BIOMECHANICS AND PHYSIOLOGY OF MOTOR VARIABILITY IN REPETITIVE MOVEMENTS OF YOUNG AND OLD FEMALE AND MALE ADULTS

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List of Abbreviations

3D	tridimensional
AD	anterior deltoid
ANOVA	analysis of variance
B-mode	brightness mode
BB	biceps brachii
BI	biceps brachii
BLSA	Baltimore Longitudinal Study of Aging
BMI	body mass index
BRA	brachialis
BRR	brachioradialis
CCV	cycle-to-cycle variability
CLSA	Canadian Longitudinal Study on Aging
CRIR	Center for Interdisciplinary Research in Rehabilitation of Montreal
CV	coefficient of variation
DKPE	Department of Kinesiology and Physical Education
EGSS	Education Graduate Students Society
EMG	electromyography
GL	gastrocnemius lateralis
HbO_2	oxygenated hemoglobin
HHb	deoxygenated hemoglobin
LT	lower trapezius
MD	middle deltoid
MPF	median power frequency
MT	middle trapezius
MTH	muscle thickness
MU	motor unit
MVIC	maximal voluntary isometric contraction
$MVIC_{max}$	maximal MVIC
N/S	neck/shoulder

NIRS	near-infrared spectroscopy
NMI	normalized mutual information
NSERC	Natural Sciences and Engineering Research Council of Canada
PD	posterior deltoid
REPAR	Quebec Rehabilitation Research Network
RF	rectus femoris
RMS	root mean square
ROM	range of motion
RPE	rating of perceived exertion
RVIC	reference voluntary isometric contraction
SD	standard deviation
TA	tibialis anterior
THb	total hemoglobin
TOI	tissue oxygen index
TRI	triceps brachii
UT	upper trapezius

Abstract

Old age and the natural variability in sensorimotor patterns (i.e. motor variability) are independently linked to injury risk in daily activities involving repetitive motion. However, how old age alters variability of biomechanical patterns (i.e. joint motions and muscle activities), whether limb, fatigue and sex affect these patterns, and how motor variability is regulated physiologically remains unclear. This dissertation aimed to determine how old age affects motor variability of upper and lower limb biomechanical outputs during low-load repetitive movements as a function of sex and fatigue, and to explore the physiological origin of motor variability.

Healthy young and old adult males and females were recruited for three different experiments to perform three different repetitive motor tasks: gait, reaching-and-lifting, and dynamic elbow flexions. The upper limb tasks were performed in the absence and presence of fatigue. Joint angle and muscle activity parameters were measured using optoelectronic motion capture and electromyography, with variability of these parameters quantified by the movement-to-movement standard deviation and/or coefficient of variation. Oxygenation and thickness of muscle were measured using near-infrared spectroscopy and brightness-mode ultrasonography. Age-related alterations in parameters were compared between sexes and with fatigue, and relationships were examined between parameters of motor variability and muscle physiology.

In gait, old age was associated with higher variability in ankle inversion/eversion, pelvic obliquity, and rectus femoris activation, but lower variability in ankle dorsiflexion/plantarflexion in both males and females. Old age was also associated with higher variability in knee flexion/extension in males only and lower variability gastrocnemius lateralis activation in females only. In reaching-and-lifting, old age was not associated with differences in the variability of neck/shoulder muscle activity without or with fatigue. Regardless of age, muscle activity variability increased with fatigue. In dynamic elbow flexions, old age was not associated with differences in the variability of arm muscle activity without or with fatigue; however, muscle activity variability decreased with fatigue in young and old adults and was correlated with the biceps brachii oxygenation response, where relationships were more local to the site of fatigue in old age.

These findings reveal that old age influences the variability of joint and muscle outputs in a complex way, indicating that aging leads to alterations in the magnitude of motor variability of

the lower limb that are sex-, joint-, and muscle-dependent, but no alterations in motor variability of the upper limb or interactions with fatigue. Further, findings support muscle oxygenation as a potential regulator of motor variability. The results of this dissertation help to better understand how aging men and women control their motion in repetitive movement activities and could be applied in rehabilitation interventions to better prevent age-related falls and chronic upper limb injuries.

Abrégé

La vieillesse et la variabilité naturelle des patrons sensori-moteurs (c'est-à-dire la variabilité motrice) sont indépendamment liées au risque de blessure durant les activités quotidiennes impliquant des mouvements répétitifs. Cependant, comment la vieillesse modifie la variabilité des schémas biomécaniques (c'est-à-dire les mouvements articulaires et les activités musculaires), si le segment corporel, la fatigue et le sexe affectent ces patrons, et comment la variabilité motrice est régulée physiologiquement restent incertains. Cette thèse visait à déterminer comment la vieillesse affecte la variabilité motrice des paramètres biomécaniques des membres supérieurs et inférieurs lors de mouvements répétitifs à faible charge en fonction du sexe et de la fatigue, et à explorer l'origine physiologique de la variabilité motrice.

De jeunes adultes hommes et des femmes et d'autres âgés en bonne santé ont été recrutés pour trois expériences différentes afin d'effectuer trois tâches motrices répétitives différentes: marche, atteinte et soulevé, et flexions dynamiques du coude. Les tâches des membres supérieurs ont été effectuées en l'absence et en présence de fatigue. Les paramètres d'angle articulaire et d'activité musculaire ont été mesurés par capture de mouvement optoélectronique et électromyographie, la variabilité de ces paramètres étant quantifiée par l'écart-type et / ou le coefficient de variation d'un mouvement à l'autre. L'oxygénation et l'épaisseur musculaire ont été mesurées par spectroscopie proche infrarouge et échographie en mode luminosité. Les changements des paramètres liés à l'âge ont été comparés entre les sexes et avec la fatigue, et les relations ont été examinées entre les paramètres de variabilité motrice et de physiologie musculaire.

Lors de l'étude sur la marche, la vieillesse était associée à une variabilité plus élevée de l'inversion / éversion de la cheville, de l'obliquité pelvienne et de l'activation du rectus femoris, mais à une variabilité plus faible de la flexion / extension de la cheville chez les hommes et les femmes. La vieillesse était également associée à une variabilité plus élevée de la flexion / extension du genou chez les hommes uniquement et à une variabilité plus faible de l'activation de gastrocnemius lateralis chez les femmes uniquement. Lors de l'étude des gestes d'atteinte et de soulever, la vieillesse n'était pas associée à des différences de variabilité de l'activité musculaire cou / épaule sans ou avec fatigue. Quel que soit l'âge, la variabilité de l'activité musculaire augmentait avec la fatigue. Durant les flexions dynamiques du coude, la vieillesse n'était pas associée à des différences de variabilité de l'activité musculaire du bras sans ou avec fatigue;

cependant, la variabilité de l'activité musculaire diminuait avec la fatigue chez les adultes jeunes et âgés et était corrélée avec la réponse d'oxygénation du biceps brachial, où les relations étaient plus locales avec le site de fatigue chez les personnes âgées.

Ces résultats révèlent que la vieillesse influence la variabilité des paramètres articulaires et musculaires de manière complexe, ce qui indique que le vieillissement entraîne des altérations de l'amplitude de la variabilité motrice du membre inférieur qui dépendent du sexe, des articulations et des muscles, mais pas d'altérations de variabilité motrice du membre supérieur ou d’interactions avec la fatigue. De plus, les résultats supportent le rôle de l'oxygénation musculaire en tant que régulateur potentiel de la variabilité motrice. Les résultats de cette thèse aident à mieux comprendre comment les hommes et les femmes vieillissants contrôlent leur mouvement dans les activités de mouvements répétitifs et pourraient être appliqués à des interventions de réadaptation pour mieux prévenir les chutes liées à l'âge et les blessures chroniques des membres supérieurs.

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Noah, Chris, and Jessica, thank you for your willingness to participate in my projects and for being such a great group of graduate and undergraduate lab mates. Shaheen Ghayourmanesh, thank you for your Matlab programming insights. Kim Emery and Gevorg Chilingaryan, you both passed far too early and the world is a less bright place for it. Thank you for your guidance on EMG and statistics, it will not be forgotten.

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To Benji, woof!

Contributions to original knowledge

This dissertation is comprised of four manuscripts. Chapters 3 and 4 have been published, Chapter 5 has been accepted for publication and is in-press, and Chapter 6 is in preparation for submission.

Chapter 3, titled *"Does variability in motor output at individual joints predict stride time variability in gait? Influences of age, sex, and plane of motion"*, is the first study to evaluate the effects and interactions of old age and sex on the stride-to-stride variability of tridimensional joint angles in gait. This study is also the first to evaluate the relationships between variability in joint motion and variability in spatiotemporal gait patterns.

Chapter 4, titled *"Sex-independent and dependent effects of older age on cycle-to-cycle variability of muscle activation during gait"*, is the first study to evaluate the effects and interactions of old age and sex on the stride-to-stride variability of muscle activity in gait. This study is also the first to evaluate the relationships between variability in muscle activity and variability in spatiotemporal gait patterns.

Chapter 5, titled *"Age-dependent control of shoulder muscles during a reach-and-lift task"*, was the first study to evaluate the effects and interactions of old age and fatigue on movement-to-movement variability and connectivity of muscle activity patterns in an upper limb activity of daily living.

Chapter 6, titled *"Muscle activation variability, oxygenation, and thickness: Changes with dynamic low-load elbow flexion fatigue and relationships in young and old females"*, is the first study to evaluate the effects and interactions of old age and fatigue on movement-to-movement variability of muscle activity, muscle oxygenation, and muscle thickness in repetitive, fatiguing upper limb exercise. This study is also the first to explore the relationships between motor variability (i.e. movement-to-movement variability of muscle activity) and the physiological status of the exercising muscle (i.e. muscle oxygenation, muscle thickness).

Contributions of authors

The four manuscripts forming this dissertation are primarily the work of Mr. Christopher A. Bailey, including the conception of ideas, research design and setup, data reduction and analyses, interpretation of results, and writing and presentation of all four manuscripts. For these reasons, he was the 1st author of each of these manuscripts.

For Chapters 3 and 4, the collaborators at the University of Cagliari, led by Dr. Massimiliano Pau and his research team consisting of Ms. Micaela Porta, Ms. Giuseppina Pilloni, and Mr. Federico Arippa, oversaw data acquisition. For this reason, Ms. Porta, Ms. Pilloni, and Mr. Arippa were included as 2nd, 3rd, and 4th authors. Mr. Bailey led the conceptualization of the research questions, assisted in data collection, and led data processing, reduction and analyses, interpretation of results, and writing of both manuscripts. Together, Drs. Pau and Julie Côté oversaw these projects and provided key insights during data analysis and preparation of the manuscripts. For this reason, they were the senior authors of these manuscripts and were assigned the final (5th and 6th) positions.

For Chapter 5, research design, recruitment and data acquisition were co-led by Mr. Bailey and Ms. Maxana Weiss. For this reason, Ms. Weiss was included as 2nd author. Mr. Bailey led statistical analyses and preparation of the published manuscript. Dr. Côté oversaw the project, provided training and guidance on data collection and analysis, and provided insights during manuscript preparation. For this reason, she was the senior author of this manuscript and was assigned the final (3rd) position.

For Chapter 6, every step, from conceptualization to testing and execution of the research and preparation of the manuscript, was led by Mr. Bailey and supported by the substantial contribution of Mr. SangHoon Yoon. For this reason, he was included as 2nd author. Dr. Côté also oversaw this project, provided guidance on data collection and analysis, and reviewed the prepared manuscript. For this reason, she was the senior author of this manuscript and was assigned the final (3rd) position.

Chapter 1. Introduction

1.1 Rationale

The population and workforce are rapidly aging. It is projected that the proportion of adults aged 60+ years will increase from 10.0% (reported in 2000), to 21.8% in 2050, and to 32.2% in 2100 (Lutz, Sanderson, & Scherbov, 2008). Many of these adults remain in the workforce well into their senior years. In Canada, one in five adults aged 65+ years (~ 1.1 million seniors) reported working in 2015, with 30% of these workers employed full-time (Statistics Canada, 2017). Older adults are also more likely to incur movement-related injuries of the lower and upper limbs compared to younger adults. One example is fall-related injuries. Fall risk is well known to rise with age and, perhaps due to increased injury susceptibility in aging adults (Rubenstein, 2006), falls are the leading cause of fatal and non-fatal unintentional injuries in adults aged 65+ years (Billette & Janz, 2011; Peel, 2011). In the workplace, incidence and prevalence of chronic neck and shoulder injuries increases with age (Cassou, 2002). Old age is clearly a key factor that influences injury risk in both lower and upper limb movements. However, the mechanisms responsible for these age-related injury risks are not fully clear. This gap constitutes an important area of research to better prevent injuries and mitigate healthcare costs as the population of Canada and the Canadian workforce continue to rapidly age.

1.2 Problem statement

1.2.1 How do age-related falls occur?

Falls in aging adults likely occur as a result of altered muscle physiology and altered motor control. One well known consequence of aging is sarcopenia, the age-related loss in muscle mass. However, age-related gait stability has been shown to be independent of strength loss (Kang & Dingwell, 2008a). Alternatively, aging adults may be at increased risk of falling due to changes in motor control. Numerous studies have identified stride-to-stride variability in spatiotemporal gait output, such as in stride time, as an important risk factor for falls (Hausdorff, 2005; Hausdorff, Rios, & Edelberg, 2001; Roos & Dingwell, 2010), suggesting that motor variability, i.e. a principle of motor control defined as the natural variability in sensorimotor actions (Newell & Slifkin, 1998; Srinivasan & Mathiassen, 2012b) is one mechanism of falls. Large sample investigations of the variability of spatiotemporal metrics provide strong support for a rise in motor variability with older age (Beauchet et al., 2017; Callisaya, Blizzard, Schmidt, McGinley, & Srikanth, 2010).

Investigations of motor variability in the individual joints and muscles of young and old adults are needed to help reveal the mechanisms of spatiotemporal gait variability. Unfortunately, how old age affects the variability of these metrics remains inconclusive. Several studies have investigated how old age affects kinematic variability in gait, but with mixed results (Buzzi, Stergiou, Kurz, Hageman, & Heidel, 2003; Chiu & Chou, 2012; Hafer & Boyer, 2018; Kurz & Stergiou, 2003; Park, Roemmich, Elrod, Hass, & Hsiao-Wecksler, 2016). Discrepancies may be due to evaluating samples with different sex distributions, as kinematic gait patterns differ between aging males and females (Ko, Tolea, Hausdorff, & Ferrucci, 2011). These studies also focused primarily on metrics of variability in the sagittal plane and may have missed age-related changes in the frontal and transverse planes that contribute to spatiotemporal gait variability. No known studies have investigated the stride-to-stride variability of neuromuscular gait patterns. Knowledge is needed on the variability of individual joint and muscle patterns in aging males and females to better understand how motor variability in gait changes with old age and to better prevent gait-related instability and falls in men and women alike.

1.2.2 How do age-related chronic upper limb injuries develop?

Epidemiological evidence links chronic upper limb injuries in adults to repetitive movement exposure (Punnett & Wegman, 2004). A popular theoretical mechanism is that prolonged low-load repetitive movement overloads “Cinderella” fibres, i.e. the type I (slow and fatigue-resistant) muscle fibres recruited first by low-threshold motor units, that are also the most active in low-load efforts according to the size principle of motor unit recruitment (Henneman, 1957). Overloading Cinderella fibres may lead to muscle fatigue and, over time, cumulative exposures, discomfort, pain and musculoskeletal disorders (MSDs) (Côté, 2014). Fatigue is a pathway to chronic upper limb injury in this theoretical framework, whereby individuals who better mitigate fatigue may be less likely to develop a chronic upper limb injury.

Several investigations provide evidence that motor variability can be accessed by humans to mitigate fatigue by providing Cinderella fibres with breaks (Côté, 2014). In this interpretation, motor variability is not representative of involuntary neuromotor noise, but rather is manipulated by the neuromuscular system to help distribute movement-to-movement loads across redundant muscles and degrees of freedom. Investigations of laboratory-based tasks that simulate occupational reaching have reported increased motor variability in young males and females (Cid

et al., 2019; Fuller, Fung, & Côté, 2011; Monjo & Forestier, 2016; Samani, Srinivasan, Mathiassen, & Madeleine, 2017; Srinivasan, Sinden, Mathiassen, & Côté, 2016), where individuals who have higher initial variability may be less fatigable (Fedorowich, Emery, Gervasi, & Côté, 2013). Motor variability findings may differ with old age in fatiguing tasks, with evidence for age and joint-dependent variability alterations during shoulder-dominant work (Qin, Lin, Faber, Buchholz, & Xu, 2014), but not in elbow dominant work (Senefeld, Yoon, & Hunter, 2017). However, no studies have explored the effect of old age on the variability of neuromuscular patterns, similar to the limitation in gait. Potential age differences in neuromuscular variability could provide new insights into why chronic upper limb injuries are more prevalent in aging adults (Cassou, 2002).

1.2.3 How is motor variability controlled?

If motor variability is manipulated by the neuromuscular system to delay fatigue, it can be expected to see this coincide with the physiological responses that reflect mitigation of fatigue. One feature of the physiological fatigue response is how oxygen perfuses the muscle (Enoka & Duchateau, 2016), as shown in studies of changes in muscle oxygenation that occur in young and old adults (Costes et al., 1999). Further, arterial oxygenation has been linked to the regulation of central neural drive to muscles (Amann et al., 2006), suggesting that oxygenation could be a key determinant linked to motor control. However, no studies to date have concomitantly analyzed the motor variability and oxygenation responses at the muscle with development of repetitive motion-induced fatigue. This could help understand the potential of muscle oxygenation as a regulating feature of motor variability and also help determine if age is an influencing factor on the muscular responses to fatigue.

1.3 General aim and research framework

1.3.1 General aim

This PhD dissertation has three aims. The first aim is to determine how old age affects the motor variability of joint and muscle outputs during dynamic movements and to compare the age effects between the lower and upper limb. The second aim is to examine how age differences in these motor variability patterns vary by sex and with fatigue. The third aim is to explore the physiological origin of motor variability. These aims were accomplished through a series of four laboratory studies conducted in three different research environments: 1) the Biomechanics and Industrial Ergonomics Laboratory in Cagliari, Italy, 2) the Centre for Interdisciplinary Research

in Rehabilitation of Greater Montreal at the Jewish Rehabilitation Hospital in Laval, Canada, and 3) the Biomechanics of Occupation and Sport Laboratory in Montreal, Canada.

1.3.2 Research framework development

The development of a research framework began during a research internship at the University of Cagliari focused on aging and gait analysis. A review of this literature identified motor variability as a relevant principle of motor control and led to the selection of appropriate motor variability metrics and analyses. As one of the most highly studied motor tasks, gait was chosen as an experimental model of lower limb motor variability and investigated using biomechanical techniques (optoelectronic motion capture, surface electromyography) for this dissertation.

A separate body of motor variability investigations focused on repetitive and fatiguing neck/shoulder tasks also emerged from the literature. One prominent task is the repetitive pointing task, requiring prolonged standing and repetitive forward reaching that leads to fatigue. This task was adapted into a seated tapping task to remove loads on the lower limbs while still inducing neck/shoulder fatigue. The selected experimental procedure (performing a reach-and-lift task following a seated repetitive pointing task) had the dual benefit of allowing the focus of the investigation to be on the upper limb, after having investigated the lower limb previously, and of investigating responses in an activity of daily living more likely to be performed by young and old adults, having more ecological validity. Surface electromyography was the primary biomechanical technique used in this upper limb model of motor variability.

Finally, findings from the upper limb model were then used to design an experiment that concurrently quantifies metrics of motor variability and of muscle physiology. The selected physiological techniques adopted from the literature (near-infrared spectroscopy, brightness-mode ultrasonography) are highly sensitive to movement and posture, and so a tightly controlled intermittent elbow flexion task was piloted and chosen as a second experimental model of upper limb motor variability.

Together, the selected laboratory models of lower and upper limb motor variability ranged from multi-jointed movements common to activities of daily living to single-joint and tightly controlled movements. These combined approaches were necessary to meet the methodological requirements of the selected biomechanical and physiological techniques, with these techniques

needed to address the aims of the dissertation. Results from these models of motor variability are reported across four manuscripts that form this dissertation; two manuscripts investigate how age affects motor variability in gait, one manuscript investigates how age affects motor variability in a reach-and-lift task, and one manuscript focuses on the relationship between motor variability and physiological outcomes in an elbow flexion task. Specific objectives, hypotheses, and rationales are detailed for each manuscript in the subsequent section (1.4). These are followed by the review of relevant literature relating to this dissertation (Chapter 2), the manuscripts for each study (Chapters 3-6), and a discussion of the combined outcomes and conclusions of this dissertation (Chapter 7).

1.4 Objectives and hypotheses

1.4.1 Chapter 3: Does variability in motor output at individual joints predict stride time variability in gait? Influences of age, sex, and plane of motion

In Section 1.2.1, I describe how the effect of age on motor variability at individual joint outputs in gait is not fully clear. Potential reasons include that metrics of variability are often studied only in males and usually in sagittal plane motion. **Therefore, the objectives of this first study were to determine the combined influences of old age and sex on the variability of tridimensional joint angles during gait, and to assess whether variability at each joint predicted variability in stride time.** ***It was hypothesized that older age would be associated with higher sagittal plane variability in lower limb joints, that older age would be associated with higher ankle variability in females than in males, and that the sagittal plane variabilities of individual joints would predict stride time variability***. In parallel with Chapter 4, this work established how old age affects the variability of individual motor outputs in males and in females during a lower-limb dominant task and how this effect was influenced by sex.

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1.4.2 Chapter 4: Sex-independent and dependent effects of older age on cycle-to-cycle variability of muscle activation during gait

In Section 1.2.1, I describe how studies of motor variability in gait frequently miss investigating a key contributor to gait output: muscle activation. Investigating the variability of muscle activation could help understand the muscular source of variability in spatiotemporal gait output and link this variability to aging motor units. **The objectives of this second study were to investigate the effects of old age and sex on the variability of muscle activation during gait, and to explore the relationships between the variability of individual muscles and the stride time variability of males and females.** ***It was hypothesized that older age would be associated with higher stride time variability and higher muscle activation variability in males and females, and that relationships between muscle activation variability and stride time variability would be stronger in females than in males.*** In parallel with Chapter 3, this work established how old age affects the variability of individual motor outputs during a lower-limb dominant task and how this effect was influenced by sex.

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1.4.3 Chapter 5: Age-dependent control of shoulder muscles during a reach-and-lift task

In Section 1.2.2, I describe findings of increased motor variability after fatigue from repetitive reaching in young adults. Another fatigue-related adaptation observed in occupational upper limb work is altered muscular functional connectivity (Kawczyński et al., 2015; Madeleine, Samani, Binderup, & Stensdotter, 2011; Samani et al., 2017), indicating that fatigue also leads to adjustments in the coordination between muscle pairs. However, how healthy aging affects muscle activation variability and functional connectivity in a repetitive upper limb task remains unclear. **The objective of this third study was to determine the age-specific effect of performing a neck/shoulder fatiguing task on muscle activation variability and functional connectivity in a reach-and-lift task.** ***It was hypothesized that fatigue would produce increases in muscle activation variability that would be higher with age and changes in functional connectivity of muscles that would be altered with age.*** This work established how old age affects the variability

of muscle outputs during a neck/shoulder dominant upper-limb task and how this effect was influenced by fatigue.

