF_E)	Sustained	Elbow	-0.035	0.336	-0.693	0.622	0.916
Avin 2012 (SF_E)	Sine	Elbow	-0.200	0.336	-0.860	0.459	0.551
			0.256	0.116	0.029	0.483	0.027

Hedges's g and 95% CI



Negative values identify young females as being more fatigue resistant (fatigue less), while positive values identify old females as being more fatigue resistant (fatigued less).

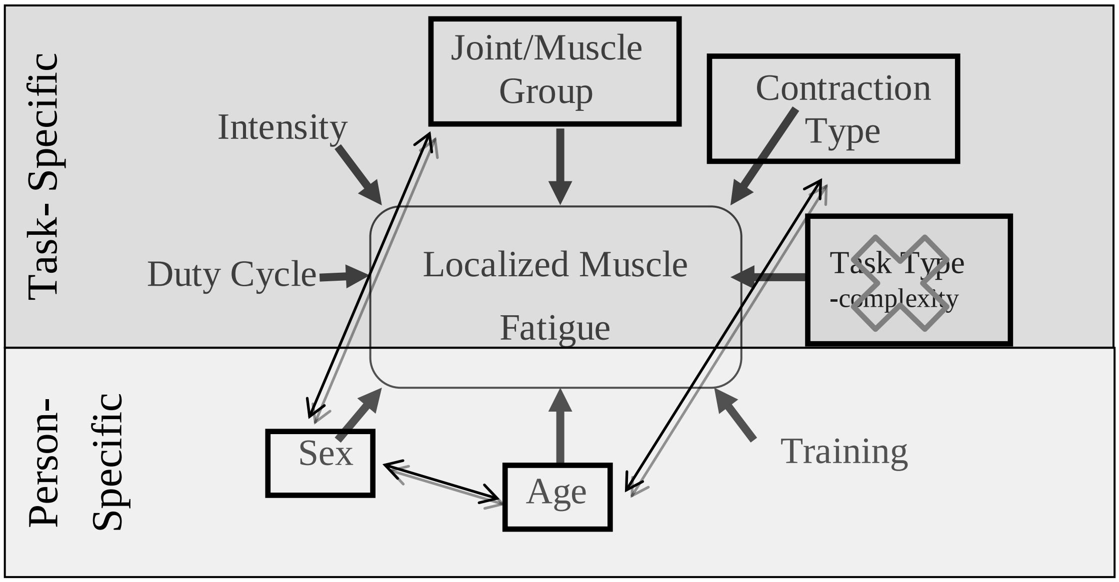


Figure 5-1. Updated schematic of fatigue interactions among moderating variables of fatigue

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