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1.4.4 Chapter 6: Muscle activation variability, oxygenation, and thickness: Changes with dynamic low-load elbow flexion fatigue and relationships in young and old females

Chapters 3-5 report on how old age influences the variability of individual motor outputs in the lower limb (gait) and the upper limb (reaching) according to predisposed (sex) and acquired (fatigue) factors. While these studies provide valuable knowledge on how the natural aging process affects motor variability, they fall short on understanding how motor variability is regulated. As described in Section 1.2.3, muscle oxygenation is a feature that may be involved in the regulation of motor control. Another common physiological feature of exercise is muscle swelling (Jensen, Jorgensen, & Sjogaard, 1994; Yasuda, Fukumura, Iida, & Nakajima, 2015), which may be partly explained by the accumulation of microvascular hematocrit (i.e. blood volume) reported in exercise (Baudry, Sarrazin, & Duchateau, 2013). It is unclear how age affects the perfusion of blood and oxygen into muscle during repetitive movement and if this perfusion is related to motor variability. **This fourth study was conducted on young and old females using an elbow flexion task and had a series of four objectives and hypotheses. First, to determine how muscle fatigue affects muscle activity variability, oxygenation, and thickness.** ***Hypothesis: Old age in females will not affect the fatigue-induced changes in muscle activation variability, oxygenation, nor thickness.*** **Second, to determine how fatigability is associated with the muscular responses to initial exercise and to muscle fatigue.** ***Hypothesis: Lower fatigability will be associated with higher initial muscle activation variability in both young and old females.*** **Third, to determine how initial muscle activation variability is associated with exercise-induced changes in muscle oxygenation and thickness.** ***Hypothesis: Higher initial variability will be associated with less muscle deoxygenation and swelling.*** **Fourth, to determine how the fatigue-induced change in muscle activation variability is associated with fatigue-induced changes in muscle oxygenation and thickness.** ***Hypothesis: A larger change in variability would be***

associated with less muscle deoxygenation and swelling. This work established how old age affects the variability of muscle outputs during an elbow dominant upper limb-task and how this effect was influenced by fatigue, as well as established whether the muscle oxygenation and swelling responses to exercise are potential features that influence motor variability.

This chapter, authored by Christopher A Bailey, SangHoon Yoon, & Julie N Côté, is in preparation for submission to the *Journal of Electromyography and Kinesiology.*

Chapter 2. Review of literature

2.1 Age-related alterations in the neuromuscular system

As adults age, several changes occur to both the structure and the physiology of the neuromuscular system. Changes can be grouped by the location in which they occur: 1) central nervous system, 2) peripheral nervous system, and 3) muscles. Age-related changes in structure and physiology within each of these categories will be briefly summarized and linked to their functional consequences for motor control.

2.1.1 Alterations in the central nervous system

In the central nervous system, one of the main effects of aging is a reduction in brain volume, affecting both grey matter and white matter (Seidler et al., 2010). These age-related reductions in brain volume seem to be more prominent in the prefrontal, parietal, and sensorimotor cortices, regions of the brain that are involved in motor control (Seidler et al., 2010). It comes as no surprise then that age-related atrophy in these regions coincides with deficits in motor output. For example, smaller frontoparietal and sensorimotor regions in old adults have been associated with poorer gait (i.e. smaller stride length and longer double support time) (Rosano et al., 2008). Further, adding cognitive complexity during a motor task (i.e. in a dual-task paradigm) is widely reported to deteriorate motor output more with older age (Li & Lindenberger, 2002). Thus with older age, it is theorized that adults have greater cognitive demand for executing movement (Seidler et al., 2010) and it seems that this demand could contribute to deficits in motor control.

2.1.2 Alterations in the peripheral nervous system

The aging peripheral nervous system is often characterized by the changes that occur to motor units (MUs). The MU is the functional unit of the neuromuscular system comprised of an α-motor neuron and all the muscle fibres it innervates. Like muscles and bones, MUs are continually remodeled so that normally, muscle fibre denervation matches muscle fibre innervation. With aging, however, MU remodeling becomes compromised, such that denervation outpaces innervation and could lead to motor neuron death (Gordon, Hegedus, & Tam, 2004; Power, Dalton, & Rice, 2013). With motor neuron death, there are fewer total MUs that are larger in average size (Hunter, Pereira, & Keenan, 2016; McKinnon, Connelly, Rice, Hunter, & Doherty, 2017; Vandervoort, 2002). In their study of the number of MUs in the tibialis anterior, McNeil et al. (2005) found that men ~65 years had 39% fewer MUs, and men 80+ years had 61% fewer MUs than men ~25 years old, providing experimental support for the progressive loss of MUs with age.

Further, the loss of MUs can have an impact on force control. Tracy & Enoka (2002) had young (19-26 years) and older (65-79 years) adults complete submaximal isometric contractions of the knee extensor muscles. They found larger force gaps during MU recruitment, which, due to the sequential recruitment threshold (from smallest size and lowest threshold to largest size and highest threshold, as per the Henneman size principle), they attributed to the combination of fewer MUs and the increase in MU size in older adults.

In addition to altering MU structure, old age also alters MU discharge patterns (Hunter et al., 2016; Narici, Maffulli, & Maganaris, 2008). One alteration reported is higher variability in the discharge of single MUs. Decomposition-based quantitative electromyography is a technique that has been used to study MU discharge variability by measuring jiggle and the variability of the discharge rate. Jiggle is the variability in the overall shape of MU potentials produced across consecutive discharges of a single MU, quantified by variability in the integrals of the MU potentials (Stålberg & Sonoo, 1994). In the lower limb, older adults have been reported to have greater jiggle than young adults in the tibialis anterior, vastus lateralis, and vastus medialis (Hourigan et al., 2015; Piasecki et al., 2016). In the upper limb, Laidlaw, Bilodeau, & Enoka (2000) reported higher variability in MU discharge rates for older adults compared to younger adults in the first dorsal interosseus during isometric and slow concentric and eccentric contractions. Results from these studies provide evidence for increases in MU discharge variability across motor unit pools of the lower and upper limbs. Evidence for the consequential loss in force control is discussed in 2.2.2.

A second commonly reported effect of aging that likely contributes to altered motor output is the change in the common modulation of MU activity (Enoka et al., 2003; Hunter et al., 2016). This can be examined by measuring MU synchronization, i.e. the strength of the common neural input to the motor neurons in the time domain, or by measuring MU coherence, i.e. the strength of the common oscillatory input to the motor neurons in the frequency domain. In a pair of studies investigating common synaptic modulation to the first dorsal interosseus, MU coherence, but not MU synchronization, was higher with older age (Semmler, Kornatz, & Enoka, 2003; Semmler, Steege, Kornatz, & Enoka, 2000). Force fluctuations were also higher with older age (Semmler et al., 2000). Indeed, higher MU coherence is believed to represent a greater ratio in the power of common synaptic input compared to independent synaptic inputs (Farina & Negro, 2015). In a more recent study of an isometric dorsiflexion task performed by adults aged 24-75 years, the

variability of the common synaptic input was a significant predictor of low-frequency MU coherence as well as the variability of dorsiflexion force (Castronovo et al., 2018). Taken together, the above studies suggest that alterations to MU structure, MU discharge variability, and the common synaptic input to MUs can each factor into the loss of control of force during isometric contractions observed with aging. However, the extent to which these factors affect motor control during dynamic contractions is unclear.

2.1.3 Alterations in muscles

In addition to MUs, aging also results in marked changes to muscle. One commonly reported change is the phenomenon of sarcopenia. Sarcopenia is defined as the age-related loss of lean muscle tissue that leads to a loss of muscle strength (Deschenes, 2004; Kirkendall & Garrett, 1998; Vandervoort, 2002). According to the literature, sarcopenia results from a combination of two changes in muscle fibers. First, studies show that there are reduced numbers of muscle fibers within a given muscle, directly affecting the ability of muscle to contract and produce force (Deschenes, 2004; Kirkendall & Garrett, 1998; Vandervoort, 2002). In turn, this loss of muscle fibers has been shown to occur especially in type II muscle fibers (speed-specialized) compared to in type I muscle fibers (endurance-specialized) (Deschenes, 2004; Erim, Beg, Burke, & de Luca, 1999; Kirkendall & Garrett, 1998; Vandervoort, 2002), further affecting the ability to exert force.

A second feature of muscles that is altered by aging is musculotendinous architecture. This refers to the physical structure of muscle and tendons, independent of their mass. Evidence of altered musculotendinous structure due to aging emerged after researchers found that sarcopenia could not fully explain losses in strength. After normalizing force production by the muscle cross sectional area, termed the specific force (Narici, Franchi, & Maganaris, 2016), it has been shown that force production remains lower in older adults, which has been attributed to changes in muscle architecture (Narici et al., 2008). These changes can be seen by comparisons of the anatomical cross-sectional area, the area when taking right angles at the muscle belly, and the physiological cross-sectional area of muscle, the area when accounting for the lower muscle fascicle lengths and pennation angles observed with old age (McKinnon et al., 2017; Narici, Maganaris, Reeves, & Capodaglio, 2003; Narici et al., 2008), and persist even after matching for physical activity level (Narici et al., 2003). The shorter fascicle lengths reported in old age are believed to reflect fewer sarcomeres in series, and smaller pennation angles reflect fewer sarcomeres in parallel (Narici et

al., 2008), meaning that age-related alterations in muscle architecture could impact the maximum contractile velocity and force of the muscle, respectively (McKinnon et al., 2017; Narici et al., 2008). Muscle force and contraction velocity may also be impacted by the lower stiffness and higher compliance of tendons in aging (McKinnon et al., 2017; Narici et al., 2008). It is believed that higher compliance leads to delayed transmission of force from muscle to bone, reducing contractile velocity, and excess actin-myosin overlap, reducing contractile force.

2.2 Age-related alterations in motor variability

2.2.1 Definition of motor variability and available metrics

Motor variability can be defined as the natural variability in sensorimotor actions (Newell & Slifkin, 1998). Sensorimotor actions include the kinetics, kinematics, and muscle activities that contribute to sustaining a posture and those that are repeated from movement to movement (e.g. gait, reaching). Accordingly, there are two main bodies of literature concerned with investigating the influence of healthy aging on motor variability: 1) literature on the variability of motor output during sustained, mostly isometric efforts (i.e. steadiness) (Christou, 2011; Enoka et al., 2003; Hunter et al., 2016) and 2) literature on the variability of motor output during repeated, dynamic efforts (i.e. movement-to-movement variability) (Hausdorff, 2005; Srinivasan & Mathiassen, 2012a, 2012b). These bodies of literature will be explored in Sections 2.2.2 and 2.2.3 respectively.

Within these bodies of literature, studies have taken a variety of approaches to quantify motor variability. First, the standard deviation or coefficient of variation (i.e. standard deviation normalized by the mean) are commonly used to quantify the "average" variability of a specific metric extracted from a motor pattern (e.g. Srinivasan, Sinden, Mathiassen, & Côté, 2016). A second approach is to investigate the "dynamical" variability of a motor pattern, using dynamical systems analyses. For example, Lyapunov exponents and Floquet multipliers have been computed to investigate the stability of motor patterns, where higher values are indicative of lower local dynamic stability and orbital stability (higher variability) respectively (e.g. Kang & Dingwell, 2008a). Third, measures of statistical persistence, such as the α scaling exponent obtained from detrended fluctuation analysis, can be used to investigate how quickly the variability of a signal is "corrected" (Dingwell & Cusumano, 2010). Fourth, the sample entropy of a continuous repeating signal can be computed such that higher values represent less statistical certainty (higher variability) (Kurz & Stergiou, 2003). Finally, the uncontrolled manifold and the goal-equivalent

manifold approaches can be used to model variability that is relevant and irrelevant to the measure of task performance (e.g. Gates & Dingwell, 2008; Verrel, Lövdén, & Lindenberger, 2012). These approaches, together, help to better understand the size and structure of motor variability, and which of these components could be impacted by states or traits such as fatigue, aging or sex.

2.2.2 Alterations in steadiness of motor output

Prior reviews of the literature are largely in agreement that the steadiness of motor output generally declines with older age (Christou, 2011; Enoka et al., 2003; Hunter et al., 2016). For instance, Laidlaw et al. (2000) found that older adults had less force steadiness than young adults during isometric contractions of the first dorsal interosseus muscle at 2.5%, 5%, and 10% of maximal voluntary isometric contraction (MVIC), as quantified by a higher coefficient of variation in force output. Further, these age differences were larger at 2.5% and 5% MVIC than at 10% MVIC (Laidlaw et al., 2000). In a simulation study, Negro et al. (2009) found that 71.8% of variability in force output was explained by a single principal component representing variability in smoothed MU discharge rates, supporting a MU origin in the control of force steadiness. Similarly, Tracy and colleagues reported larger coefficients of variation in the force output of older adults compared to young adults for low load isometric contractions of the first dorsal interosseus muscle (Tracy, Maluf, Stephenson, Hunter, & Enoka, 2005) and of the knee extensors (Tracy & Enoka, 2002). The age difference in the steadiness of motor output seems to be accentuated with cognitive demand, particularly in older females compared to older males (Pereira et al., 2015), and to be present in very slow dynamic contractions; older adults were reported to have higher standard deviation of the angular acceleration of the wrist during lifting and lowering of light loads using the elbow flexors (Graves, Kornatz, & Enoka, 2000). Finally, a recent review by Jakobi, Haynes, & Smart (2018) highlights the importance of considering sex differences in aging responses, as females tend to have less force steadiness than males and this sex difference is less apparent with increasing age. Thus, age-related decrements in upper and lower limb force steadiness could vary by sex, though the interaction between age and sex has not yet been evaluated systematically in the literature.

2.2.2 Alterations in movement-to-movement variability of lower limb motor output

Like the reduced steadiness (higher variability) reported in statically controlled motor outputs, aging is also believed to increase the variability in dynamically controlled motor outputs.

Variability in repeated dynamic outputs can be referred to as movement-to-movement variability. In the lower limb, most evidence originates from the study of stride-to-stride variability in gait. This attention was stimulated by Hausdorff et al. (2001) who conducted a prospective study of community-living older adults and found that fallers had significantly higher magnitude of stride time variability than non-fallers, suggesting that a common cause of the quality of life in older adults could be their elevated gait variability. Movement-to-movement variability of gait across the lifespan has since been explored in depth. Callisaya et al. (2010) and Beauchet et al. (2017) analyzed spatiotemporal variability in a total of 1365 adults aged 65+ years using standard deviations and coefficients of variation respectively, with both studies finding that higher age was associated with higher variability in stride time, stride length, and stride width. This variability may be linked with local dynamic stability, i.e. the ability of the body to respond to perturbations. Kang & Dingwell (2008a) analyzed gait at each participant's preferred walking speed and found that dynamic stability of the trunk, quantified using maximum Lyapunov exponents and Floquet multipliers, was lower in older than in young adults. Since gait speed has been shown to slow with old age (Menz, Lord, & Fitzpatrick, 2003), higher stride-to-stride variability could be explained by gait speed rather than the physiological processes of aging. Callisaya et al. (2010) showed that adjusting for self-selected gait speed reduced the estimated effect of age on stride-to-stride variability parameters. However, Kang & Dingwell (2008a, 2008b) found that the higher variabilities of stride time and length and lower dynamic stability of the trunk in older adults were independent of any age differences in self-selected gait speed. These results suggest that the influence of old age on stride-to-stride variability in gait is not only a factor of self-selected gait speed and that the physiological processes of aging contributes directly to the higher variability of gait motion in older adults.

Insights into the *structure* of movement-to-movement variability in spatiotemporal gait motion has also been gathered. A research group led by Dingwell & Cusumano has investigated variability in gait using the goal-equivalent manifold, which partitions goal-relevant from non-goal-relevant variability (Cusumano & Cesari, 2006; Cusumano & Dingwell, 2013). Setting consistent stride speed as a goal variable and stride time and length as the fluctuating variables, the authors provided experimental evidence showing that old age did not affect the structure of goal-relevant or non-goal-relevant variability (Dingwell, Salinas, & Cusumano, 2017). However, in the same study, older adults were found to have higher standard deviations of stride time, length,

and speed (Dingwell et al., 2017), indicating that the *structure* of stride-to-stride variability was independent of the *size* of stride-to-stride variability in the old adult group. The authors suggest then that the higher quantity of variability is attributable to higher neuromotor noise with older age, which supports the hypothesis that variability in locomotor output stems from minute changes to the central and peripheral systems (Hausdorff et al., 2001).

If neuromotor noise is a source of stride-to-stride variability of gait, we could expect to see higher variability in the movement patterns of joints and in the activation patterns of muscles with aging. Studies of single joint patterns provide evidence for higher variability in sagittal plane joint kinematics with older age, as quantified by higher coefficients of variation and lower Lyapunov exponents in ankle, knee, and hip positions (Buzzi et al., 2003), and by higher sample entropy in knee and hip joint angles (Kurz & Stergiou, 2003). In terms of the literature on interjoint coordination, Chiu & Chou (2012) measured the standard deviation of the continuous relative phase in gait of young and old adults, indicative of variability in the coordination between two selected joints, finding no significant age effect on variability of hip-knee or knee-ankle coordination. Park et al. (2016) measured the drift and area of a centroid derived via phase analysis, indicative of variability in the joint angle-angular velocity profiles, finding no significant age difference in variability of the hip, knee, or ankle profiles. Finally, Hafer & Boyer (2018) recently measured the standard deviation of segment-segment angle profiles, indicative of variability in the coordination between two selected segments, finding lower variability in pelvis-thigh, thigh-shank, and shank-ankle coordination during terminal swing. Taken together, these studies indicate that the age-related alterations in movement-to-movement variability of sagittal plane gait motor output are not ubiquitous, with higher variability of lower limb joint motions, no difference in variability of inter-joint coordination, and lower variability of inter-segment coordination. Moreover, how older age influences the variability of non-sagittal plane joint motions and of muscle activity during gait remains unknown. Knowledge on this issue could help better understand the mechanisms responsible for higher spatiotemporal gait variability seen in old adults.

2.2.3 Alterations in movement-to-movement variability of upper limb motor output

There is also evidence of natural variability from movement to movement in upper limb patterns (Srinivasan & Mathiassen, 2012a, 2012b). Under several upper limb work conditions, Mathiassen, Möller, & Forsman (2003) found significant inter-individual differences in the

variability of trapezius activation and arm kinematics in the same work condition, and different individual responses to changed work conditions. Recently, the inter-individual differences in kinematic variability during repetitive pipetting were found to be consistent between days, particularly for individuals with lower variability (Sandlund, Srinivasan, Heiden, & Mathiassen, 2017), and so the authors concluded that movement-to-movement variability may represent a personal trait that differs between individuals. The literature has sought to understand which personal factors contribute to these individual differences in motor variability, with pain studied as one such factor. Madeleine, Mathiassen, & Arendt-Nielsen (2008) investigated differences in movement-to-movement variability during 3-5 minutes of butchering in the absence of pain, following injection of hypertonic saline in the trapezius and infraspinatus (acute pain), and in workers with chronic neck-shoulder pain, finding increased variability in arm and trunk kinematics with acute pain and lower variability in kinematics and infraspinatus activation in workers with chronic pain compared to individuals with absence of pain. Similarly, variability of arm kinematics in butchers decreased in novice workers who developed sub-chronic pain in the first six months of work and was higher in asymptomatic experienced workers than novice workers (Madeleine, Voigt, & Mathiassen, 2008). Variability has not always been shown to be lower in people with chronic pain; although butchers with neck/shoulder discomfort were reported to have lower variability of head-shoulder displacement during deboning compared to asymptomatic butchers, variability of elbow-hip displacement was higher with discomfort (Madeleine & Madsen, 2009). The authors interpreted this higher elbow-hip variability as a compensatory response to neck/shoulder discomfort (Madeleine & Madsen, 2009). It may be interpreted then that the acute pain-related increases in movement-to-movement variability reflect a search for motor patterns to mitigate pain, while lower variability in chronic pain reflects an avoidance of pain-provoking motor patterns (Srinivasan & Mathiassen, 2012a). These studies, alongside evidence that repetitive motion is an occupational risk factor for incurring a neck/shoulder musculoskeletal disorder (Punnett & Wegman, 2004) provide considerable support towards the theorized link between the size of movement-to-movement variability in upper limb motor output and development of neck/shoulder musculoskeletal disorders (Madeleine, 2010).

As the prevalence and incidence rates of upper limb musculoskeletal disorders rise with older age (Cassou, 2002), the added risk with older age could be due in part to age-related changes in movement-to-movement variability of upper limb motor output. Indeed, a higher magnitude of

variability was reported in older compared to young adults, with higher coefficients of variation in elbow kinematics during a flexion/extension targeting task (Cooke, Brown, & Cunningham, 1989) and higher standard deviation of endpoint position during a computer mouse targeting task (Walker, Philbin, & Fisk, 1997). The quality of movement variability has also been investigated in the upper limb using the uncontrolled manifold. Similar to the lower limb, age did not alter task-relevant or task-irrelevant variability during a repetitive pointing task (Verrel et al., 2012). In fact, in another study, it was shown that older adults had lower task-irrelevant variability during a machine-assembly task, leading the authors to suggest that under such controlled tasks, control of upper limb movement may not be impaired with old age (Xu, Qin, Catena, Faber, & Lin, 2013). Together, these studies point to discrepancies in the literature on old age and the structure of motor variability, which could reflect the hypothesized task dependency of variability control.

Age-related differences in movement-to-movement variability of the upper limb may appear though in more prolonged, fatiguing tasks. In a pair of studies, Qin et al. (Qin, Lin, Buchholz, & Xu, 2014; Qin, Lin, Faber, et al., 2014) had young and older adults perform 80 minutes of repeated light occupational assembly work. They found myoelectric evidence of fatigue in the upper trapezius and deltoid muscles of both age groups (Qin, Lin, Buchholz, et al., 2014), similar increases in shoulder posture variability in both age groups (Qin, Lin, Faber, et al., 2014), and larger decreases in elbow posture variability in the older than the young group (Qin, Lin, Faber, et al., 2014). These results suggest that older adults reach a similar state of fatigue as young adults, with similar shoulder kinematic variability, at the expense of more stereotypical distal joint patterns with older age, which could reflect an attempt to develop a simpler pattern to mitigate the fatigue effects. Fatigue could mediate the relationship between exposure to repetitive motions and the later development of pain and musculoskeletal disorders (Côté, 2014), and so Section 2.3 is dedicated to defining fatigue, identifying valid fatigue metrics, and further exploring how motor variability changes as a function of fatigue and aging.

2.3 Alterations in motor variability with fatigue

2.3.1 Definition of fatigue and available metrics

Fatigue can be measured in many ways depending on the specific research question (Cairns, Knicker, Thompson, & Sjøgaard, 2005). Some studies have focused on clinical fatigue reported in populations such as in persons with chronic fatigue syndrome (Fukuda et al., 1994; Smets, Garssen,

Bonke, & De Haes, 1995), on everyday occupational fatigue reported in the workplace (Åhsberg, 2000; Åhsberg, Garnberale, & Kjellberg, 1997), and on experimental fatigue reported in laboratory-based motor tasks (Barry & Enoka, 2007; Enoka & Stuart, 1992; Gandevia, 2001). As a result of these broad perspectives, taxonomies have been recently developed to better classify different biomechanical and psychosocial aspects of fatigue (Enoka & Duchateau, 2016; Kluger, Krupp, & Enoka, 2013). For this dissertation, fatigue is defined as "a disabling symptom in which physical and cognitive function is limited by interactions between performance fatigability and perceived fatigability" (Enoka & Duchateau, 2016). Performance fatigability refers to the declines in objective performance that are based on muscle activation and contractile mechanisms, whereas perceived fatigability refers to the changes in subjective sensations that are based on psychological state and homeostasis (Enoka & Duchateau, 2016). Accordingly, performance fatigability and perceived fatigability may be measured by the changes in mechanical output and perception rating scales, respectively. Using appropriate measures, the muscular mechanisms that contribute to performance and perceived fatigability can then be further explored. Electromyography (EMG) is commonly used to explore the excitatory output from MUs to the muscle during fatigue, with changes in muscular output characterized as localized muscle fatigue and frequently used to provide objective evidence of fatigue at the muscle (De Luca, 1997; Farina, Gazzoni, & Merletti, 2003; Fedorowich et al., 2013; Merletti, Knaflitz, & De Luca, 1990; Qin, Lin, Buchholz, et al., 2014; Shi, Zheng, Chen, & Huang, 2007; Tse, McDonald, & Keir, 2016). Thus, fatigue can be evaluated more holistically by simultaneously measuring the changes in mechanical output, EMG, and perception rating scales. These fatigue measures will be further explored before giving further attention to the motor variability response during fatigued movement.

Mechanical output. Repeated measurements of mechanical output, such as force, torque, or power output, can be used in two types of experimental designs that test a between-group effect: 1) all participants complete the same task duration and the decline in maximal mechanical output is compared between groups (e.g. (Senefeld et al., 2017)), or 2) all participants complete the task to the same decline in mechanical output and the task duration is compared between groups (ex. (Hunter, Critchlow, & Enoka, 2005)). Both designs can be used to characterize performance fatigability, although there can be differences in the criteria used to terminate a task. The second design will be used as an example. In this design, termination criteria have included a 10% decline in the torque during sustained isometric elbow flexion at 20% MVIC (Hunter et al., 2005) and 40%

decline in maximal power during dynamic knee extensions at maximal power (Dalton, Power, Paturel, & Rice, 2015). The task duration in each of these studies was up to 23 minutes for Hunter et al. (2005) and no longer than a few minutes for Dalton et al. (2015). Loads are typically low in the workplace, so contractions at 20% MVIC are often used to mimic low loads (Hunter, Critchlow, & Enoka, 2004; Hunter et al., 2005; Mouser et al., 2017; Senefeld, Pereira, Elliott, Yoon, & Hunter, 2018; Yoon, Schlinder Delap, Griffith, & Hunter, 2007). However, since fatigability in aging is highly dependent on the characteristics of the task (Christie, Snook, & Kent-Braun, 2011; Hunter et al., 2016), it is recommended that mechanical output be monitored in combination with other indicators when exploring the age-related fatigue response.

Perception rating scales. Several fatigue perception rating scales have been created and validated, including holistic scales like the Multidimensional Fatigue Inventory (Smets et al., 1995), the Swedish Occupational Fatigue Inventory (Åhsberg et al., 1997), and the Pittsburgh Fatigability Scale (Glynn et al., 2015). While these holistic scales provide useful information on everyday perceptions of fatigue, they are impractical to use to study perceptions relating to real-time development of fatigue. For this purpose, several analog scales have been designed to quickly evaluate the rating of perceived exertion (RPE), including the Borg scale (Borg & Kaijser, 2006; Borg, 1998) that measures RPE on a scale from 6-20 to match linearly with changes in heart rate, the Borg CR-10 scale (Borg & Kaijser, 2006; Borg, 1998; Borg, 1982) that measures RPE on a ratio-normalized 0-10 scale, and the Borg CR-100 scale that measures RPE on a more finely-graded 0-100 scale (EBorg & Kaijser, 2006). Each scale associates descriptive ratings to different scores (e.g. a score of "4" on the Borg CR-10 scale represents a "somewhat strong" exertion). These scales are easy and quick to use, and so are useful to estimate RPE frequently throughout experimental fatigue. Since the Borg scale was designed to be highly correlated to heart rate, it is most useful for evaluating exertion during whole-body, cardiovascular exercise. In contrast, the normalized Borg CR-10 and CR-100 scales are more typically used in applications of localized muscle fatigue, where individuals rate their perceived exertion at a specific joint or muscle region. Out of these ratio-normalized scales, the Borg CR-10 is more commonly used, and changes in RPE on this scale have been related to changes in myoelectric indicators of fatigue (Otto, Emery, & Côté, 2018; Troiano et al., 2008). Therefore, the Borg CR-10 scale will be used to evaluate RPE in this dissertation.

There have been only a few investigations on the effect of old age on RPEs during fatiguing efforts. Allman & Rice (2003) reported higher early RPEs in older adults than in young adults during fatigue from intermittent isometric elbow flexions at 60% MVIC. Meanwhile, measuring the temporal progression of RPE in young and old adult at normalized time points, Hunter et al. (Hunter et al., 2004) reported no difference in the RPEs at 25%, 50%, 75%, and 100% of task failure from sustained isometric elbow flexion at 20% MVIC. Finally, John et al. (2009) had older and young adults produce isometric elbow flexions corresponding to their RPEs of 1, 3, 5, 7, and 9, finding that older adults produced less torque than young adults, particularly at higher RPEs. Together, these results suggest that older adults perceive absolute loads as more exerting than young adults, but that this aging effect is mitigated at low absolute and relative loads.

Surface EMG. Surface EMG is another technique that can be used to investigate fatigue. Surface EMG measures the electrical activity of muscles (i.e. muscle activity) using electrodes that are placed on the surface of the skin. The measurement is non-invasive. EMG signals represent the summation of the number and size of action potentials that originate from the motor units. In low-load tasks, where fatigue develops gradually, the EMG signal is generally characterized by an increased amplitude, likely due in part to increases in the number of active MUs, and spectral compression to lower frequencies, likely due in part to decreases in the discharge rate of the average MU and increases in the durations of action potentials (De Luca, 1997). Accordingly, localized muscle fatigue is often measured as a statistically significant change in the EMG root mean square (RMS; measures average signal amplitude) and/or median power frequency (MPF; measures average signal frequency) during exercise (De Luca, 1997; Farina et al., 2003; Fedorowich et al., 2013; Merletti et al., 1990; Qin, Lin, Buchholz, et al., 2014; Shi et al., 2007; Tse et al., 2016). The previously described effect of aging on the total number of MUs and their discharge rates likely contributes to differences in the non-fatigued RMS and MPF values in the muscles of older adults than younger adults (Bailey, Corona, Pilloni, et al., 2018; Kienbacher et al., 2015; Roberto Merletti, Farina, Gazzoni, & Schieroni, 2002). As Bilodeau et al. (2001) identified a smaller RMS increase and Merletti et al. (2002) identified a smaller MPF decrease in older adults than young adults during sustained isometric elbow flexion at submaximal loads, aging adults may have a reduced capacity to modulate their MUs to prolong performance as fatigue develops.

Relationships between measures of fatigue. The temporal changes in measures of fatigue, (i.e. force output, RPE, and EMG RMS and MPF) are interrelated (Hummel et al., 2005; Nussbaum, Clark, Lanza, & Rice, 2001; Troiano et al., 2008). For example, Hummel et al. (2005) measured the rates of change in RPE and EMG mean power frequency of the upper trapezius during isometric shoulder elevation at 30% MVIC, finding that the rate of increase in RPE over two six-minute efforts was strongly correlated to the rate of decrease in EMG mean power frequency. Moreover, Nussbaum et al. (2001) found that participant-averaged endurance times for repetitive overhead work under eight different conditions were strongly correlated to participant-averaged RPE and EMG amplitudes during MVICs. When assessing the interrelationships among individual participants, however, the correlations were mitigated or no longer statistically significant (Nussbaum et al., 2001). This suggests that individual factors, like age, may affect the relationships between these measures of fatigue.

2.3.2 Effect of fatigue on motor variability

Increases in the size of motor variability with fatigue are widely reported in healthy young adults. One experimental approach has been to investigate changes during repetitive pointing tasks once participants reach a set rating of perceived exertion on the Borg CR-10 scale of 8 (Cid et al., 2019; Fedorowich et al., 2013; Fuller et al., 2011; Srinivasan et al., 2016). In these studies, muscle fatigue is typically confirmed by the myoelectric changes in EMG (i.e. an increase in RMS and/or a decrease in MPF). For example, Fuller et al. (Fuller et al., 2011) evaluated the reach-to-reach variability of participants completing a low-load repetitive forward reaching task, finding that the variability of shoulder angle and position, elbow position, and centre of mass each increased from pre- to post-fatigue. Similar findings were found for the reach-to-reach variability of muscle activation, measured using the standard deviation and coefficient of variation, with fatigue-related increases reported for the upper trapezius, anterior deltoid, and supraspinatus during repetitive forward reaching (Fedorowich et al., 2013; Srinivasan et al., 2016), for the upper trapezius, anterior deltoid, latissimus dorsi, and triceps brachii during repetitive pipetting (Samani et al., 2017), and for the middle trapezius, lower trapezius, and serratus anterior during precise reaching (Cid et al., 2019). Similar findings are also reported in faster velocity upper limb tasks, with increased variability of anterior deltoid activity during ballistic shoulder flexions (Monjo & Forestier, 2016), and in fatiguing lower limb tasks, with increased variability of arm and leg displacements during cross-country skiing (Cignetti, Schena, & Rouard, 2009). Further, possessing higher variability of

motor patterns may protect against fatigue. Perceived fatigability (i.e. time to Borg CR-10 scale rating of 8) was lower in repetitive forward reaching in females who possessed higher initial variability in upper trapezius and supraspinatus activation (Fedorowich et al., 2013) and performance fatigability (i.e. loss in maximal torque) was lower in a repetitive eccentric knee extension task in males who possessed higher variability of torque fluctuation (Skurvydas, Brazaitis, & Kamandulis, 2010). Thus, in the context of fatigue, these increases in motor variability can be viewed as a voluntary search for new motor patterns to maintain task performance (Côté, 2014).

How fatigue influences the structure of motor variability is less clear. In an investigation of spatiotemporal motion during a fatiguing push-pull task, Gates & Dingwell (2008) did not observe a difference in the size of variability or in goal-relevant or goal-irrelevant variability, but did find decreased statistical persistence in these parameters with fatigue. As goal performance was stable (goal-relevant variability exceeded goal-irrelevant variability), the authors interpreted these findings to mean that goal performance was stabilized by quicker correction of spatiotemporal deviations (Gates & Dingwell, 2008). Goal-relevant deviations were also more quickly corrected in a sawing task following shoulder flexor fatigue, however, when additional muscles were also fatigued, deviations were corrected less quickly (Cowley, Dingwell, & Gates, 2014). The changes in the structure of variability may therefore depend on the specific task-relevant muscle that is fatigued as well as how many task-relevant muscles are fatigued. Findings seem to differ in the lower limb, with findings of a fatigue-related increase in task-relevant variability of M-modes (i.e. principal components of muscle activity) during postural sway that are suggestive of performance-stabilizing variability (Singh & Latash, 2011), but a fatigue-related decrease in the ratio between task-relevant and task-irrelevant variability of frontal plane gait motion (Qu, 2012) and a fatigue-related increase in task-irrelevant variability during running (Möhler, Ringhof, Debertin, & Stein, 2019) that are each suggestive of less stable movement performance. That fatigue has been associated with different influences on the structure of variability in the studies cited above may be indicative of results that are approach-dependent (uncontrolled manifold vs. goal-equivalent manifold) and/or limb dependent (upper limb vs. lower limb).

2.3.3 Effect of personal factors on fatigue-related alterations in motor variability

The fatigue-related adjustments in motor variability may also depend on personal factors like sex and age. Bouffard et al. (2018) investigated motor variability in young males and females during fatiguing repetitive pointing, finding increased variability in average humerothoracic angle from the first to the final minute of the task in females but not in males. Comparing the changes in the same task at the level of the muscle, Srinivasan et al. (2016) found that females had a smaller increase than males in upper trapezius activation variability and that females had increased biceps brachii activation variability, where males had decreased variability. These results show that the motor variability responses to repetitive and fatiguing upper limb motion differ with sex. One interpretation is that females adapt to shoulder fatigue by varying activation of elbow musculature while males vary activation of shoulder musculature (Srinivasan et al., 2016). However, subsequent studies have been unable to replicate these findings, with no sex differences reported in the fatigue-induced muscle activation variability responses to precision reaching tasks (Cid et al., 2019; Minn & Côté, 2018).

Old age seems to produce an altered motor variability response to fatigue. In addition to the larger decrease in elbow flexion angle variability with old age, reported in Section 2.2.3, older adults were reported to have increased variability of peak velocity with fatigue from repeated knee extensions, with young adults having no such change (Senefeld et al., 2017), but there was no age differences in the variability of peak velocity with fatigue from repeated elbow flexions (Senefeld et al., 2017). This indicates that the influence of old age on motor variability responses may be limb specific. Presently, there are no known studies that have investigated how old age affects the movement-to-movement variability of muscle activation patterns during fatigue. Given the sex differences in movement-to-movement variability observed in a fatiguing repetitive pointing task (Bouffard et al., 2018; Srinivasan et al., 2016), age-related alterations in motor variability could also be sex-specific. Understanding how the aging male and female neuromuscular systems affect the changes in muscle activation variability during fatigue development is particularly pertinent since age and exposure to repetitive movements (implying exposure to fatigue) are well-linked to the development of MSDs (Cassou, 2002; Gallagher & Heberger, 2013; Punnett & Wegman, 2004).

2.4 Muscle oxygenation in exercise

The lack of knowledge on how variability is controlled from movement to movement (without and with aging) calls for a closer examination of the muscular contributions to fatigue. One area that contributes to fatigue, but can be overlooked by the disciplines of biomechanics, ergonomics, and motor control is the oxygenation of skeletal muscle (Enoka & Duchateau, 2016).

2.4.1 Definition of muscle oxygenation and available indicators

Having been interpreted as muscular oxygen transfer (Boushel et al., 2001) and the matching of oxygen delivery to oxygen utilization in the muscle (Barstow, 2019), muscle oxygenation will be defined as the dynamic oxygen status of microvascular structures and tissue within the muscle. In theory, the increasing metabolic demand of the exercising muscle leads to an increase in oxygen utilization, requiring a matching increase in oxygen supply. Development of fatigue would assume that the energy requirements of the muscle are not met, in part due to inadequate oxygen supply. This theory is supported by evidence of fatigue following blood flow occlusion, where the compromised microvascular oxygen supply leads to the accumulation of metabolites that stimulate type III/IV afferents (Barry & Enoka, 2007). Accordingly, muscle oxygenation factors directly into the taxonomy of fatigue (Enoka & Duchateau, 2016) and is likely an important feature for understanding an individual's fatigue response.

The main technique used to study non-invasive skeletal muscle oxygenation during exercise is near-infrared spectroscopy (NIRS). A NIRS optode is positioned on the skin over the muscle and monitors the quantities of four parameters in the detecting area of the sensor; 1) oxygenated hemoglobin (HbO_2), 2) deoxygenated hemoglobin (HHb), 3) total hemoglobin (THb), and 4) the ratio of oxygenated to total hemoglobin, typically termed the oxygen saturation or tissue oxygen index (TOI). These parameters are derived from the known relationship in how near-infrared light (wavelengths of 700-1000 nm) is absorbed/scattered by chromophores (Ferrari, Mottola, & Quaresima, 2004). Details on the derivations of these parameters are available elsewhere (Boushel et al., 2001; Ferrari et al., 2004). Briefly, near-infrared light penetrates skin, subcutaneous fat, and muscle, but is absorbed to a relatively high degree by hemoglobin, myoglobin, cytochrome oxidase, and melanin. Melanin levels are constant and cytochrome oxidase levels negligible relative to hemoglobin and myoglobin, so melanin and cytochrome oxidase are assumed to not influence temporal changes in the NIRS signal. The contribution of

myoglobin to the NIRS signal is approximated to be 10% which is typically considered negligible (Ferrari et al., 2004). What is left is the assumption that temporal changes in the NIRS signal are representative, predominantly, of changes in hemoglobin concentration. Near-infrared light is absorbed at different levels for HbO_2 and HHb, allowing for the differentiation of these parameters, THb, and TOI. Levels of HbO_2 and HHb may be indicative of oxygen availability in microvascular structures within the muscle. Levels of THb are a direct measure of microvascular hematocrit (Barstow, 2019). Since hematocrit fluctuates with blood volume, THb can be an indirect indicator of muscle blood volume. Finally, TOI is representative of the dynamic balance between oxygen supply and consumption (Ferrari et al., 2004).

2.4.2 Effect of exercise on muscle oxygenation

While some studies report alterations in muscle oxygenation with low-load upper extremity exercise (Crenshaw, Djupsjöbacka, & Svedmark, 2006; Murthy, Kahan, Hargens, & Rempel, 1997), results are not unanimous (Flodgren, Hellström, Fahlström, & Crenshaw, 2006). Murthy et al. (1997) investigated the time course of extensor carpi radialis oxygenation during 1-minute isometric wrist extensions at varying intensities. Their qualitative findings were that TOI tended to rise in the first 10 seconds, drop to below baseline values in the subsequent 30 seconds, then plateau for the final 20 seconds; the drop below baseline was statistically significant at efforts ≥ 10% MVIC but not at 5% MVIC. In contrast with this exercise-induced drop in TOI, Crenshaw et al. (2006) reported increased extensor carpi radialis TOI and THb following 60 minutes of computer mouse work. Differences between these studies may reflect decreased muscle oxygenation during low-load isometric efforts but increased oxygenation during low-load dynamic efforts, potentially a result of adequate muscle reperfusion during dynamic exercise. The lack of an oxygenation response observed by Flodgren et al. (2006) during their occupational reaching task was likely a function of the very low task load (trapezius activation of 9.3% relative to maximal exertion), providing further support that efforts ≥ 10% MVIC are necessary to elicit a significant muscle oxygenation response.

Responses are more pronounced in studies with objective, mechanical evidence of fatigue. In fatiguing isometric tasks, studies have reported decreased tibialis anterior TOI during one-minute dorsiflexions at 30%, 60%, and 100% MVIC, with more rapid decreases at higher intensities (McNeil, Allen, Olympico, Shoemaker, & Rice, 2015), and decreased erector spinae

HbO_2 and blood volume following a one-minute back extension (Yoshitake, Ue, Miyazaki, & Moritani, 2001). Ferguson et al. (2013) also observed decreased HbO_2 in the trapezius and anterior deltoid following two hours of fatiguing pestle-work, as further evidence of reduced oxygen supply in the fatigued state. However, the reduction in oxygen supply did not disrupt oxygen saturation, as the authors also reported small TOI increases (Ferguson et al., 2013). The lack of disruption in muscle oxygenation in the fatigued state has been corroborated by investigations of low-load elbow flexion fatigue. While biceps brachii oxygenation has been reported to decrease with initial low-load elbow flexion exercise (Baudry et al., 2013; Blangsted, Vedsted, Sjogaard, & Sogaard, 2005), the same studies reported subsequent increases in TOI and THb during fatigue development from isometric and dynamic elbow flexion exercise respectively (Baudry et al., 2013; Blangsted et al., 2005). Therefore, there seems to be a biphasic muscle oxygenation pattern in fatiguing exercise, consisting of an initial decline in oxygenation and a subsequent reoxygenation response. This response has been observed in the dynamic balance of muscle oxygenation (i.e. TOI) and of muscle blood volume (i.e. THb).

2.4.3 Exercise induced muscle swelling

Muscle blood volume accumulating during prolonged, dynamic exercise is not surprising, as muscles also have a clear swelling response to submaximal fatiguing contractions. This muscle swelling has been identified using brightness-mode (B-mode) ultrasonography as the temporal increase in muscle thickness (MTH) in response to exercise (Bakke et al., 1996; Brancaccio, Limongelli, D'Aponte, Narici, & Maffulli, 2008; Jensen et al., 1994; Yasuda et al., 2015). Muscle swelling likely stems from increased vascular perfusion for oxygen delivery and metabolite removal (Brancaccio et al., 2008). In addition to the perfusion of blood and oxygen into the muscle, muscle swelling has been attributed to three other phenomena in the literature: 1) inflammation, 2) edema, and 3) musculotendinous compliance.

Inflammation. Muscle swelling has been attributed to the inflammation occurring with exercise-induced muscle damage. Briefly, muscle damage sustained from exercise promotes an inflammatory response where various immune cells infiltrate the damaged muscle to begin the muscle remodeling process (Chazaud, 2016). The swelling-induced immune response is typically associated with an increase in muscle soreness that is reported 24-48 hours following exercise-induced muscle damage (Buckner et al., 2017; MacIntyre, Reid, & McKenzie, 1995). However,

inflammatory biomarkers cannot currently be measured without invasive procedures. The contribution of inflammation may instead be inferred. In one experiment, Buckner et al. (2017) evaluated muscle swelling over eight days that occurred from several bouts of biceps curls. Participants completed 4 x 10 biceps curls at 70% of 1-repetition maximum on Days 1, 3, 5, and 8, with MTH evaluated for biceps brachii and muscle soreness evaluated for the exercising arm. The authors found that MTH was significantly higher *before* Day 8 when compared to *before* Day 1, indicating that there was sustained muscle swelling lasting 72 hours after the last exercise bout (Day 5). Inflammation may have been responsible for the sustained muscle swelling given its similar response time. Since muscle swelling is also reported immediately after exercise (Bakke et al., 1996; Buckner et al., 2017; Counts et al., 2016; Jensen et al., 1994; Kubo, Kanehisa, Kawakami, & Fukunaga, 2001; Loenneke et al., 2017; Thiebaud, Yasuda, Loenneke, & Abe, 2013; Yasuda et al., 2015), the immediate swelling response may be influenced by other factors.

Edema. Immediate muscle swelling has been attributed to edema (Jensen et al., 1994; Loenneke et al., 2017). Jensen et al. (1994) attributed swelling of the supraspinatus following isometric muscle fatigue to edema from a combination of net filtration of fluid from capillaries to the interstitium, impaired fluid transport from the interstitium to the lymphatic system, and impaired lymphatic drainage. This shift in fluid from capillaries to muscle cells is supported by Sjøgaard, Savard, & Juel (1988), who observed increased water content in the vastus lateralis after an hour-long isometric knee extension at 5% MVIC. While these studies focused on isometric exercise, edema has also been attributed to the increased MTH following dynamic exercise. Loenneke et al. (2017) observed vastus lateralis swelling in response to dynamic knee extension exercises at a variety of intensities, both with and without fatigue, and similar drops in plasma volume across these exercise conditions. This led the authors to attribute the muscle swelling response to edema and to note that the shift in fluid from the blood vessel to the muscle was similar across a range of intensities (Loenneke et al., 2017), including low effort contractions to fatigue.

Tendinous creep/compliance. The immediate increase in MTH, used to indicate muscle swelling, may be influenced by tendinous creep or compliance. Creep refers to the increased strain that occurs while maintaining a constant stress, while compliance refers to the increased strain that occurs from the same repeated stress. Creep and compliance of tendons may have important impacts on the measurement of the muscular contribution to fatigue. In one study (Kubo et al., 2001), participants completed a fatiguing task that consisted of repeated ankle plantar flexion

MVICs, and tendon compliances before and after the fatiguing task were evaluated in ramped isometric contractions from 0-100% MVIC. The authors found a mean increase of 22.7% in tendon compliance that altered the force-length relationship of the tendon and increased the electromechanical delay after the fatiguing task, occurring with a simultaneous increase in medial gastrocnemius MTH (Kubo et al., 2001). This implies that there are fatigue-dependent relationships between tendon mechanics, muscle architecture, and the recorded EMG. Subsequent studies have provided further support for these relationships (Mademli & Arampatzis, 2005; Rudroff, Staudenmann, & Enoka, 2008). Mademli & Arampatzis (2005) observed an increased pennation angle, a decreased fascicle length, and a higher EMG amplitude in the medial gastrocnemius following fatiguing isometric plantar flexion at 40% MVIC. They interpreted the architectural changes to be due to creep of the tendon and aponeurosis, which would act to shorten the contractile element, reduce the muscle force potential, and increase the EMG amplitude, independent of the fatigue-related alterations in MU discharge (Mademli & Arampatzis, 2005). While Rudroff et al. (2008) also observed an increased pennation angle following isometric fatigue of the brachialis at 20% MVIC, which was strongly related (r = 0.75) to the increased brachialis MTH, these architectural changes were not related to the amplitude of the surface EMG recording (Rudroff et al., 2008). Tendon creep and compliance appear to contribute to the interpretation of muscle swelling (measured as an increase in MTH), but their influence on the surface EMG signal is less clear.

Although the precise contributions of these muscle swelling mechanisms to different task conditions are not fully understood, the resulting swelling responses are very similar across tasks. Increases in muscle thickness, measured using ultrasonography, have been observed in the quadriceps (9%), supraspinatus (14%), masseter (9-14%), and biceps brachii (20%) immediately after cycling (Brancaccio et al., 2008), isometric shoulder abduction (Jensen et al., 1994), isometric and dynamic jaw clenching (Bakke et al., 1996), and repeated arm curls (Yasuda et al., 2015), respectively, indicating that the swelling response occurs across several muscles and in both static and dynamic conditions. Further, the relative MTH increases were similar in these studies (9-20%) despite large differences in the absolute MTH at baseline for each muscle (32 mm for the quadriceps, 22 mm for the middle of the supraspinatus, 10 mm for the masseter, and about 33 mm for the biceps brachii) (Bakke et al., 1996; Brancaccio et al., 2008; Jensen et al., 1994; Yasuda et al., 2015).

2.4.4 Effect of personal factors on exercise-related alterations in muscle oxygenation

Sex and age each seem to affect the muscle oxygenation response to exercise. Generally, muscle oxygenation at rest and in exercise is lower in males than in females, with evidence of lower TOI and higher HHb and THb in the vastus lateralis during cycling (Bhambhani, Buckley, & Susaki, 1999; Smith & Billaut, 2012; Takagi et al., 2016), and lower TOI in forearm muscles during isometric hand gripping (Mantooth, Mehta, Rhee, & Cavuoto, 2018). Muscle oxygenation responses to exercise also differ with sex. Elcadi, Forsman, & Crenshaw (2011) investigated the changes in extensor carpi radialis and upper trapezius oxygenation during isometric wrist extension and arm elevation, finding that TOI and THb decreased with initial exercise in both males and females. However, prolonged responses differed by sex; extensor carpi radialis THb increased more in females than in males and upper trapezius TOI increased in males but continued to decrease in females (Elcadi et al., 2011). This study provides two interesting insights into muscle oxygenation: first, it shows that the response to exercise varies between males and females, with females accumulating more forearm blood volume and losing more oxygen saturation than males; second, it provides further evidence for a biphasic oxygenation response to exercise (the initial and prolonged phases) that supports findings from other studies on fatigue and low-load elbow flexion (Baudry et al., 2013).

Muscle oxygenation also appears to be lower with older age. Comparing the responses to incremental cycling between old and young adults, Costes et al. (1999) reported lower VL TOI in older adults at rest, and Takagi et al. (2013) reported lower BF, GL, and TA TOI at rest and during exercise. Further, the drops in VL TOI with incremental exercise were larger in older adults at the same absolute oxidative workload but not at the same relative workload, which may be attributable to the lower maximal power and oxidative capacity reported in older adults (Costes et al., 1999). However, oxidative capacity may not necessarily be impaired with age, as no age differences were reported in rate of gastrocnemius HHb recovery (indicative of muscle reoxygenation), popliteal blood flow, or convective oxygen delivery following dynamic incremental plantar flexion exercise (Hart et al., 2015). These studies each used incremental tasks, meaning the effect of age on the muscle oxygenation response in prolonged low-load tasks is less certain. So far, only one known study has investigated such responses (Kutsuzawa, Shioya, Kurita, Haida, & Yamabayashi, 2001), where the authors found slower forearm flexor HbO_2 and HHb recovery with old age following

repeated hand gripping. Thus, how old age influences the muscle oxygenation response *during* repetitive low load exercise remains unclear.

2.4.5 Associations between oxygenation and the control of repetitive movement

Interestingly, the deoxygenation response during fatigue may be related to the neural control of repetitive movement. In a landmark study, Amann et al. (2006) found that under conditions with increasing arterial oxygenation (e.g. hypoxia, normoxia, hyperoxia), 5 km time trial cycling was characterized by increased integrated EMG amplitude, increased mean cycling power, and faster performance, but no difference in the exercise-induced change in quadriceps twitch force. Interpreting the EMG amplitude as central neural drive and the change in twitch force as the magnitude of peripheral fatigue, the authors developed the hypothesis that there is a critical threshold of peripheral muscle fatigue that is protected by up or down-regulating central neural drive to muscles, altering exercise performance (Amann et al., 2006). Importantly, arterial oxygenation was directly linked to the regulation of this neural response. This link was recently supported in a study of motor unit discharge behaviour during brief isometric elbow flexions at 25% MVIC before and after hypoxia (McKeown, Simmonds, & Kavanagh, 2019). Matching arterial oxygen saturation among participants to 80% of the resting value, the authors showed that the four participants who had decreased MU discharge frequency had faster arterial desaturation than the six participants who had increased MU discharge frequency. This indicates that oxygen desaturation with exercise may also help to explain individual motor responses; the mechanism(s) responsible for inter-individual differences are unclear but the authors suggest that different afferent input to motor neurons, neuromodulators, and sympathetic nerve activity may be responsible (McKeown et al., 2019).

Some other studies provided evidence for a link between biomechanical patterns and muscle oxygenation. Mehta, Lavender, & Jagacinski (2014) evaluated back muscle oxygenation, trunk kinematics, and trunk kinetics during a one-hour repetitive lifting task, finding that participant-specific decreases in erector spinae HbO_2 were correlated with increases in back extension and lateral bending velocity, and increases in lateral bending moment. The kinematic and kinetic changes were interpreted as a change in motor behaviour to accomplish each lift quicker, providing the participant with more rest between repeated lifts (Mehta et al., 2014). Thus, some evidence seems to indicate that the oxygenation of contracting muscle can affect how

repetitive biomechanical patterns are controlled, although this evidence is currently limited to the study of arterial oxygenation, missing muscle oxygenation, Further, this previous study analyzed average motor responses, ignoring that it would rather be the natural variability in movement-to-movement output that could be linked to muscle oxygenation aspects of fatigue and injury (Côté, 2014).

2.5 Conclusions from review of literature

This review of literature has established that the age-related remodeling of the nervous system plays a significant role in how aging adults control their movement. In addition, age-related adjustments in movement control have been observed across a range of tasks, including sustained and dynamic contractions, single and multijointed movements, and the lower and upper extremities. Across these varied tasks, motor variability has emerged as one principle that explains age differences in motor control, with key observations from gait related to fall risk and observations from repetitive arm work related to fatigue and musculoskeletal disorders. Finally, the literature has identified muscle oxygenation as a potential physiological factor that regulates biomechanical patterns of motor control.

This review of literature also established current gaps in the understanding of motor variability in aging adults, including a) potential sex-dependent age differences, b) potential fatigue-dependent age differences, c) potential age differences in variability of muscle activity, and d) a potential association between motor variability and muscle oxygenation. Addressing these gaps requires a range of experimental studies that recruit large numbers of male and female adults across the lifespan, and expertise in an array of instruments to quantify biomechanical and physiological parameters.

Chapters 3-6 describe a series of four experimental studies undertaken to address these literature gaps. Theses studies include investigations of potential sex differences in age-related variability of lower extremity motor patterns (i.e. gait, Chapters 3 and 4), investigations of age differences in the variability of upper extremity muscle patterns in the absence and presence of fatigue (Chapters 5 and 6), and an investigation of the associations between muscle activation variability and oxygenation patterns (Chapter 6). An additional study on the sex-dependent age differences in ensemble-averaged muscle activity patterns preceded the studies reported in Chapters 3-6. This preceding study did not examine motor variability patterns, and so is outside

the scope of this dissertation; however, the novel findings reported in this study, consisting of sex-dependent effects of old age on muscle activity patterns, was a strong motivator to investigate sex differences in Chapters 3 and 4. For this reason, this preceding study has been included as supplementary material to this dissertation in Appendix A.

Chapter 3. Does variability in motor output at individual joints predict stride time variability in gait? Influences of age, sex, and plane of motion

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3.1 Preface

This chapter introduces results from a large cohort study on gait that investigates variability in spatiotemporal motion as well as in joint kinematics. This work was completed on a dataset owned by Dr. Massimiliano Pau's research team at the University of Cagliari. With much of the motor variability and aging literature in the lower limb focused on understanding sagittal plane movement-to-movement variability in gait at the levels of the whole gait and individual joint patterns (see Chapter 2), this study sought to supplement these findings by addressing gaps in knowledge on 1) how age-related changes in the joint kinematics variability differed by sex and plane of motion, and 2) how variability at these levels (whole gait patterns and individual joint patterns) were related.

Optoelectronic motion capture was used to acquire lower limb and pelvis marker positions. A tri-dimensional kinematic model was constructed to output measures of spatiotemporal motion and lower limb joint angles during gait. Variability of these measures was quantified by the stride-to-stride standard deviation and coefficient of variation. Effects of age and sex on these measures were analyzed, and kinematic variability predictors of spatiotemporal variability were identified.

Results from this study were intended to better understand how lower limb motor variability patterns change in aging males and females. Sections 3.2 to 3.13 are a copy of the manuscript published by the *Journal of Biomechanics*. Formatting has been altered to allow insertion into this thesis.

3.2 Highlights

- Older age was associated with lower ankle flexion/extension variability
- Older age was associated with higher frontal plane ankle and pelvis variability
- In males, older age was associated with higher knee flexion/extension variability
- Higher sagittal and frontal plane ankle variability predicted stride time variability

3.3 Abstract

Old age is associated with variability in gait motor output, particularly in females, and is linked to fall risk. However, little is known about how older age and sex affect variability in the

outputs of individual joints, and how these variabilities contribute to the collective gait output. Healthy adults aged 18-99 years (N = 102, 57 females) completed six trials of straight walking at self-selected speed. Stride time variability (coefficient of variation) and variabilities of lower limb tridimensional joint angles (standard deviations: SD) were calculated. Age*Sex (A*S) mixed models were conducted on all measures and year-by-year rates of change were subsequently estimated. Correlations and stepwise linear regression analyses were computed between joint angular variabilities and stride time variability. Each year of age was associated with 0.022% higher stride time variability (A: $p = .002$), 0.07° lower variability in peak ankle dorsiflexion (A: $p = .004$), 0.002-0.098° higher variability in mean ankle inversion/eversion, mean pelvic obliquity, and pelvic rotation range of motion (A: $p < .05$), and 0.024° higher variability in knee flexion/extension range of motion in males (A*S: $p = .003$). Higher variability in mean ankle and hip flexion/extension and in mean ankle inversion/eversion correlated with ($\rho = .211$-$.336$; ps $< .05$) and independently predicted higher stride time variability (ps $< .05$), together explaining 21.9% of variance. Results suggest that higher stride time variability with older age may be produced by a shift from sagittal plane variability to frontal plane variability at the ankle.

3.4 Introduction

Gait variability, the natural variability in an individual's gait motion from stride-to-stride, is well-linked to fall risk in aging adults. Following a cohort of older adults for one year, Hausdorff et al (2001) found that the risk of falling was higher in those with higher stride time variability. Subsequent studies have since highlighted the association between aging and higher stride time variability (Beauchet et al., 2017; Callisaya, Blizzard, Schmidt, et al., 2010), and aging and gait instability (van Kooten, Hettinga, Duffy, Jackson, & Taylor, 2018) in healthy adults. Excess stride time variability may lead to gait instability and to a fall in aging adults. Thus, understanding how stride time variability is mechanically produced is needed to better prevent falls.

There is a good likelihood that the higher stride time variability associated with aging is produced, at least in part, by variability in the output of individual joints. Using a combination of linear (e.g. standard deviation, coefficient of variation, coefficient of multiple determination) and nonlinear variability measures (e.g. entropy, Lyapunov exponents, deviation phase), some (Buzzi et al., 2003; Kurz & Stergiou, 2003), but not all (Chiu & Chou, 2012; Hafer & Boyer, 2018; Park et al., 2016) studies indicate that older adults have higher variability in sagittal plane joint

kinematics than young adults. Differences could be due to the confounding influence of sex, with only two of these studies identifying the sex of their samples (Buzzi et al., 2003; Chiu & Chou, 2012). Indeed, several studies have identified sex differences in the variability of motor output at individual joints, with evidence for lower entropy in the navicular height (Rathleff et al., 2010) and higher coefficients of multiple determination (lower variability) in the sagittal plane ankle angles and the transverse plane ankle, knee, and hip angles of females compared to males (Barrett, Noordegraaf, & Morrison, 2008). Ankle motor output also changes with older age more rapidly in females than in males, with evidence of lower variability in gastrocnemius lateralis activation amplitude during the stance phase and higher overall duration of ankle dorsiflexion (Bailey, Porta, et al., 2019; Ko et al., 2011). These results suggest that the influence of aging on the variability of ankle kinematics may also be sex-dependent. However, the variability of ankle activity was not related to stride time variability and the relationships between joint kinematic variability and stride time variability are, to the best of our knowledge, not known. Identifying the contributors to the higher stride time variability occurring with old age could help target fall prevention interventions to the most relevant joints and planes of motion.

Therefore, this study sought to determine the influences of older age and sex on the variabilities of tridimensional (3D) joint angles during gait, and to assess whether variability at each individual joint could predict stride time variability. We hypothesized that older age would be associated with higher sagittal plane variability in lower limb joints, that older age would be associated with higher ankle variability in females than in males, and that the sagittal plane variabilities of individual joints would predict stride time variability.

3.5. Methods

3.5.1 Participants

We recruited 102 adults (57 females) from the University of Cagliari and the University of the Third Age of Quartu S. Elena. Participants were included if they were ≥ 18 years old and were excluded if they had any neurologic or orthopedic condition that severely impaired gait, balance, and muscular strength. Ethics approval was obtained from the institutional ethics board. All participants provided informed consent to participate in the study.

3.5.2 Gait Analysis

An eight-camera optoelectronic motion capture system (Smart-D, BTS Bioengineering, Italy) was used to analyze the joint kinematics of the participant during barefoot gait. Twenty-two retroreflective markers (diameter = 14 mm) were placed bilaterally on the participant's lower limbs and pelvis according to the Davis model (Davis, Õunpuu, Tyburski, & Gage, 1991) (Table 3.1). Following marker instrumentation, the participant practiced walking over a level 10-metre platform, then completed six trials of walking at their self-selected speed. Participants rested 30 seconds between trials to avoid any fatigue accumulation. Marker positions were sampled at 120 Hz and saved for further data analysis.

Table 3.1. Summary of marker positions. Precise procedures are located in Davis et al (1991).

Segment	Markers
Foot (bilateral)	heel, fifth metatarsal head
Shank (bilateral)	lateral malleolus, two markers on lateral aspect of shank (distal marker projected out with wand attachment)
Thigh (bilateral)	lateral epicondyle, two markers on lateral aspect of thigh (distal marker projected out with wand attachment)
Pelvis	right and left anterior superior iliac spine, base of sacrum (marker projected out with wand attachment)
Trunk	right and left shoulders (mid-point between C7 spinous process and lateral aspect of shoulder), C7 spinous process (projected out with wand attachment

From the six trials, we identified 5-8 total strides in each limb that were valid for each participant (straight-line, constant speed gait) and processed these data using the Smart Analyzer software program (BTS Bioengineering, Italy) to calculate stride time variability, gait speed, and tridimensional variabilities in joint angles. Foot and shank marker positions were used to identify the first and second heel strike events of a given limb (left or right), defining a single gait stride. The time between these events was identified as stride time; stride time variability was calculated as the stride-to-stride coefficient of variation (SD/mean*100) of stride time. Gait speed was calculated as the quotient of stride length and stride time, then averaged across strides. Stride time variabilities and gait speeds were averaged across legs for each participant. Finally, 3D joint angle variabilities were assessed by measuring the stride-to-stride standard deviations (SD) of 3D joint angles. The SD of a kinematic variable is an accepted measure of the magnitude of movement-to-movement variability (Srinivasan & Mathiassen, 2012b). Joint angles were extracted according to

the procedures of Davis et al (1991). Several discrete angle parameters within a gait stride (mean, peaks, and range of motion (ROM) were calculated and averaged across legs for the following joints and motions:

1. Ankle: dorsiflexion/plantarflexion; inversion/eversion.
2. Knee: flexion/extension; valgus/varus; internal rotation/external rotation.
3. Hip: flexion/extension; abduction/adduction; internal rotation/external rotation.
4. Pelvis: posterior/anterior tilt; drop/hike (obliquity); backward/forward rotation.

Pelvic obliquities and rotations described pelvic movement on the side contralateral to the stride.

3.5.3 Statistical analyses

Independent t-tests were conducted on height and mass to test for a Sex (males, females) effect. Mixed effects models tested for effects of Age (as a continuous variable), Sex, and Age x Sex interactions on gait speed, stride time variability, and discrete parameters of joint angle variability. Age-based effects were further explored in linear regression models by computing β-coefficients to estimate year-by-year rates of change. This statistical design allowed for the evaluation of Age as a continuous measure (Bailey, Corona, Pilloni, et al., 2018; Bailey, Porta, et al., 2019) rather than forming more arbitrarily defined age groups. All models of joint angle variability covaried for gait speed (Kang & Dingwell, 2008b). Spearman correlation coefficients were computed to test for relationships between these parameters and stride time variability. Finally, these parameters were entered into a stepwise linear regression to determine which parameter(s) best predicted stride time variability. Statistical significance was set at $p < .05$.

3.6 Results

3.6.1 Participant characteristics

Sample sizes of males and females are summarized for each decade in Table 3.2. Males averaged 53.6 ± 21.3 years in age (range: 19-99 years) and females averaged 56.2 ± 18.7 years (range: 21-82). Males were taller (1.73 ± 0.06 m) and heavier (73.1 ± 9.7 kg) than females (1.59 ± 0.07 m, 57.7 ± 10.4 kg; ps < .05). There were no sex differences in gait speed (males: 1.18 ± 0.20, females: 1.15 ± 0.17 m/s) or stride time variability (males: 3.36 ± 1.67, females: 3.01 ± 1.27 %) (ps > .05). With older age, participants had slower gait speed and higher stride time

variability (ps < 0.05), with estimated changes of -0.003 m/s (β = -.003, p = .003) and 0.022% (β = .022, p = .002) per year respectively.

Table 3.2. Sample sizes of males and females for each decile.

Decile	**Males (N)**	**Females (N)**	**Total (N)**
20-29 years [a]	13	13	26
30-39 years	1	0	1
40-49 years	4	0	4
50-59 years	3	5	8
60-69 years	13	29	42
70-79 years	10	8	18
80-89 years	0	2	2
90-99 years	1	0	1
All	45	57	102

[a] Contains one male participant aged 19 years

3.6.2 Age, Sex, Age x Sex effects

Age and Age x Sex effects are illustrated in Figure 3.1 and mean variabilities are reported in Table 3.3.

3.6.2.1 Ankle. There were significant Age effects on peak dorsiflexion SD (p = .002) and on mean inversion/eversion SD (p = .014). The associations with each year of age were estimated at 0.007° lower variability of peak dorsiflexion (β = -.007, p = .004) and 0.007° higher variability of mean inversion/eversion (β = .007, p = .013). A significant Sex effect on peak dorsiflexion SD (p = .039) was found, where males had less variability than females.

3.6.2.2 Knee. There was a significant Age x Sex effect on flexion/extension ROM SD (p = .018) where each year of age was associated with 0.024° higher variability in males (β = .025, p = .003) but no change in females (β = -.007, p = .391). No Age or Sex effects were found on other knee variability parameters.

3.6.2.3 Hip. There were no significant Age or Sex based effects on the variability of hip joint angles.

3.6.2.4 Pelvis. There were significant Age effects on mean obliquity SD (p = .006) and on rotation ROM SD (p = .007), where each year of age was associated with 0.002° higher variability of mean obliquity (β = .002, p = .006) and 0.098° higher variability of rotation ROM (β = .098, p = .006). There was also greater peak drop SD in males than in females (Sex effect: p = .015).

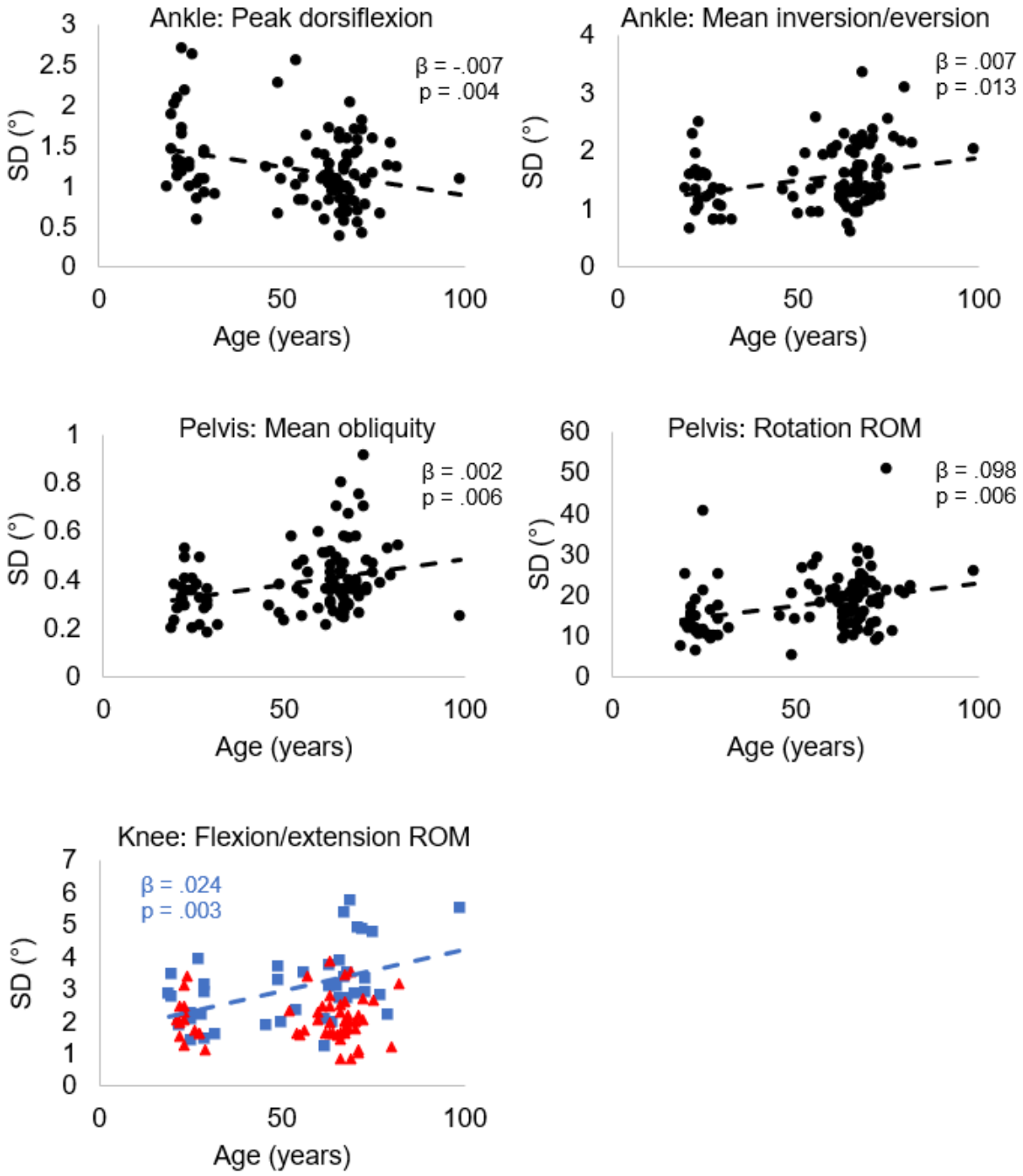

Figure 3.1. Stride-to-stride standard deviations (SD) of joint angle parameters as a function of age. Displayed are peak dorsiflexion (upper left) and mean inversion/eversion SDs (upper right) of the ankle, mean obliquity (middle left) and rotation range of motion (ROM) SDs of the pelvis (middle right), and flexion/extension ROM SD of the knee (lower left). Sexes were pooled for sex-independent relationships and shown separately (males: blue squares; females: red triangles) for sex-dependent relationships. Linear best-fits (dashed lines) show significant relationships with older age.

Table 3.3. Stride-to-stride variabilities of 3D joint angle parameters in males and females. Group means (standard deviations) are presented. Age was statistically analyzed as a continuous variable and is only stratified here to show the Age-based effects.

	Measure	20-29 years		60-69 years		70-79 years	
		Males (N=13)	Females (N=13)	Males (N=13)	Females (N=29)	Males (N=10)	Females (N=8)
Ankle	Flexion/extension (FE)						
	Mean SD (°)	0.80 (0.39)	0.75 (0.18)	0.68 (0.16)	0.70 (0.17)	0.73 (0.22)	0.65 (0.43)
	Peak dorsiflexion SD (°) †,‡	1.23 (0.35)	1.61 (0.62)	1.03 (0.39)	1.08 (0.31)	1.15 (0.31)	1.13 (0.54)
	Peak plantar flexion SD (°)	2.68 (1.43)	2.35 (0.75)	1.85 (0.43)	2.35 (0.92)	2.29 (0.97)	2.48 (1.18)
	Range of motion SD (°)	7.25 (3.21)	7.59 (2.37)	7.10 (2.22)	8.12 (3.16)	9.78 (3.72)	7.32 (2.85)
	Inversion/eversion						
	Mean angle SD (°) †	1.21 (0.32)	1.48 (0.50)	1.39 (0.39)	1.62 (0.56)	1.64 (0.39)	1.83 (0.55)
	Peak inversion SD (°)	2.29 (0.85)	2.64 (0.77)	2.07 (0.60)	2.85 (0.74)	2.98 (0.59)	3.37 (0.71)
	Peak eversion SD (°)	1.50 (0.30)	1.79 (0.66)	1.63 (0.27)	1.85 (0.55)	1.79 (0.41)	2.08 (0.98)
	Range of motion SD (°)	16.27 (6.97)	16.77 (3.88)	12.6 (3.90)	17.28 (5.33)	20.00 (6.39)	17.97 (3.96)
Knee	Flexion/extension						
	Mean SD (°)	0.83 (0.23)	0.94 (0.35)	0.99 (0.50)	0.91 (0.33)	1.15 (0.40)	0.92 (0.30)
	Peak flexion SD (°)	1.24 (0.27)	1.54 (0.61)	1.51 (0.67)	1.64 (0.58)	1.73 (0.38)	1.70 (0.55)
	Peak extension SD (°)	1.04 (0.33)	1.29 (0.50)	1.01 (0.43)	1.42 (0.49)	1.50 (0.81)	1.24 (0.58)
	Range of motion SD (°) *	2.54 (0.80)	3.34 (1.05)	3.27 (1.28)	3.49 (1.16)	3.69 (1.09)	3.36 (1.11)
	Valgus/varus						
	Mean SD (°)	0.29 (0.10)	0.39 (0.14)	0.34 (0.17)	0.35 (0.17)	0.34 (0.13)	0.35 (0.15)
	Peak valgus SD (°)	0.94 (0.30)	0.94 (0.33)	0.87 (0.26)	0.74 (0.42)	0.93 (0.44)	0.88 (0.35)
	Peak varus SD (°)	0.56 (0.33)	0.95 (0.68)	0.58 (0.46)	0.86 (0.53)	0.52 (0.48)	0.80 (0.42)
	Range of motion SD (°)	10.18 (4.18)	11.81 (6.32)	10.88 (6.93)	11.08 (4.27)	9.62 (4.70)	17.46 (7.46)
	Internal/external rotation						
	Mean SD (°)	0.96 (0.27)	1.09 (0.40)	0.84 (0.17)	0.99 (0.49)	1.09 (0.34)	1.02 (0.36)
	Peak internal rotation SD (°)	1.37 (0.35)	1.72 (0.38)	1.29 (0.41)	1.64 (0.47)	1.45 (0.37)	1.34 (0.33)
	Peak external rotation SD (°)	1.28 (0.47)	1.68 (0.47)	1.06 (0.32)	1.77 (0.68)	1.38 (0.42)	1.59 (0.64)
	Range of motion SD (°)	8.34 (2.75)	10.28 (2.85)	9.34 (3.56)	12.29 (3.22)	9.42 (3.12)	11.89 (3.23)
Hip	Flexion/extension						
	Mean SD (°)	0.96 (0.40)	0.95 (0.51)	0.70 (0.25)	0.94 (0.46)	0.86 (0.33)	0.91 (0.41)

	Peak flexion SD (°)	1.31 (0.38)	1.34 (0.63)	1.07 (0.40)	1.28 (0.38)	1.31 (0.38)	1.54 (0.71)
	Peak extension SD (°)	1.28 (0.35)	1.17 (0.54)	1.01 (0.41)	1.32 (0.63)	1.43 (0.54)	1.33 (0.55)
	Range of motion SD (°)	3.93 (0.78)	3.96 (1.62)	3.78 (1.34)	3.62 (1.01)	4.41 (0.98)	4.65 (2.38)
	Abduction/adduction						
	Mean SD (°)	0.45 (0.09)	0.57 (0.22)	0.42 (0.12)	0.57 (0.15)	0.66 (0.21)	0.64 (0.29)
	Peak abduction SD (°)	0.84 (0.33)	1.05 (0.40)	0.71 (0.15)	1.06 (0.34)	0.98 (0.32)	1.12 (0.40)
	Peak adduction SD (°)	0.84 (0.18)	1.06 (0.34)	0.79 (0.21)	0.85 (0.22)	0.77 (0.23)	1.03 (0.56)
	Range of motion SD (°)	9.58 (4.33)	9.07 (3.14)	8.53 (3.59)	8.79 (3.67)	9.30 (2.39)	10.58 (3.43)
	Internal/external rotation						
	Mean SD (°)	0.64 (0.23)	0.65 (0.26)	0.69 (0.23)	0.71 (0.38)	0.77 (0.35)	0.74 (0.41)
	Peak internal rotation SD (°)	1.11 (0.28)	1.35 (0.59)	0.95 (0.43)	1.27 (0.50)	1.29 (0.47)	1.24 (0.40)
	Peak external rotation SD (°)	1.28 (0.41)	1.46 (0.45)	1.44 (0.41)	1.51 (0.55)	1.57 (0.46)	1.85 (0.93)
	Range of motion SD (°)	11.90 (4.13)	11.71 (4.89)	9.15 (2.58)	11.06 (3.74)	10.07 (3.55)	14.76 (5.05)
Pelvis	Tilt						
	Mean SD (°)	0.68 (0.31)	0.76 (0.40)	0.67 (0.26)	0.68 (0.22)	0.76 (0.27)	0.75 (0.25)
	Peak posterior tilt SD (°)	0.75 (0.34)	0.82 (0.46)	0.79 (0.31)	0.81 (0.25)	0.84 (0.37)	0.86 (0.19)
	Peak anterior tilt SD (°)	0.93 (0.36)	0.93 (0.36)	0.74 (0.28)	0.86 (0.22)	0.84 (0.30)	0.90 (0.30)
	Range of motion SD (°)	23.31 (8.87)	22.94 (6.52)	21.77 (6.48)	22.26 (7.56)	24.14 (12.52)	20.64 (5.40)
	Obliquity						
	Mean SD (°) †	0.29 (0.07)	0.36 (0.09)	0.36 (0.10)	0.43 (0.14)	0.43 (0.13)	0.52 (0.21)
	Peak drop SD (°) ‡	0.59 (0.17)	0.81 (0.36)	0.59 (0.15)	0.74 (0.20)	0.72 (0.32)	0.74 (0.11)
	Peak hike SD (°)	0.63 (0.17)	0.78 (0.28)	0.59 (0.14)	0.69 (0.21)	0.60 (0.15)	0.71 (0.20)
	Range of motion SD (°)	13.43 (5.24)	10.66 (5.04)	12.65 (6.08)	12.48 (4.59)	17.26 (8.97)	12.73 (3.33)
	Rotation						
	Mean SD (°)	0.90 (0.29)	1.17 (0.44)	0.99 (0.19)	1.30 (0.38)	1.13 (0.36)	1.33 (0.55)
	Peak backward rotation SD (°)	1.43 (0.53)	1.63 (0.65)	1.41 (0.29)	1.70 (0.43)	1.43 (0.73)	1.67 (0.41)
	Peak forward rotation SD (°)	1.38 (0.48)	1.89 (0.55)	1.31 (0.27)	1.77 (0.51)	1.50 (0.42)	1.78 (0.71)
	Range of motion SD (°) †	17.43 (9.33)	12.67 (3.43)	17.5 (4.47)	18.87 (4.96)	21.30 (12.75)	19.92 (7.31)

† Significant Age effect ($p < .05$)
‡ Significant Sex effect ($p < .05$)
* Significant Age*Sex effect ($p < .05$)

3.6.3 Relationships between joint angle variabilities and stride time variability

Correlation results are presented in Table 3.4. Higher stride time variability was positively correlated to sagittal plane parameters of joint angle variability at the ankle, knee, hip, and pelvis (ρ = .200-.349, ps < .05), and to frontal plane parameters of joint angle variability at the ankle and hip (ρ = .198-.211, ps < .05).

Modeled by stepwise linear regression, stride time variability was best predicted by mean flexion/extension SD of the ankle, mean flexion/extension SD of the hip, and mean inversion/eversion SD of the ankle. This optimal model explained 21.9% of the variance in stride time variability (R^2 = .219, $F_{3,88}$ = , p < .001), with each parameter as a significant independent predictor (ankle, mean flexion/extension SD: β = 1.564, p = .008; hip, mean flexion/extension SD: β = .317, p = .002; ankle, mean inversion/eversion SD: β = .520, p = .030).

Table 3.4. Correlations between 3D joint angle variability features and stride time variability. Significant correlations are bolded (p < .05).

	Measure	**Stride time variability (%)**	
Ankle	Flexion/extension	Spearman's ρ	p-value
	Mean SD (°) †	**.336**	**.001**
	Peak dorsiflexion SD (°)	.076	.445
	Peak plantar flexion SD (°)	**.242**	**.014**
	Range of motion SD (°)	.170	.088
	Inversion/eversion		
	Mean SD (°) †	**.211**	**.034**
	Peak inversion SD (°)	.094	.351
	Peak eversion SD (°)	.192	.055
	Range of motion SD (°)	-.027	.789
Knee	Flexion/extension		
	Mean SD (°)	**.266**	**.007**
	Peak flexion SD (°)	**.200**	**.045**
	Peak extension SD (°)	.092	.360
	Range of motion SD (°)	**.302**	**.002**
	Valgus/varus		
	Mean SD (°)	.184	.066
	Peak valgus SD (°)	.080	.425
	Peak varus SD (°)	.031	.757
	Range of motion SD (°)	.010	.919
	Internal/external rotation		
	Mean SD (°)	-.014	.887
	Peak internal rotation SD (°)	-.004	.968
	Peak external rotation SD (°)	.038	.709

	Range of motion SD (°)	-.001	.990
Hip	Flexion/extension		
	Mean SD (°) †	**.319**	**.001**
	Peak flexion SD (°)	**.286**	**.004**
	Peak extension SD (°)	**.225**	**.023**
	Range of motion SD (°)	**.349**	**<.001**
	Abduction/adduction		
	Mean SD (°)	.188	.059
	Peak abduction SD (°)	.182	.068
	Peak adduction SD (°)	**.198**	**.047**
	Range of motion SD (°)	.146	.146
	Internal/external rotation		
	Mean SD (°)	.184	.070
	Peak internal rotation SD (°)	.042	.673
	Peak external rotation SD (°)	.126	.210
	Range of motion SD (°)	.103	.303
Pelvis	Tilt		
	Mean SD (°)	**.201**	**.044**
	Peak posterior tilt SD (°)	.151	.133
	Peak anterior tilt SD (°)	.173	.084
	Range of motion SD (°)	.017	.865
	Obliquity		
	Mean SD (°)	**.246**	**.013**
	Peak drop SD (°)	**.247**	**.013**
	Peak hike SD (°)	.180	.071
	Range of motion SD (°)	.159	.113
	Rotation		
	Mean SD (°)	.102	.311
	Peak backward rotation SD (°)	.127	.207
	Peak forward rotation SD (°)	.058	.562
	Range of motion SD (°)	.057	.505

† independent predictor of stride time variability ($p < .05$)

3.7. Discussion

3.7.1 Do older age and sex interact to affect the variability of 3D joint angles?

Of the 44 total discrete features of joint angle variability, older age only influenced two features of sagittal plane variability at the ankle (lower with age) and knee (higher with age in males), two features of frontal plane variability at the ankle and pelvis (both higher with age), and one feature of transverse plane variability at the pelvis (higher with age). The effects on only 5/44 total features suggest that older age has a more limited influence on joint angle variability than previously thought (Buzzi et al., 2003; Kurz & Stergiou, 2003). The interpretations in these studies

are likely driven by analyzing non-linear measures of kinematic variability and by conducting gait analysis on a treadmill. While these methodological decisions can allow for the calculation of singular measures of kinematic variability over many gait cycles, non-linear measures may mask the different contributions from different planes of motion and variability patterns on a treadmill may differ from overground walking (Dingwell, Cusumano, Cavanagh, & Sternad, 2001).

The associations between joint angle variability and age were small in absolute magnitude and large in relative magnitude. This is highlighted by the mean variability differences between adults aged 20-29 years and adults aged 70-79 years (Table 3), which ranged from 0.14° to 7.25°. While these differences in variability seem small in absolute magnitude, the relative differences were sizable (7.0-48.3% in males and 23.6-57.2% in females) and comparable to reported differences in non-linear kinematic variability (Buzzi et al., 2003; Kurz & Stergiou, 2003). Further, the reported difference in absolute magnitude between healthy adults and those with age-related disease (e.g. Parkinson's disease) is only a coefficient of variation of 1.7% for stride time variability (Hausdorff, Cudkowicz, Firtion, Wei, & Goldberger, 1998). Thus, small changes in joint angle variability with older age are likely meaningful.

Our results also contradict the hypothesis that the age effect on ankle joint variability would differ between males and females. This hypothesis was generated due to the age-based sex differences described by other research groups (Barrett et al., 2008; Ko et al., 2011; Rathleff et al., 2010) as well as in this specific experimental sample (Bailey, Corona, Pilloni, et al., 2018; Bailey, Porta, et al., 2019). Females in our sample, but not males, had lower gastrocnemius lateralis activation variability with older age (Bailey, Porta, et al., 2019); combined with a lack of a sex difference in ankle joint variability, our results seem to suggest a lack of coupling between the variability of muscle activity and the variability of joint motion at the ankle. We did, however, observe a male-specific association between older age and higher knee flexion/extension ROM variability that may be a sex-specific kinematic adjustment with age. As males also had lower knee valgus/varus variability than females, we speculate that aging males may access sagittal plane variability to compensate for more rigid knee patterns in the frontal plane. This interpretation is limited by low valgus/varus signal-to-noise ratio (Davis et al., 1991), likely from a combination of small ROM during walking and the influence of skin motion artifact on thigh and shank marker motion (Benoit, Damsgaard, & Andersen, 2015). The sex difference in knee valgus/varus

variability may then be a factor of higher motion artifact in females than in males, yet Gao & Zheng (2008) report no such sex difference.

Our results highlighted the relevance of variability in frontal plane ankle and pelvic motion, where higher variability was observed with older age. This agrees with Kang & Dingwell (2008) who observed an association between higher trunk roll and older age. These associations may reflect more variable control in balance, as Hausdorff (2005) previously suggested for variability in stride width, another frontal plane feature of gait motor output. Indeed, older age has been associated with higher mediolateral centre of mass displacement and peak velocity during self-selected speed gait (Schrager, Kelly, Price, Ferrucci, & Shumway-Cook, 2008), and such parameters of mediolateral balance can be predictive of falls in older adults (Brauer, Burns, & Galley, 2000). Accordingly, the variability of frontal plane motor output during gait appears to be a potential contributor to age-related falls.

3.7.2 From what joints does stride time variability originate?

Higher stride time variability was positively correlated with many sagittal plane parameters of joint motion and predicted by the variabilities of mean ankle and hip flexion/extension. Thus, we accept our final hypothesis that variability in sagittal plane joint motion predicts stride time variability. Further, this variability was predicted best by ankle and hip parameters, pointing towards joint dependencies. We speculate that variability in knee angle did not predict stride time variability due to less motor redundancy than at the more mobile ankle and hip that allow tridimensional movement. Though this hints that aging adults may leverage their motor redundancy, it remains to be determined whether altered kinematic variabilities precede or are a consequence of age-related losses in strength, flexibility, and proprioception (Anson et al., 2017; Callisaya, Blizzard, McGinley, Schmidt, & Srikanth, 2010; Kang & Dingwell, 2008b) .

More surprising was that variability in *frontal plane* joint motion, specifically the variability of mean ankle inversion/eversion, predicted stride time variability. This forces us to revisit the theory that variability in the frontal plane reflects control of balance (ex. variability of step width) and variability in the sagittal plane reflects control of gait timing (ex. variability of stride time) (Gabell & Nayak, 1984; Hausdorff, 2005). The fact that variability in frontal plane ankle motion predicted variability in gait timing in our large sample (N = 102) of adult males and

females across the lifespan points toward frontal plane variability as a control surrogate of *both* balance and gait timing.

3.7.3 Do older adults compensate sagittal plane variability with frontal plane variability in the ankle?

Interestingly, combining our main results thus far reveals a potential age-specific mechanism in how stride time variability is produced. We saw 1) a concurrent fall in sagittal plane variability and rise in frontal plane variability in the ankle with older age, and 2) that these ankle variabilities contribute to stride time variability, indicating that with older age, adults may shift from sagittal plane variability to frontal plane variability at the ankle. This supports Ko et al (2011), who made a similar "sagittal-frontal plane compensation" interpretation after finding that older females, compared to older males, had less sagittal plane but greater frontal plane range of motion in the hip. These two interpretations hint that the processes underlying balance control and gait timing are not as mutually exclusive as previously thought (Gabell & Nayak, 1984; Hausdorff, 2005), but may be better understood in aging by studying the shifts from sagittal to frontal plane variability. As such, the potential age-related shift to frontal plane variability may reflect poorer control of both balance and gait timing and help to better explain the risk of gait-related falls in aging adults.

3.7.4 Limitations

Our sample, while large in number and in age-range, contained a low number of adults aged 30-59 years. The relationship between age and kinematic variability appeared to be linear for our dataset, but inclusion of more middle-aged results may reveal non-linear tendencies (Monda, Goldberg, Smitham, Thornton, & McCarthy, 2015). Further, while we were able to quantify the magnitude of variability in different planes of motion, we were unable to know with certainty whether the age-based changes in kinematic variability were a compensation for or a consequence of the aging process; further, perhaps longitudinal studies are needed to elucidate this. Finally, the reliability of our joint angle variability values was untested and such reliability studies could not be located. Stride time variability may require 50 strides to be reliable (König, Singh, von Beckerath, Janke, & Taylor, 2014). We therefore advise readers to interpret our findings cautiously and recommend further investigation into the reliability of joint angle variability metrics during gait analysis.

3.8 Conclusion

The influence of older age on stride-to-stride variability of joint angles is sex-independent at the ankle and pelvis but sex-dependent at the knee, with women showing less variability. Variabilities of sagittal plane ankle and hip motion and frontal plane ankle motion predict variability in stride time. A potential shift from ankle variability in the sagittal plane to variability in the frontal plane may help explain why aging adults have higher stride time variability.

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3.11 Conflicts of interest

The authors declare no known conflicts of interest.

3.12 Financial disclosure

The authors declare no financial conflicts.

3.13 Manuscript references

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Chapter 4. Sex-independent and dependent effects of older age on cycle-to-cycle variability of muscle activation during gait

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4.1 Preface

Chapter 4 outlines further analysis of the same large gait cohort dataset owned by Dr. Massimiliano Pau and his research team at the University of Cagliari. This analysis was completed in parallel with Chapter 3. In addition to the lack of evidence on how stride-to-stride variability differs between aging males and females, Chapter 2 revealed the paucity of knowledge on the variability of muscle activity patterns. This came as a surprise since age-related alterations in the variability of motor unit activity are well documented. Understanding how age affects muscle activation variability could help link motor variability findings across the motor chain, beginning at the motor unit (Chapter 2) and ending with individual joint and whole motor output (Chapters 2 and 3). The objectives of Chapter 4 were therefore to investigate 1) how age and sex affected muscle activation variability in gait and 2) relationships between the variability of muscle activity and of spatiotemporal gait patterns.

In Chapter 4, surface electromyography data were acquired from three lower limb muscles key to gait production in order to measure muscle activation. Spatiotemporal parameters of gait were measured using the same optoelectronic motion capture procedure and kinematic model as Chapter 3. Variability of muscle activation and spatiotemporal gait patterns were computed as the stride-to-stride coefficient of variation (termed cycle-to-cycle variability in Chapter 4).

Results from Chapter 4 build on findings of Chapter 3 by focusing on variability of individual muscle patterns rather than joint angle patterns. Sections 4.2 to 4.10 are a copy of the manuscript published by *Experimental Gerontology*. Formatting has been altered to allow insertion into this thesis.

4.2 Abstract

Older age is associated with higher stride time variability in female and male gait, which may have a neuromuscular origin. We sought to determine how older age and sex affect muscle activation variability during gait, and how these patterns relate to stride time variability.

Ninety-three adults (51 females; aged 20-82 years) completed six gait trials at their self-selected speed. Cycle-to-cycle variabilities (CCVs) were calculated for stride time, and for amplitude of electromyography (EMG) of the rectus femoris (RF), tibialis anterior (TA), and

gastrocnemius lateralis (GL) recorded over different gait phases. Statistical models tested for Age x Sex x Muscle effects and for relationships between EMG CCVs and stride time CCVs.

Significant Age and Age x Muscle effects on EMG CCV were observed in several phases of gait ($p < 0.05$), where each year of age was associated with 0.11-0.18% *higher* EMG CCV, generally in the RF. A significant Age x Sex x Muscle effect on EMG CCV at mid-stance ($p < .05$) indicated that, in females, each year of age was associated with 0.11% *lower* GL CCV. Significant but low strength correlations ($\rho = .298$-$.351$) were found between EMG CCV and stride time CCV.

Associations between older age and higher muscle activation variability were generally sex-independent. A sex-dependency in GL activation variability may contribute to gait instability in aging females. Individual variabilities of muscle activation were not strongly related to stride time variability.

4.2 Introduction

With older age, adults are more likely to suffer a fall. Around 30-60% of adults aged 65+ years fall each year, with 20% of these falls resulting in injury, hospitalization and/or death (Rubenstein, 2006). Risk of falling is also sex-dependent, where risk is higher in older females than older males (O'Loughlin, Robitaille, Boivin, & Suissa, 1993). One frequently cited factor linked to the risk of falling in older age is high gait variability; more specifically, the cycle-to-cycle variability of stride time during gait (Hausdorff, 2005). This is supported by evidence that older age is associated with higher stride time variability (Beauchet et al., 2017; Callisaya, Blizzard, Schmidt, et al., 2010), most strongly in females (Callisaya, Blizzard, Schmidt, et al., 2010), and by a cohort study that followed older adults for one year and found that those with higher stride time variability were more likely to fall (Hausdorff et al., 2001). Taken together, these results suggest that stride time variability has a role in age-related falls, particularly for females.

As it is speculated that stride time variability is a factor of the collective inputs and feedback from the central and peripheral nervous systems (Hausdorff et al., 2001), its association with age may be a consequence of age-related changes to neuromuscular structure and physiology. Older age is associated with neural alterations to both central (Seidler et al., 2010) and peripheral (Hunter et al., 2016; Power et al., 2013) structures, including to motor units (MUs). It is believed that with older age, the MUs of adults increase in size with motor neuron death, such that surviving motor neurons innervate a larger number of muscle fibres (Hunter et al., 2016; Power et al., 2013).

In addition, the discharge behaviour of these MUs change. In the upper limb, Laidlaw et al (Laidlaw et al., 2000) found that MU discharge rate was more variable in older adults than young adults. Similar findings have been reported in muscles that produce gait. Hourigan et al (2015) and Piasecki et al (2016) each reported higher near-fibre jiggle, a measure reflecting variations in individual MU potential shape, in older adults than young adults. Further, Negro et al (2009) showed that MU discharge rate variability can explain up to 70% of the variance in force output during isometric contractions. Thus, Christou (2011) argues that the more variable activation of MUs is responsible for the lower steadiness (higher variability) of motor output found with older age.

The variability of motor output in the gait of older adults may then be better understood by investigating how older age affects the activation of individual muscles, as measured by electromyography (EMG). In fact, several studies have carried out such investigations (Bailey, Corona, Pilloni, et al., 2018; Marques et al., 2016; Schmitz, Silder, Heiderscheit, Mahoney, & Thelen, 2009). Schmitz et al (2009) measured muscle activations in young and older adults walking at their preferred-speed, grouping males and females together. They found that older adults had higher normalized muscle activation than young adults during loading for the gastrocnemius lateralis (GL), and at mid-stance for the vastus lateralis, soleus, tibialis anterior (TA), and rectus femoris (RF). Marques et al (2016) also observed the same age difference in TA activation during stance. In contrast, they identified lower RF activation in older adults than young adults, which may have been due to investigating females only. Thus, our recent study (Bailey, Corona, Pilloni, et al., 2018) grouped males and females separately, finding that, though older age was generally associated with higher ankle muscle activation during the gait cycle, there were sex-dependent age associations with higher RF activation (in males) and higher GL activation (in females). Together, these studies highlight that the muscle activations involved in the gait of aging males and females can differ; perhaps the activation of knee extensors is more relevant in aging males and the activation of ankle plantar flexors is more relevant in aging females. However, the extent to which older age and sex influence the *variability* of these muscular activations (i.e. EMG), from gait cycle to gait cycle, is uncertain and may ultimately lead to variability in the motor output of gait.

Therefore, this study investigated the effects of older age and sex on muscle activation variability during gait and explored the relationships between the activation variability of

individual muscles and the stride time variability of males and females. We hypothesized that older age would be associated with higher stride time variability and higher muscle activation variability in males and females, and that relationships between muscle activation variability and stride time variability would be stronger in females than in males.

4.3 Methods

4.3.1 Participants

Healthy adults aged 20 years and older (N = 93, 51 females) were recruited by the Laboratory of Biomechanics and Industrial Ergonomics of the University of Cagliari (Italy) among students and individuals who regularly attend the University of the Third Age of Quartu S. Elena (Italy) through convenience sampling. Participants were excluded if they had any neurologic or orthopedic condition that severely impaired gait, balance, and muscular strength; borderline cases were examined by a physician. All participants provided informed consent to participate in the study, which was given ethics clearance from the institutional ethics board.

4.3.2 Procedure

On arrival, participants were instrumented for EMG gait analysis. Wireless surface EMG sensors (1000 Hz; FreeEMG, BTS Bioengineering, Italy) were placed over the RF, TA, and GL of each lower limb according to SENIAM guidelines (Hermens, Freriks, Disselhorst-Klug, & Rau, 2000), as described in Bailey et al (2018). The reader is referred to Bailey et al (2018) for a detailed explanation on why these muscles were selected. Briefly, the RF was located as the midpoint on the line between the anterior superior iliac spine and the superior aspect of the patella, the TA was located as one-third distal on the line between the fibular head and the medial malleolus, and the GL was located as one-third distal on the line between the fibular head and the heel. Reflective markers (14 mm diameter) were placed on the participant's trunk and lower limbs according to the Davis protocol (Davis et al., 1991) and gait kinematics were analyzed using an optoelectronic eight-camera system (120 Hz; Smart-D, BTS Bioengineering, Italy). After instrumentation, participants practiced walking forwards at their preferred speed over a 10 m platform, then completed six trials of gait with 30 s of rest between trials. Participants self-initiated their gait for each trial. Marker position data and EMG data from forward, straight-walking and constant-speed strides of each leg were subsequently analyzed.

4.3.3 Data analysis

4.3.3.1 Calculation of gait speed and stride time variability. Marker position data were used to identify the first and second heel strike events using Smart Analyzer (BTS Bioengineering, Italy). The time between these events defined the stride time for each gait cycle. Gait cycles were analyzed from the middle four metres of the platform to extract straight-walking and constant-speed cycles. Thus, cycles within the acceleration and deceleration phases were not studied. From six trials of gait, this resulted in analyzing five to eight gait cycles from each leg for each participant. From each cycle, gait speed was extracted as the quotient of stride length (heel marker displacement between heel strike events) and stride time and was averaged across gait cycles for each leg. Stride time variability was extracted as the cycle-to-cycle variability (CCV) using the coefficient of variation and reflects the variability between steps. Stride time CCV was calculated independently for each leg. A preliminary analysis confirmed that there were no significant between-leg differences in gait speed or stride time CCV; therefore we calculated mean values across legs and used these for all subsequent analyses.

4.3.3.2 Calculation of muscle activation variability. EMG cycles were located with respect to the gait cycles identified above. EMG cycles were filtered to remove the DC bias, bandpass filtered using a dual-pass Butterworth filter (2^{nd} order, 20-450 Hz), then linear enveloped with a dual low-pass Butterworth filter (4^{th} order, 6 Hz cut-off) (Bailey, Corona, Pilloni, et al., 2018; Schmitz et al., 2009). The enveloped EMG cycles were time-normalized to 101 points relative to the gait cycle (0-100%), with 0% and 100% representing the first and second heel strike events that define a gait cycle, and amplitude-normalized to the peak value of the gait cycle (Sousa & Tavares, 2012; Yang & Winter, 1984). These normalized EMG cycles were subdivided into the loading (0-10%), mid-stance (10-30%), terminal stance (30-60%), initial swing (60-73%), mid-swing (73-87%), and terminal swing (87-100%) phases (Bailey, Corona, Pilloni, et al., 2018; Schmitz et al., 2009). Root mean square values were extracted for each combination of muscle, phase, and leg within each gait cycle. For each combination, EMG CCV was then calculated as the cycle-to-cycle coefficient of variation of the root mean squares. Like with gait speed and stride time CCV, there were no between-leg differences in EMG CCV and so mean EMG CCV values were calculated between legs and subsequently analyzed for each muscle and phase.

4.3.4 Statistical analyses

Mixed effect models tested for effects and interactions of Age (as a continuous variable) and Sex (male, female) on participant height, mass, gait speed, and stride time variability. Age-based effects on stride time variability were further explored in a linear regression model by computing the β-coefficient to estimate the year-by-year rate of change. Gait speed was entered as a covariate in this model since there is evidence that gait speed influences age-related differences in gait variability (Kang & Dingwell, 2008b).

EMG CCVs were then analyzed for each gait phase using mixed effect models, testing for effects of Age, Sex, and Muscle (RF, TA, GL), as well as Age-based two- and three-way interactions. Model residuals were visually inspected and confirmed to approximate a normal distribution. Age-based effects were also explored in linear regression models to estimate year-by-year rates of change. These regression models included Bonferroni corrections to mitigate type I error and gait speed as a covariate.

EMG CCVs with a significant Age-based effect were then compared to stride time variability in correlation analyses. Since some muscle and phase combinations of EMG CCV were not normally distributed (Shapiro-Wilks $p < .05$), Spearman ρ coefficients were computed to test for relationships between the variabilities of individual muscle activations and the motor output of gait. The strength of coefficients was categorized as negligible (.00-.29), low (.30-.49), moderate (.50-.69), high (.70-.89) or very high (.90-1.00) (Mukaka, 2012). Correlations analyses were performed for three scenarios: sexes pooled, males only, and females only. Statistical significance for all analyses was set at $p < .05$.

4.4 Results

4.4.1 Participant characteristics

Sample sizes of males and females in each decade are summarized in Table 4.1 and characteristics of participants are summarized in Table 4.2. Males were taller and heavier than females (ps < .05). Age was associated with shorter height, slower gait speeds, and higher variability in stride time (ps < .05). With gait speed as a covariate, the association between Age and stride time variability did not reach significance ($\beta = .012$, $p = .175$). No Age x Sex effects were observed in participant characteristics.

Table 4.1. Sample sizes of males and females for each decade.

Decade	Males (N)	Females (N)	Total (N)
20-29 years	13	6	19
30-39 years	1	0	1
40-49 years	3	0	3
50-59 years	2	4	6
60-69 years	13	30	43
70-79 years	10	9	19
80-89 years	0	2	2

Table 4.2. Effects of Age and Sex on participant characteristics. Values are means (standard deviations). Age was statistically analyzed as a continuous variable and is only stratified here to show the Age-based effects. Variability characteristics are calculated as cycle-to-cycle coefficients of variation.

Characteristic	20-29 years		60-69 years		70-79 years	
	Males	Females	Males	Females	Males	Females
Height (cm) † ‡	173 (6)	161 (6)	173 (5)	156 (6)	170 (6)	158 (5)
Mass (kg) ‡	70.2 (8.1)	52.9 (4.8)	73.4 (10.9)	57.2 (10.8)	75.2 (10.4)	61.1 (12.5)
Gait speed (m/s) †	1.21 (0.14)	1.22 (0.14)	1.15 (0.25)	1.12 (0.16)	1.10 (0.23)	1.10 (0.22)
Stride time variability (%) †	3.4 (2.1)	2.2 (0.6)	4.2 (2.2)	3.2 (1.2)	3.5 (1.4)	3.5 (1.6)

† significant Age effect ($p < .05$)
‡ significant Sex effect ($p < .05$)

4.4.2 Muscle activation variability

Significant Age, Age x Muscle, and Age x Sex x Muscle effects were found and are summarized below for each gait phase (see also supplementary material 1). No significant Sex or Age x Sex effects were observed in any model (supplementary material 1).

4.4.2.1 Loading

There was an Age x Muscle interaction on CCV ($p = .036$), where each year was associated with 0.11% higher RF CCV ($\beta = .112$, $p = .041$) (Figure 4.1A).

4.4.2.2 Mid-stance

There was an Age x Muscle x Sex interaction on CCV ($p = .033$), where each year was associated with 0.18% lower GL CCV in females ($\beta = -.179$, $p = .017$) but no change in males ($\beta = -.056$, $p = .473$) (Figure 4.2).

4.4.2.3 Terminal stance

There was an Age effect on CCV ($p = .002$), but no two-way or three-way interactions. Each year was associated with 0.11% higher CCV ($\beta = .111$, $p = .019$). Post-hoc inspections of muscle-specific regressions revealed that the Age effect was driven mainly by higher RF CCV ($\beta = .184$, $p = .003$) (Figure 4.1B).

4.4.2.4 Initial swing

There was an Age x Muscle interaction on CCV ($p = .015$), where each year was associated with 0.17% higher RF CCV ($\beta = .174$, $p = .022$) (Figure 4.1C).

4.4.2.5 Mid-swing

There was an Age effect on CCV ($p = .010$), but no two-way or three-way interactions. Each year was associated with 0.16% higher CCV ($\beta = .160$, $p = .001$). Post-hoc inspections of muscle-specific regressions revealed that the Age effect was driven mainly by higher RF CCV ($\beta = .249$, $p = .009$) (Figure 4.1D).

4.4.2.6 Terminal swing

There were no significant Age-based effects or interactions on CCV ($p > .05$).

4.4.2.7 Full gait cycle

There were no significant Age-based effects or interactions on CCV ($p > .05$). There was a trend towards an Age x Muscle effect ($p = .068$) where higher age tended to be associated with higher RF CCV ($\beta = .050$, $p = .011$).

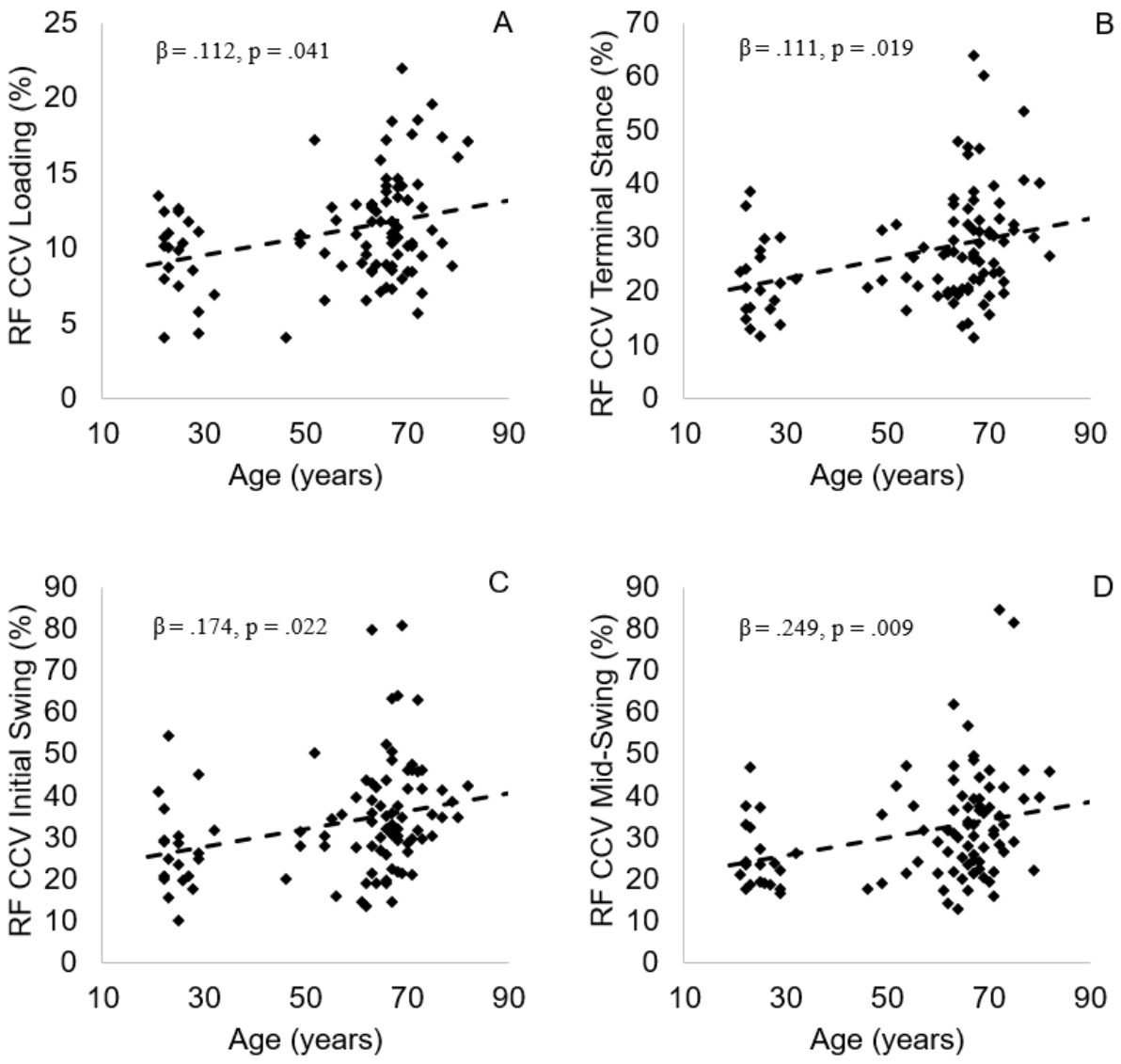

Figure 4.1. Rectus femoris activation variabilities (RF CCVs) during loading (A), terminal stance (B), initial swing (C), and mid-swing (D). Values are cycle-to-cycle coefficients of variation and males and females are pooled. The dashed lines illustrate the significant associations between age and RF CCV.

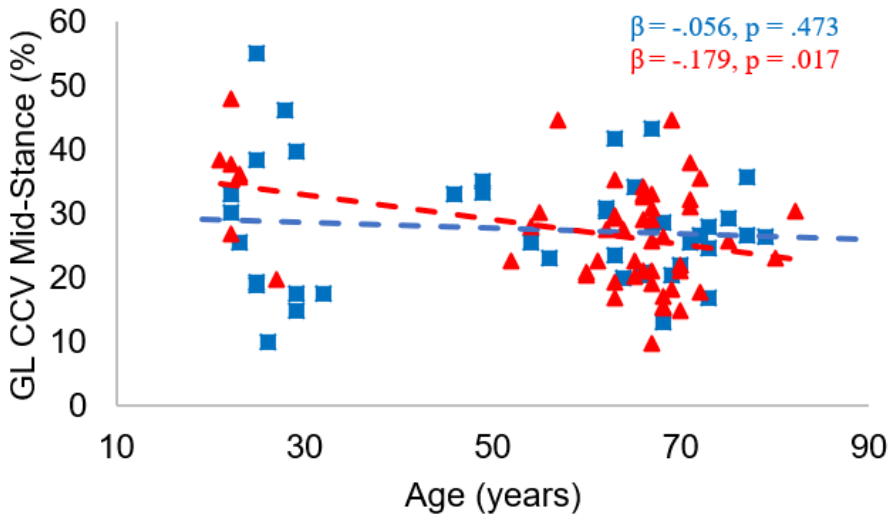

Figure 4.2. Gastrocnemius lateralis activation variability (GL CCV) during mid-stance. Values are cycle-to-cycle coefficients of variation for males (blue squares) and females (red triangles). The red dashed line illustrates the significant association between age and GL CCV in females.

4.4.3 Relationships between muscle activation variabilities and stride time variability

Correlations analyses are summarized in Table 4.3. With sexes pooled, higher stride time variability was significantly correlated to higher RF CCV at terminal stance (ρ = .342, p = .001) and at initial swing (ρ = .298, p = .004). In males, a significant but low correlation was found between higher stride time variability and higher RF CCV at initial swing (ρ = .328, p = .036), and the correlations with RF CCV at terminal stance, mid-swing, and over the gait cycle approached significance (ρ = .302-.305). In females, significant but low correlations were found between higher stride time variability and higher RF CCV at loading (ρ = .326, p = .018), at terminal stance (ρ = .351, p = .011), and at initial swing (ρ = .299, p = .031).

Table 4.3. Spearman correlation coefficients (ρ) between stride time variability and muscle activation variability measures. Measures analyzed are those in which there was a significant Age-based effect or an Age-based trend.

Muscle activation variability measure	Sexes pooled (N = 93)	Males (N = 41)	Females (N = 52)
RF CCV at loading	.146	-.070	.326 *
GL CCV at mid-stance	.071	.035	.161
RF CCV at terminal stance	.342 **	.302 ^{T}	.351 *
RF CCV at initial swing	.298 **	.321 *	.299 *
RF CCV at mid-swing	.146	.302 ^{T}	.067
RF CCV over the gait cycle	.154	.305 ^{T}	.086

* significant correlation ($p < .05$)
** significant correlation ($p < .01$)
^{T} correlation trend ($.05 \leq p \leq .10$)

4.5 Discussion

This study represents the first known attempt to examine how older age and sex affect the cycle-to-cycle variability of muscle activation during gait, and how this variability relates to the variability of gait motor output. Our main findings are: 1) older age is associated with higher RF muscle activation variability during several phases of gait; 2) the influence of older age on muscle activation variability is muscle- and sex-dependent at mid-stance; 3) the individual activation variabilities of the RF, TA, and GL do not have a substantial role in producing stride time variability.

3.4.1 Sex-independent effects of older age

In partial agreement with our hypothesis, older age was associated with higher stride time variability and higher muscle activation variability in some, but not all, phases of gait. This mimics the higher stride time variability seen in older age in this study and in previous studies containing large cross-sectional samples (Beauchet et al., 2017; Callisaya, Blizzard, Schmidt, et al., 2010). Like in Callisaya et al (2010), influences of age on gait speed seem to contribute highly to stride time variability, meaning that a better understanding of the control of gait speed may help to better understand the production of stride time variability.

The associations between higher age and higher muscle activation variability add to the body of investigations on the neuromuscular features that control gait. Features studied in healthy young adults include both the variability of EMG amplitude shape (Kadaba et al., 1989; Kadaba, Wootten, Gainey, & Cochran, 1985) and the variability of activation modality (Di Nardo & Fioretti, 2013; Di Nardo, Ghetti, & Fioretti, 2013). These studies highlight the inherent variability that

exists in the EMG signal from cycle-to-cycle, but not the source of variability. Although the precise mechanisms are unclear, higher variability with higher age may be partly due to changes in neurophysiology, such as higher neuromuscular noise (Kang & Dingwell, 2016; Kurz & Stergiou, 2003). Although there are no known studies on how age affects muscle activation variability during gait for comparison to our study, recent studies have analyzed entropy, a non-linear measure of complexity where higher values may indicate higher variability. Kurz & Stergiou (2003) found higher entropy in the knee and hip kinematics of older adults than young adults during gait, while Kang & Dingwell (2016) found higher entropy in the GL EMG. However, the authors also observed lower entropy of vastus lateralis and biceps femoris EMG (Kang & Dingwell, 2016), contrasting our finding of higher RF muscle activation variability with age in gait. They interpreted their findings to indicate that the fewer MUs of older adults contributed to less complex proximal muscle patterns, and the higher complexity of GL compensated for a loss in proximal muscle pattern complexity (Kang & Dingwell, 2016). The mechanism driving our finding remains uncertain, but is likely linked to higher variability in MU firing patterns within a single muscle (Hourigan et al., 2015; Laidlaw et al., 2000; Piasecki et al., 2016) and to altered interactions between the MU firing patterns of multiple muscles. These contrasting results and uncertain interpretations point to a need to better understand how entropy and CCV measures of EMG can be combined to explore EMG variability during gait.

As the associations between older age and muscle activation variability were driven mainly by the RF, it seems that the influence of older age on the variability of EMG amplitude is more pronounced in proximal muscles of the lower limb than in distal muscles. This complements previous evidence for muscle- and age-dependent gait muscle patterns, focusing on EMG amplitude (Bailey, Corona, Pilloni, et al., 2018; Marques et al., 2016; Schmitz et al., 2009; Van Criekinge et al., 2018) and EMG entropy (Kang & Dingwell, 2016). One potential explanation for the muscle-dependence is that the age-related alterations to MU properties are also muscle-dependent (Power et al., 2013). However, the difference in the variability of MU potential shape between young and older adults appears to be similar between distal gait muscles (tibialis anterior) and more proximal gait muscles (vastus medialis and lateralis) (Hourigan et al., 2015; Piasecki et al., 2016). An alternative explanation is that the RF-specific effect on muscle activation variability represents a motor adaptation with aging to maintain gait stability. The RF generally activates during the transition from terminal swing to loading and during terminal stance (Di Nardo &

Fioretti, 2013), pointing to its dual purpose in not only propagating forward motion, but also in stabilizing the upper body. Higher variability in RF activation may then be from a change to the central pattern generator of locomotion to avoid overly rigid muscle patterns and reach the optimal state of variability described by Stergiou & Decker (Stergiou & Decker, 2011). Thus, peripheral (changes in MU physiology) and central (changes in the central pattern generator of locomotion) mechanisms with aging may drive the higher proximal muscle activation variability seen in gait.

4.5.2 Sex-dependent effect of older age

The association between older age and lower GL CCV in females at mid-stance contrasts with the general effect of older age on EMG CCV, suggesting that there are instances where the variability of muscle activation differs between aging males and aging females. This mirrors our earlier finding where higher GL activation during mid-swing was associated with higher age in females, contrasting the age-independent association with lower TA activation (Bailey, Corona, Pilloni, et al., 2018). Together, these results suggest that aging alters neuromuscular control of the GL during gait in a phase-specific and sex-dependent way.

A loss in GL activation variability at mid-stance likely indicates a lack of flexibility in the motor patterns able to be selected by older females. This seems to align with previous evidence (Barrett et al., 2008; Rathleff et al., 2010; van Kooten et al., 2018). Barrett et al (2008) reported lower variability of ankle dorsiflexion/plantar flexion in females in their sample of young adults and Rathleff et al (2010) reported lower variability of the navicular height during stance in females in their sample of middle aged adults. Our results seem to suggest that this sex difference in motor variability at the ankle is maintained in older age. Interestingly, the lack of flexibility of ankle motor patterns in aging females may help explain sex- and age-based gait instability. In a recent study, van Kooten et al (2018) measured the gait instability of 114 healthy older females and males aged 55-84 years old. After controlling for gait speed, they found higher instability with older age during loading and higher instability in females than in males during mid-stance and terminal stance, indicating higher instability with older age and in females. Further, they showed that age- and sex-based instability only occurred during the stance phase, aligning with our age and sex effects on GL activation variability. Although the interaction effect of older age and sex on gait instability remains to be determined, these studies suggest that instability during single-leg support

in aging females may originate from a lack of flexibility in the available neuromuscular and kinematic patterns.

4.5.3 Associations between the variability of muscle activation and variability of gait motor output

In contrast with our hypothesis, associations between muscle activation variability and stride time variability were not stronger in females than males. In fact, the correlations we found were mostly in the RF and poor in strength, suggesting that the variability in RF EMG, and not TA or GL EMG, minimally affects the variability in gait motor output. This was somewhat surprising since older adults in our sample had both higher RF activation variability and higher stride time variability. We speculate that the variabilities of individual muscle activations may sum to produce variability in gait motion; that is to say, activation variabilities may sum to produce variability in each joint motion, and the variabilities of each joint motion may sum to produce stride time variability. Our RF-specific correlations, taken with the theorized shift to greater hip control during gait in healthy older adults (DeVita & Hortobagyi, 2000), suggests that the hip is a particular joint of interest. In fact, Schloemer et al (2017) observed higher activity of hip extensors (gluteus maximus and gluteus medius) and lower activity of hip flexors (iliacus and psoas) in older adults than young adults during gait. The authors assessed the contribution of these muscles to center of mass support, finding that they had a greater role in older adults than in young adults, but not in compensation for decreases in the contribution at other muscles of the knee and ankle joints. These results were interpreted as evidence for an age-related change in neuromuscular control at the hip (Schloemer et al., 2017); however, the cycle-to-cycle variability patterns of these muscles remain to be evaluated. Clearly, further investigation is needed to understand how variability in lower limb muscle activation produces variability in joint motion, particularly at the hip, to help better identify the neuromuscular origin of stride time variability.

4.5.4 Limitations

Interpretations of our results are limited by the sample, definitions of gait subphases, and muscles analyzed. Our sample consisted of a large number of males and females for an experimental study, allowing us to model age as a continuous variable. However, as described in our previous study (Bailey, Corona, Pilloni, et al., 2018), these adults were concentrated in the 20-29 and 60+ years ranges and may underrepresent adults aged 30-59 years. Also, we defined phases

of gait by subdividing the gait-normalized EMG signal, in line with prior studies (Bailey, Corona, Pilloni, et al., 2018; Schmitz et al., 2009). While an accepted practice for analyzing EMG during gait, this procedure does not factor in the inter-individual differences that may exist in gait timing; these inter-individual differences may be reduced by synchronizing EMG with signals on gait progression (for example, information on foot-floor contact using foot switches or pressure mats). Finally, the RF, TA, and GL were a focus of this investigation since previous studies have reported various influences of age on their activation patterns (Bailey, Corona, Pilloni, et al., 2018; Marques et al., 2016; Schmitz et al., 2009) and we were limited to three EMG sensors on each leg; effects on the activation variability of other muscles could differ, such as those that produce motion in other planes (non-sagittal). Thus, detailed investigations of the knee and hip musculature that produce non-sagittal plane motion may help better understand how age influences muscle activation variability and how stride time variability is produced.

4.6. Conclusions

Older age was associated with higher RF muscle activation variability during gait. Sex-dependencies at mid-stance, however, point towards lower flexibility in muscle activity to the ankle during single-leg support for aging females, which may contribute to gait instability. The variability of RF muscle activation was weakly related to stride time variability; further investigation is needed to determine how the EMG patterns of multiple muscles interact to produce variability in the motor output of individual joints during gait.

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4.8 Author Contributions

C.A.B. and J.N.C. were responsible for study conception, while M.P., G.P., F.A., and M.P. were responsible for the study organization and execution. C.A.B. and J.N.C. designed and executed the statistical analyses. C.A.B. wrote the first draft of this manuscript, which was reviewed and critiqued by M.P. and J.N.C. All authors read and approved the final manuscript.

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Chapter 5. Age-dependent control of shoulder muscles during a reach-and-lift task

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5.1 Preface

From Chapters 3 and 4, it can be concluded that joint and muscle variability patterns in gait are, indeed, affected by old age and in a sex-specific way. The extent to which age affected motor variability patterns in repetitive upper limb activities, however, was beyond the scope of these first two studies. Chapter 2 highlighted the relevance of fatigue to the upper limb muscle activation variability response, with this fatigue-based motor variability response linked to upper limb musculoskeletal disorders. Fatigue also leads to alterations in functional connectivity between muscles, reflecting the non-linear coordination between muscles. Therefore, Chapter 5 sought to determine the effects and interactions of old age and fatigue on these neuromuscular control patterns (i.e. muscle activation variability, functional connectivity between muscles) in a repetitive upper limb task.

In Chapter 5, surface electromyography data were acquired from several regions of the trapezius and deltoid muscles to measure muscle activity during several trials of a reach-and-lift task, performed before and after repetitive motion-induced fatigue of the neck and shoulder musculature. Muscle activation variability was quantified as the trial-to-trial coefficient of variation and functional connectivity was quantified as the normalized mutual information between muscle pairs.

Sections 5.2 to 5.9 are a copy of the manuscript accepted by and in-press with the *Journal of Aging and Physical Activity*. Formatting has been altered to allow insertion into this thesis.

5.2 Abstract

Aging affects fatigability and is a risk factor for incurring a fatigue-related injury in the neck/shoulder (N/S) region. Age-related changes in electromyographical (EMG) features of motor control may be partly responsible.

Young (N=17) and older (N=13) adults completed a reach-and-lift task at their self-selected speed, before and after a fatiguing task targeting the N/S. EMG amplitude (RMS), amplitude variability (RMS CV), functional connectivity (NMI), and functional connectivity variability (NMI CV) were extracted from several muscles and analyzed for effects and interactions of Age using general estimating equation models.

RMS CV and deltoid NMI CV increased from pre- to post-fatigue (ps < .05). Upper trapezius-deltoid NMI decreased for young but increased for older adults while the opposite response was found for lower trapezius-deltoid NMI (ps < .05).

Older adults seem to adapt to fatigue in reach-and-lift movement with a cranial shift in control of the scapula.

5.3 Introduction

Healthy aging has been linked to alterations in the structures and physiology of the neuromuscular system. With age, motor unit (MU) remodeling becomes compromised (Gordon et al., 2004; Power et al., 2013), leading to fewer total MUs that fire at lower frequencies, with higher variability, and with higher coherence than in young adults (Hunter et al., 2016; Narici et al., 2008). These alterations likely impact movement variability and motor coordination (Hunter et al., 2016).

Healthy aging also affects fatigability from dynamic contractions (Hunter et al., 2016). In the neck/shoulder (N/S) region, MSDs are frequently associated with exposure to repetitive upper extremity movements (Gallagher & Heberger, 2013; Punnett & Wegman, 2004). The injury mechanism likely involves muscle fatigue, the decrease in functional capacity that leads to increased perceived difficulty in maintaining force production (Enoka & Stuart, 1992). While this is evaluated locally by analyzing the amplitude of the electromyogram (EMG) (Vøllestad, 1997), EMG-based characteristics beyond amplitude may also relate fatigue to N/S MSD development (Madeleine, Mathiassen, & Arendt-Nielsen, 2008; Madeleine, Xie, Szeto, & Samani, 2016).

One such characteristic is motor variability, the natural variability in sensorimotor actions (Newell & Slifkin, 1998). Motor variability generally increases with fatigue from repeated low force upper extremity movement (Fedorowich et al., 2013; Samani et al., 2017; Srinivasan et al., 2016), which is interpreted as a voluntary search for new motor patterns to maintain task performance (Côté, 2014). Moreover, Madeleine et al (2008) identified lower muscle activation variability during repeated shoulder movements in workers with chronic N/S pain than in healthy controls, suggesting a link between low variability and chronic pain.

Changes in the functional connectivity between pairs of muscles has also been related to N/S injury. Generally, fatigue of the upper extremity has been associated with increased functional connectivity (Kawczyński et al., 2015; Madeleine et al., 2011; Samani et al., 2017), although not

always (Fedorowich et al., 2013). Samani et al (2017) suggest that this response represents a change in the motor control strategy to maintain the needs of the ongoing task, like the motor variability response. Further, Madeleine et al (2016) found that individuals with chronic N/S pain had lower trapezius connectivity than healthy individuals during typing and texting, suggesting that inadequate functional connectivity of muscles could also be involved in the mechanism of N/S pain and injury development.

The extent to which inter-movement and inter-muscle activation patterns may help explain the higher prevalence and incidence rates of MSDs in older adults (Cassou, 2002) is unclear. Qin et al (2014) observed higher variability of scapular elevation in older adults than young adults throughout a fatiguing light occupational assembly task, and Potvin et al (1980) observed poorer coordination with higher age during non-fatiguing clinical tests of grasping and arm tracking. Together, these studies suggest that age may have a fatigue-independent effect on movement variability and coordination. Yet, the effect of age on the variability and coordination of the underlying muscle patterns, and how they may change with fatigue, remains to be determined.

The purpose of this study was to determine the age-specific effect of performing a N/S fatiguing task on EMG variability and functional connectivity in a reach-and-lift task. We hypothesized that with fatigue, increases in muscle activation variability would be higher with age and changes in functional connectivity of muscles would be altered with age.

5.4 Methods

5.4.1 Participants

A convenience sample of 17 young adults (20-29 years; 9 females; age: 24.8 (2.8) years; height: 1.77 (0.10) m; mass: 69.6 (12.9) kg) and 13 older adults (55+ years; 10 females; age: 73.9 (7.3) years; height: 1.61 (0.11) m; mass: 73.8 (16.4) kg) were recruited from the local community. Participants were excluded if they had a previous or current N/S MSD, or N/S pain, or were unable to be physically active due to an existing medical condition. All participants cleared these exclusion criteria and provided informed consent to the study. The study followed the Declaration of Helsinki and received approval by the institutional research ethics board.

5.4.2 EMG instrumentation

The placement of EMG sensors at each muscle site was performed by the same experimenter according to SENIAM guidelines for skin preparation, sensor location, and sensor placement (Hermens et al., 2000). Skin was shaved and lightly abraded with alcohol, then pairs of circular and pre-gelled Ag/AgCl surface electrodes (Ambu, Denmark; diameter = 1cm) were placed parallel to the muscle fibres at an interelectrode distance of 2 cm. Skin-electrode impedance was estimated to be 500 Ω. In all, EMG sensors were placed on eight muscle sites on the side of the participant's dominant upper limb: upper trapezius (UT), middle trapezius (MT), lower trapezius (LT), anterior deltoid (AD), middle deltoid (MD), posterior deltoid (PD), biceps brachii (BI), and triceps brachii (TRI) (Table 4.1). EMG data from the sensors were sampled with a data acquisition system (Telemyo 900, Noraxon, USA) at a frequency of 1000 Hz. Signals were differentially amplified with an effective common-mode rejection ratio of 130 dB DC (100 dB at 60 Hz), input impedance of > 100 MΩ and gain of 2000 per channel. These analog signals were then digitally converted using a 16 bit A/D board with a ±10 V range. Wires connecting the sensors to the system were secured with medical tape to prevent motion artifacts.

5.4.3 Protocol

5.4.3.1 RVICs. Once instrumented, participants completed reference voluntary isometric contractions (RVICs) of all muscles. Each RVIC consisted of a 10 s isometric contraction held in a specific posture (Table 5.1). For each RVIC, participants moved their upper extremity into the specified posture at their self-selected speed, held the posture statically during data recording, then relaxed their upper extremity when instructed by the experimenter. The postural angles were confirmed using a goniometer.

Table 5.1. Electrode locations, Reference Voluntary Isometric Contraction (RVIC) postures and rationale for each muscle.

Muscle	Electrode Location	RVIC Posture	Rationale
Upper trapezius (UT)	Midpoint of the acromion and C7 spinous processes	Standing, holding the arms straight and shoulders abducted 90° in the frontal plane	Based on previous reported positioning (S.E. Mathiassen, Winkel, & Hägg, 1995)

Middle trapezius (MT) & lower trapezius (LT)	**MT**: midpoint of the medial border of the scapula and T3 spinous process **LT**: midpoint of the inferior angle of the scapula and T8 spinous process	Standing, holding the arms straight and shoulders abducted 120° in the frontal plane	Adapted from the UT RVIC to target middle and lower trapezius specifically
Anterior deltoid (AD)	One fingerbreadth distal and anterior to the acromion process	Standing, holding the arm straight and shoulder flexed at 90° in the sagittal plane, hand flat	Based on previously reported positioning (Boettcher, Ginn, & Cathers, 2008; Farias Zuniga & Côté, 2017; S.E. Mathiassen et al., 1995)
Middle deltoid (MD) & posterior deltoid (PD)	**MD**: most prominent bulge on the line between the acromion process and the lateral epicondyle **PD**: two fingerbreadths posterior to the angle of the acromion	Standing, holding the arm straight and shoulder flexed at 90 in the sagittal plane, thumb down	Adapted from the AD RVIC to target middle and posterior deltoid specifically
Biceps brachii (BI) & triceps brachii (TRI)	**BI**: two thirds distal on the line between the acromion process and the cubital fossa **TRI**: two finger breadths medial to the midpoint of the posterior aspect of the acromion process and the olecranon process	Standing, elbow flexed at 90 and palm open facing up, holding a 2.2 kg mass	Light mass to ensure sufficient muscular effort

5.4.3.2 Reach-and-lift task. Participants then completed the reach-and-lift task. This task was created to evaluate self-selected speed movement required in many upper limb activities of daily living. Specifically, the reach-and-lift task simulates reaching and lifting a small object, mimicking the first two phases of drinking (Murphy, Sunnerhagen, Johnels, & Willén, 2006). Participants were seated on a chair with no backrest, facing a table. with their back straight,

shoulders relaxed, and palms down resting on the table. The chair and table heights were adjusted and feet support added to achieve an ergonomic posture of the upper and lower limbs (Figure 5.1). This posture was the starting position for each trial. A cylinder (diameter = 6.5 cm; mass = 0.5 kg) was placed 40 cm from the front edge of the table, centred in front of the participant. The distance of the cylinder was normalized to each participant by measuring their normalized reach distance, calculated as the proportional distance relative to their functional reach. Functional reach was measured as the standing distance from the acromion to the middle finger tip with the shoulder flexed to 90° and the elbow, wrist, and fingers fully extended. Participants were then verbally instructed to imagine they were drinking from a glass of water. This movement consists of reaching and grasping the cylinder, lifting the cylinder to their mouth, drinking, lowering and releasing the cylinder, then putting their palm down at the same place as for the starting position (Murphy et al., 2006). Emphasis was provided by the experimenters to the participants to move at their comfortable pace, and to return the cylinder and their palm to their starting positions. The participants performed five trials of the reach-and-lift task after feeling they had adequate practice, with a brief rest interval (~3 s) between each trial.

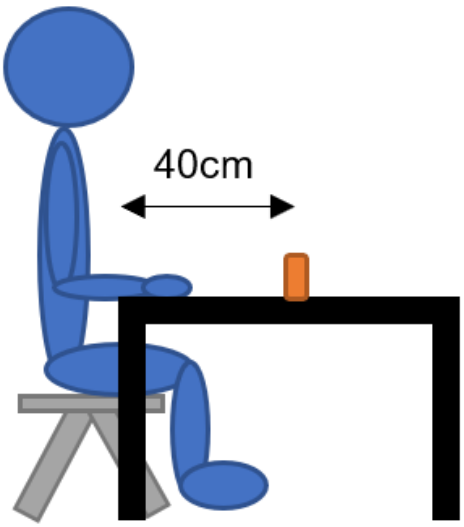

Figure 5.1. The starting position of the reach-and-lift task.

5.4.3.3 Fatiguing task. The fatiguing task involved repetitive forward reaching and was designed to specifically fatigue the N/S musculature. Participants repetitively tapped with the middle finger of their dominant hand between two targets placed on the table at 30% and 100% of

functional reach (Figure 5.2). Movements followed a 2 Hz rhythm produced by a metronome, such that a forward reach was performed in 0.5 s followed by a reverse reach performed in 0.5s, which was repeated continuously. At the end of each minute of the fatiguing task, participants reported their rating of perceived exertion (RPE) for the N/S region, according to the Borg CR-10 scale (Borg, 1982). While reporting RPE, participants did not stop the fatiguing task and continuously reached between the two targets. Task termination was defined as one-minute after a RPE $\geq$ 8, or at a task duration of 45 min (Fedorowich et al., 2013; Fuller et al., 2011; Srinivasan et al., 2016).

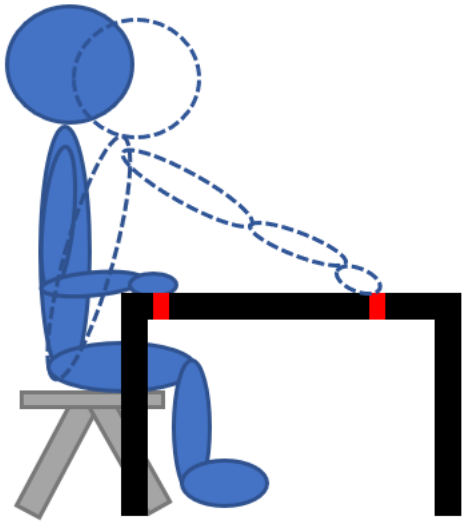

Figure 5.2. The fatiguing task. Example positions are shown at the close target (30% of functional reach) and far target (100% of functional reach).

After completion of the fatiguing task, participants immediately completed a second block of five reach-and-lift task trials.

5.4.4 Data analysis

EMG data were analyzed from all RVIC trials and all reach-and-lift task trials performed before (pre-fatigue) and after (post-fatigue) the fatiguing task. The electrical noise from heart beats was removed from each trial using a subtraction technique described by Minn & Côté (2018). In short, we identified a clear reference beat (ie. QRS) in the most contaminated EMG channel, removed the artifacts not belonging to the QRS with a low-pass filter at 40 Hz, manually tagged the starts of all other contaminated beats and used a cross-correlation function to more precisely adjust these tags, then applied the QRS removals to the EMG channel. This was then applied to all

other contaminated EMG channels within the trial and repeated for each trial. These data were then filtered using a dual-pass, 2nd order, bandpass Butterworth filter (10-450 Hz). All filtered EMG data were smoothed using a root-mean-square moving average with 100 ms windows overlapping by 1 ms. Smoothed EMG data from the reach-and-lift task were then partitioned into the reach and lift phases by locating peaks in the anterior-posterior velocity profile of a marker located on the radial styloid process. The velocity profile was sampled at 100 Hz using an optoelectronic camera system (MX3, Vicon, UK) that was synchronized with the EMG system. The root-mean-square (RMS) values of these reach and lift partitions were then calculated. These values represented the muscle activation magnitudes and were normalized to the EMG RMS from the corresponding RVIC.

Functional connectivity of all within-trapezius, within-deltoid, and trapezius-deltoid muscle pairs was calculated as the normalized mutual information (NMI) (Johansen, Samani, Antle, Côté, & Madeleine, 2013; Kawczyński et al., 2015; Madeleine et al., 2011; Madeleine et al., 2016; Samani, Pontonnier, Dumont, & Madeleine, 2015). For the two filtered EMG signals of a muscle pair, the information contained in each signal is first calculated as its entropy H (Equation 5.1),

$$H(X) = -\sum_i p_X(x_i)\ \log\ (p_X(x_i)) \tag{5.1}$$

where $p_X(x_i)$ is the probability distribution function of EMG signal X estimated by a histogram and $p_X(x_i)$ is the ith bin of the normalized histogram. The histogram was constructed with forty bins. The mutual information, MI, of EMG signals X and Y was then defined according to Equation 5.2,

$$MI_{XY} = \sum_{i,j} p_{XY}(x_i, y_j)\ \log \frac{p_{XY}(x_i,y_j)}{p_X(x_i)p_Y(y_j)} \tag{5.2}$$

where $p_{XY}(x_i, y_j)$ is the joint probability distribution function of EMG signals X and Y. MI was estimated over 500 ms non-overlapping epochs, then normalized by the minimum H of EMG signals X and Y (Equation 5.3),

$$Nrm - MI_{XY} = \frac{MI_{XY}}{\min(H(X),H(Y))} \tag{5.3}$$

where $Nrm - MI_{XY}$ is the NMI. Thus, NMI has a minimum value of 0 that indicates complete functional independence between EMG signals X and Y, and a maximum value of 1 that indicates complete functional dependence between the signals.

Individual subject means of RMS and NMI were calculated across the five trials performed in each pre-fatigue and post-fatigue single block. Trial-to-trial coefficient of variation (CV) of RMS and NMI were also calculated to quantify inter-trial variability. The movement speed during the reach phase was calculated as $\Delta d/\Delta t$, where Δd was the change in anterior-posterior displacement of the radial styloid process and Δt was the change in time from the start to end of the reach phase; the mean movement speed across trials quantified the participant's self-selected speed and the CV across trials quantified the self-selected speed variability. In summary, each participant's dataset included two phases of the reach-and-lift task (reach and lift) and two conditions (pre-fatigue and post-fatigue), with the means and CVs of the following measures: self-selected speed, RMS (eight muscles), within-trapezius and within-deltoid NMI (six muscle pairs), and trapezius-deltoid NMI (nine muscle pairs).

5.45.5 Statistical analysis

A set of statistical analyses was first conducted to test for age differences in participant characteristics. Independent t-tests were conducted on age, height, mass, BMI, functional reach distance, normalized reach distance, and time to fatiguing task termination. As self-selected speed and self-selected speed variability of the reach-and-lift task were calculated independently for the pre- and post-fatigue conditions, two-way ANOVAs were conducted on these measures to test for Age (young adults, older adults), Condition, and Age x Condition effects. These ANOVAs included Sex as a covariate since the proportions of males and females differed between the young and older groups.

The EMG measures were then analyzed using general estimating equation models. Six models were created for the reach and lift phases to analyze each EMG measure: 1) mean RMS, 2) RMS CV, 3) mean within-trapezius and within-deltoid NMI (within-muscle NMI), 4) mean trapezius-deltoid NMI (between-muscle NMI), 5) within-muscle NMI CV, and 6) between-muscle NMI CV. These models included Age as a between-subjects factor, Condition and Muscle as within-subjects factors for RMS and RMS CV, and Condition and Muscle Pair as within-subjects fixed factors for within- and between-muscle NMI and NMI CV. As self-selected speed likely

mediates the effect of Age on inter-movement variability and inter-muscle coordination (Hortobágyi et al., 2009; Kang & Dingwell, 2008b; Menz et al., 2003), self-selected speed (RMS and NMI models) and self-selected speed variability (RMS CV and NMI CV models) were included as covariates. Sex was also included as a covariate in all models. Main effects of Age, Condition, and Muscle (or Muscle Pair), and two-way and three-way interaction effects were assessed using Wald X^2 statistics. Interaction effects were explored by contrasting the estimated marginal means using post-hoc Wald X^2 tests, with sequential Bonferroni adjustments to p-values to compensate for multiple comparisons.

5.5 Results

5.5.1 Participant characteristics

Means of participant characteristics for the young and older groups are reported in Table 5.2 and self-selected speed and self-selected speed variability are reported in Table 5.3. The older group had a higher normalized reach distance (Age effect: $t_{28} = 2.279$, $p = .031$) and a lower time to fatiguing task termination (Age effect: $t_{28} = 2.064$, $p = .048$), so these variables were added as additional covariates in all EMG analyses. The Age effect on time to fatiguing task termination was partially driven by the number of participants that completed the full 45 min, with 9/17 young and 3/13 older participants completing the maximum allowable duration. The mean (SD) of the final RPEs for these young and older participants were 6 (1) and 7 (1) respectively. There were no effects or interaction of Age and Condition on either self-selected speed or self-selected speed variability ($p > .05$). However, Sex was influential on these parameters. Removing Sex as a covariate led to observing increased self-selected speed following the fatiguing task (Condition effect: $F_{1,28} = 11.863$, $p = .002$) and increased self-selected speed variability in the young group but decreased variability in the older group (Age*Condition effect: $F_{1,28} = 4.215$, $p = .049$). The inclusion/removal of Sex as a covariate did not affect statistical effects on time to fatiguing task termination nor on any EMG measure.

Table 5.2. Participant characteristics for the young and older groups. Values are means (SD).

Characteristic	Young	Older
Age (y)*	24.8 (2.8)	73.9 (7.3)
Height (m)*	1.77 (0.10)	1.61 (0.11)
Mass (kg)	69.6 (12.9)	73.8 (16.4)
BMI (kg/m^2)*	22.1 (2.2)	28.4 (4.5)
Functional reach distance (cm)	75.6 (4.6)	73.0 (3.7)

Normalized reach distance (% functional reach)*	77.0 (4.8)	81.4 (5.7)
Time to fatiguing task termination (min)*	33.8 (14.0)	22.8 (14.8)

* Significant Age effect ($p < .05$)

Table 5.3. Self-selected speed and self-selected speed variability of the young and older groups during the drinking-like task, pre- and post-fatigue. Values are means (SD).

Characteristic	**Young**		**Older**	
	Pre-Fatigue	Post-Fatigue	Pre-Fatigue	Post-Fatigue
Self-selected speed (m/s)	.171 (.046)	.187 (.054)	.165 (.034)	.186 (.048)
Self-selected speed variability (%)	15.5 (5.78)	11.0 (3.27)	12.9 (5.58)	15.1 (8.28)

5.5.2 Muscle activation amplitude (RMS)

For the reach phase, there was a significant Age x Muscle interaction on RMS (X^2_7 = 31.941, p = .009) where the RMS was higher in older adults than young adults in the UT (mean ± standard error: .519 ± .110 vs. .240 ± .034, p = .017), AD (.755 ± .085 vs. .472 ± .039, p = .002), and BI (.406 ± .048 vs .276 ± .023, p = .011), but the RMS was lower in older adults than young adults in the LT (.229 vs. .458, p = .015) (Figure 5.3A). RMS also significantly increased from pre-fatigue to post-fatigue across all muscles for both groups (Condition effect: .391 ± .020 to .413 ± .019, X^2_1 = 6.846, p = .009).

For the lift phase, there was a significant Age x Muscle interaction on RMS (X^2_7 = 22.039, p = .003) where the UT RMS was higher in older adults than young adults (1.351 ± .273 vs. .552 ± .066, p = .005), but the LT RMS was lower in older adults than young adults (.594 ± .063 vs. .996 ± .173, p = .035) (Figure 5.3B). There was also a significant Condition x Muscle interaction on RMS (X^2_7 = 26.124, p < .001) where the RMS increased from pre-fatigue to post-fatigue in the UT (.888 ± .136 to 1.015 ± .142, p < .001), AD (.761 ± .038 to .823 ± .045, p = .002), PD (.624 ± .049 to .707 ± .065, p = .027), and TRI (.587 ± .027 to .628 ± .030, p = .046).

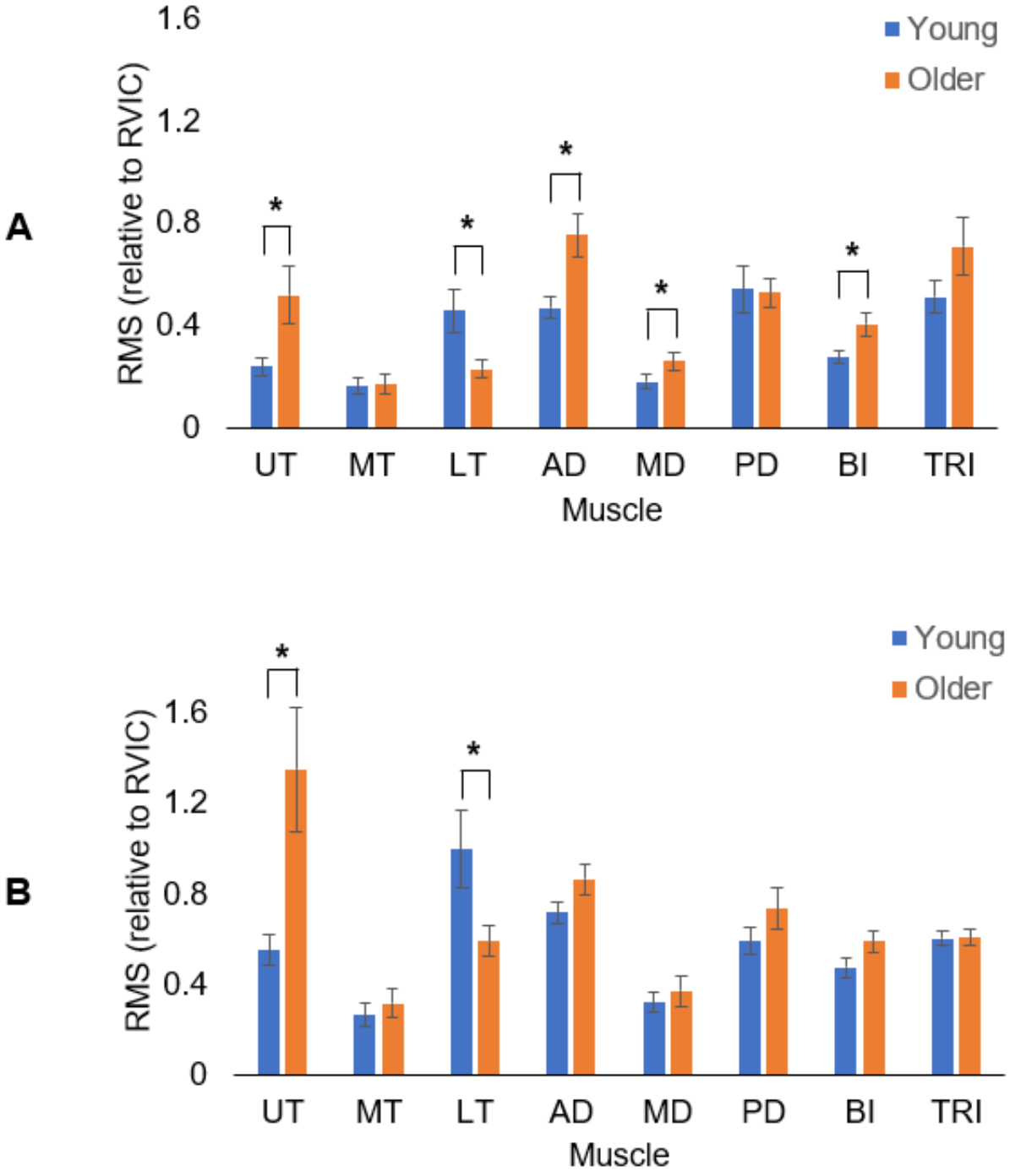

Figure 5.3. Estimated marginal means of RMS, expressed relative to the RVIC, for the reach phase (a) and lift phase (b) of the reach-and-lift task. Error bars indicate the SEM. Asterisks indicate significant age differences. RMS = root mean square; RVIC= reference

5.5.3 Variability of muscle activation (RMS CV)

There were significant Condition effects on RMS CV at both the reach phase (14.3 ± .7% to 18.4 ± 1.2%, $X^2_1 = 11.322$, p = .001) and lift phase (9.1 ± .4% to 11.1 ± .6%, $X^2_1 = 11.304$, p = .001). At both phases, RMS CV increased across muscles and age groups from pre-fatigue to post-fatigue, identifying an increase in muscle activation variability following fatigue. Muscle-specific means and % changes are reported in Table 5.4. No age-based effects were found on RMS CV (p > .05).

Table 5.4. Root mean square variability (RMS CV) during the drinking-like task. Values are estimated marginal means of coefficients of variability (standard error of measurement), averaging across the young and older adult groups.

Muscle	**Reach Phase**			**Lift Phase**		
	Pre-Fatigue	Post-Fatigue	% Change	Pre-Fatigue	Post-Fatigue	% Change
Upper trapezius	19.9 (1.8)	26.9 (3.0)	35.2	11.4 (1.0)	12.1 (0.8)	6.1
Middle trapezius	13.8 (1.9)	16.1 (2.4)	16.7	10.0 (0.9)	9.7 (0.8)	-3.0
Lower trapezius	19.4 (2.3)	23.8 (2.2)	22.7	9.8 (1.1)	10.8 (1.1)	10.2
Anterior deltoid	12.3 (1.1)	14.1 (3.0)	14.6	8.0 (0.7)	10.1 (1.3)	26.2
Middle deltoid	12.3 (1.1)	16.9 (1.5)	37.4	9.2 (0.9)	12.8 (1.0)	39.1
Posterior deltoid	11.4 (1.3)	12.6 (1.6)	10.5	7.7 (0.7)	10.2 (2.3)	32.5
Biceps brachii	12.3 (1.0)	14.6 (1.4)	18.7	9.1 (0.6)	10.5 (0.9)	15.4
Triceps brachii	17.5 (3.2)	21.9 (3.2)	25.1	7.6 (1.0)	12.3 (1.9)	61.8

5.5.4 Variability of muscle functional connectivity (NMI CV)

5.5.4.1 Within-muscle NMI CV. There was a significant Age x Condition x Muscle Pair interaction on within-muscle NMI CV at the reach phase ($X^2_5 = 12.771$, p = .026) but no significant effects at the lift phase (p > .05). Post-hoc analyses at the reach phase revealed that deltoid connectivity variability increased from pre-fatigue to post-fatigue in both age groups, with increased AD-MD NMI CV in young adults (5.8 ± .4% to 7.4 ± .6%, p = .041) and increased AD-PD NMI CV in older adults (6.4 ± .7% to 7.5 ± .6%, p = .016) (Figure 5.4).

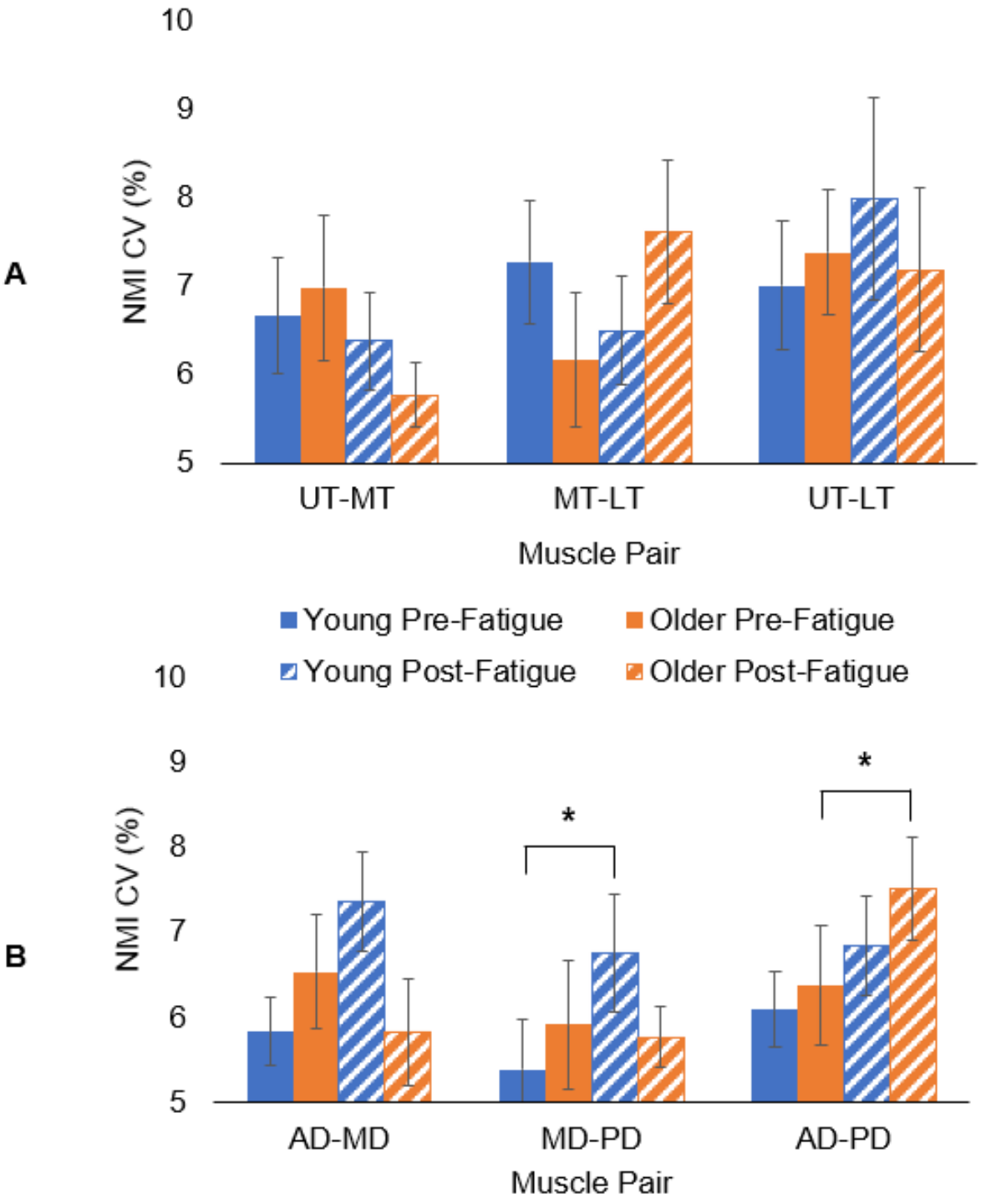

Figure 5.4. Estimated marginal means of NMI CV within the trapezius (a) and deltoid (b) during the reach phase of the reach-and-lift task. Error bars indicate the SEM. Asterisks indicate significant differences. NMI CV = normalized mutual information coefficient of variation; UT = upper trapezius; MT= middle trapezius; LT = lower trapezius; AD = anterior deltoid; MD= middle deltoid; PD = posterior deltoid.

5.5.4.2 Between-muscle NMI CV. There were significant age-based effects on between-muscle NMI CV, with an Age x Condition x Muscle Pair interaction at the reach phase (X^2_8 = 21.977, p = .005) and an Age x Muscle interaction at the lift phase (X^2_8 = 18.623, p = .017). At the reach phase, older adults had lower MT-PD NMI CV than young adults pre-fatigue (5.4 ± .6% vs 7.9 ± .7%, p = .006) and MT-MD NMI CV decreased for young adults (6.9 ± .6% to 5.4 ± .6%, p = .040), indicating that the initial higher variability of between-muscle connectivity in young adults disappeared following fatigue (Figure 5.5). For the lift phase, no post-hoc analyses reached significance following sequential Bonferroni adjustments, although there were trends for lower NMI CV in older adults than young adults for UT-AD (4.2 ± .5% vs. 5.4 ± .3%, p = .061), UT-MD (4.6 ± .4% vs. 5.8 ± .5%, p = .065), and MT-MD (4.4 ± .5% vs. 5.6 ± .4%, p = .078).

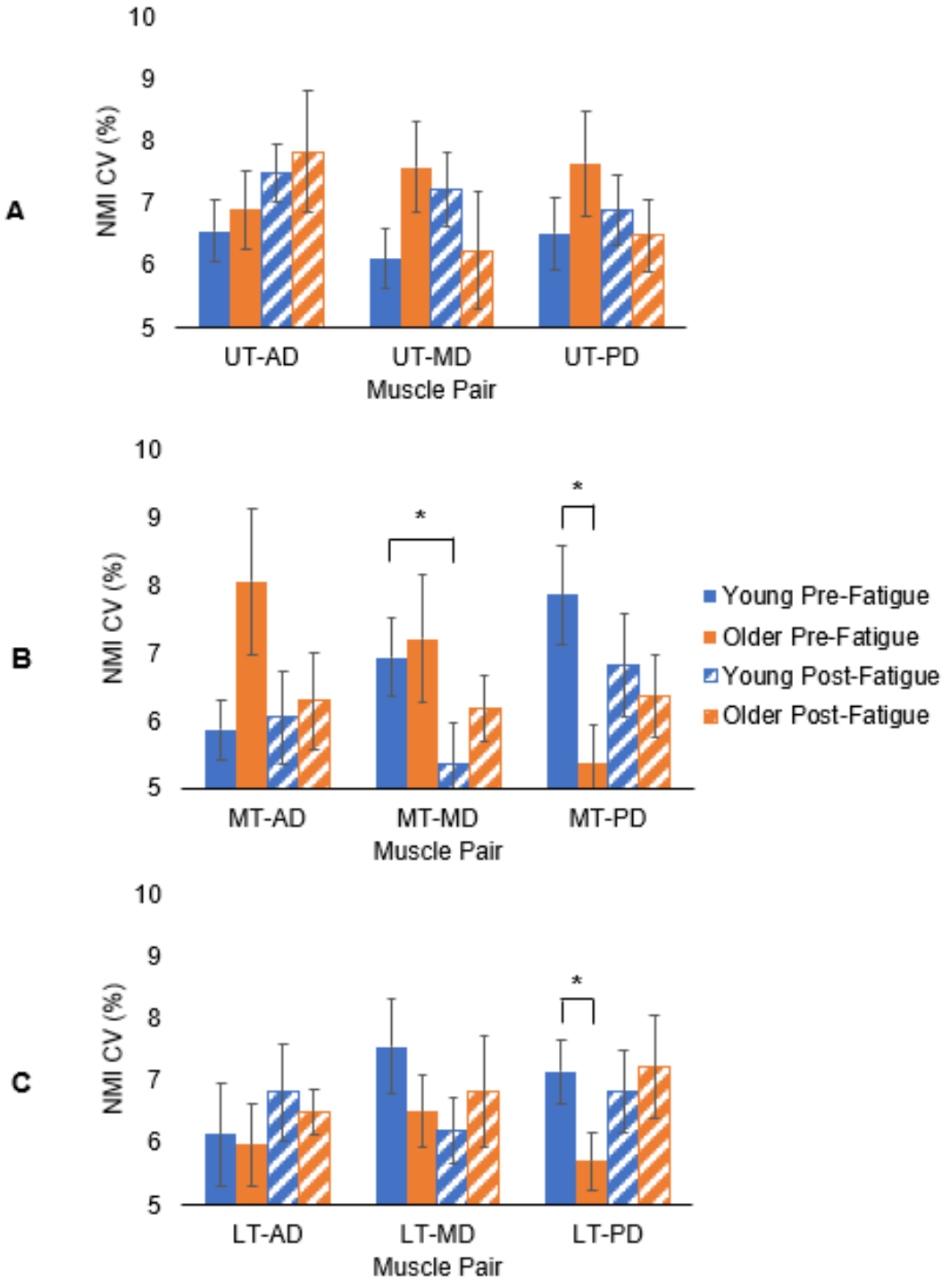

Figure 5.5. Estimated marginal means of NMI CV between the trapezius and deltoid during the reach phase of the reach-and-lift task. Error bars indicate the SEM. Asterisks indicate significant differences. NMI CV = normalized mutual information coefficient of variation; UT = upper trapezius; MT = middle trapezius; LT = lower trapezius; AD = anterior deltoid; MD= middle deltoid; PD = posterior deltoid5.4.5 Muscle functional connectivity (NMI)

5.5.5.1 Within-muscle NMI. There were significant Condition x Muscle Pair interactions on within-muscle NMI at both the reach phase (X^2_5 = 15.672, p = .008) and lift phase (X^2_5 = 16.686, p = .005). The interaction at the reach was driven by an increase in MD-PD NMI from pre-fatigue to post-fatigue (.238 ± .002 to .244 ± .002, p = .002) and the interaction at the lift was driven by a decrease in UT-MT NMI from pre-fatigue to post-fatigue (.247 ± .002 to .243 ± .002, p = .002) (Figure 5.6). No age-based effects were found for within-muscle NMI.

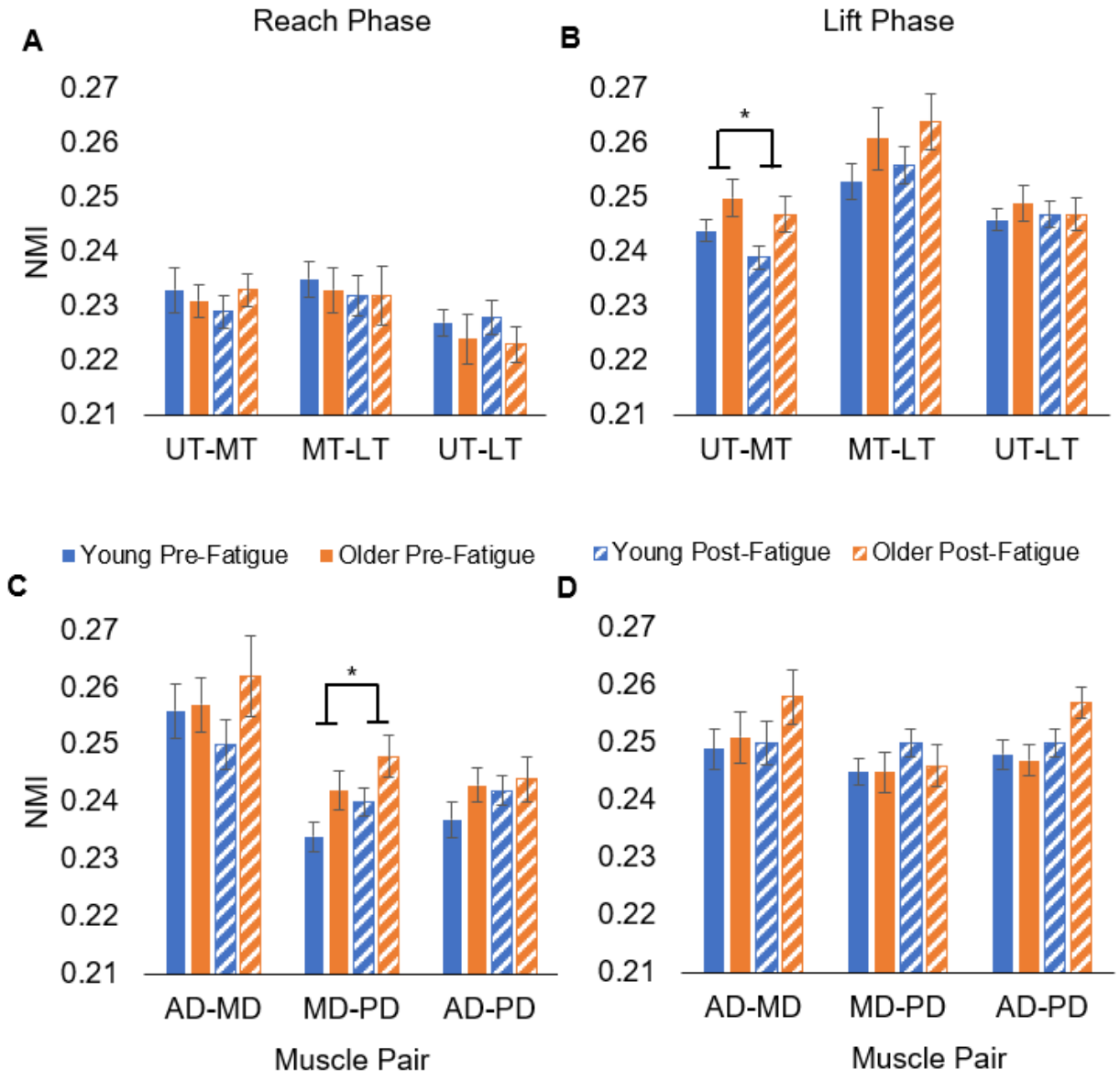

Figure 5.6. Estimated marginal means of NMI within the trapezius and deltoid during the reach-and-lift task. Shown are the trapezius NMIs at the reach (a) and lift (b) phases and the deltoid NMIs at the reach (c) and lift (d) phases. Error bars indicate the SEM. Asterisks

indicate significant Condition differences. NMI = normalized mutual information; UT = upper trapezius; MT= middle trapezius; LT = lower trapezius; AD = anterior deltoid; MD= middle deltoid; PD = posterior deltoid.

5.5.5.2 Between-muscle NMI. Age-based effects were found for between-muscle NMI, with Age x Condition x Muscle Pair interactions at both the reach phase ($X^2_8 = 20.375$, $p = .009$) and lift phase ($X^2_8 = 32.808$, $p < .001$). Post-hoc analyses revealed age-dependent effects on connectivity of the deltoid to the LT and UT (Figure 5.7). The NMI between the LT and deltoid increased after fatigue in young adults (Reach LT-MD: .230 ± .003 to .238 ± .004, p = .014; Lift LT-AD: .248 ± .002 to .252 ± .002, p = .023; Lift LT-PD: .248 ± .002 to .252 ± .003, p = .048) but decreased after fatigue for older adults (Reach LT-AD: .239 ± .004 to .232 ± .004, p = .047). Comparing older adults to younger adults, LT-deltoid NMI was higher pre-fatigue (Lift: LT-AD: .256 ± .003 vs. .248 ± .002, p = .045) and lower post-fatigue (Reach LT-MD: .226 ± .004 vs. .238 ± .004, p = .035). In contrast, the NMI between the UT and deltoid decreased after fatigue in young adults (Lift UT-PD: .245 ± .002 to .241 ± .002, p = .037) but increased after fatigue in older adults (Lift UT-MD: .238 ± .003 to .241 ± .003, p = .020).

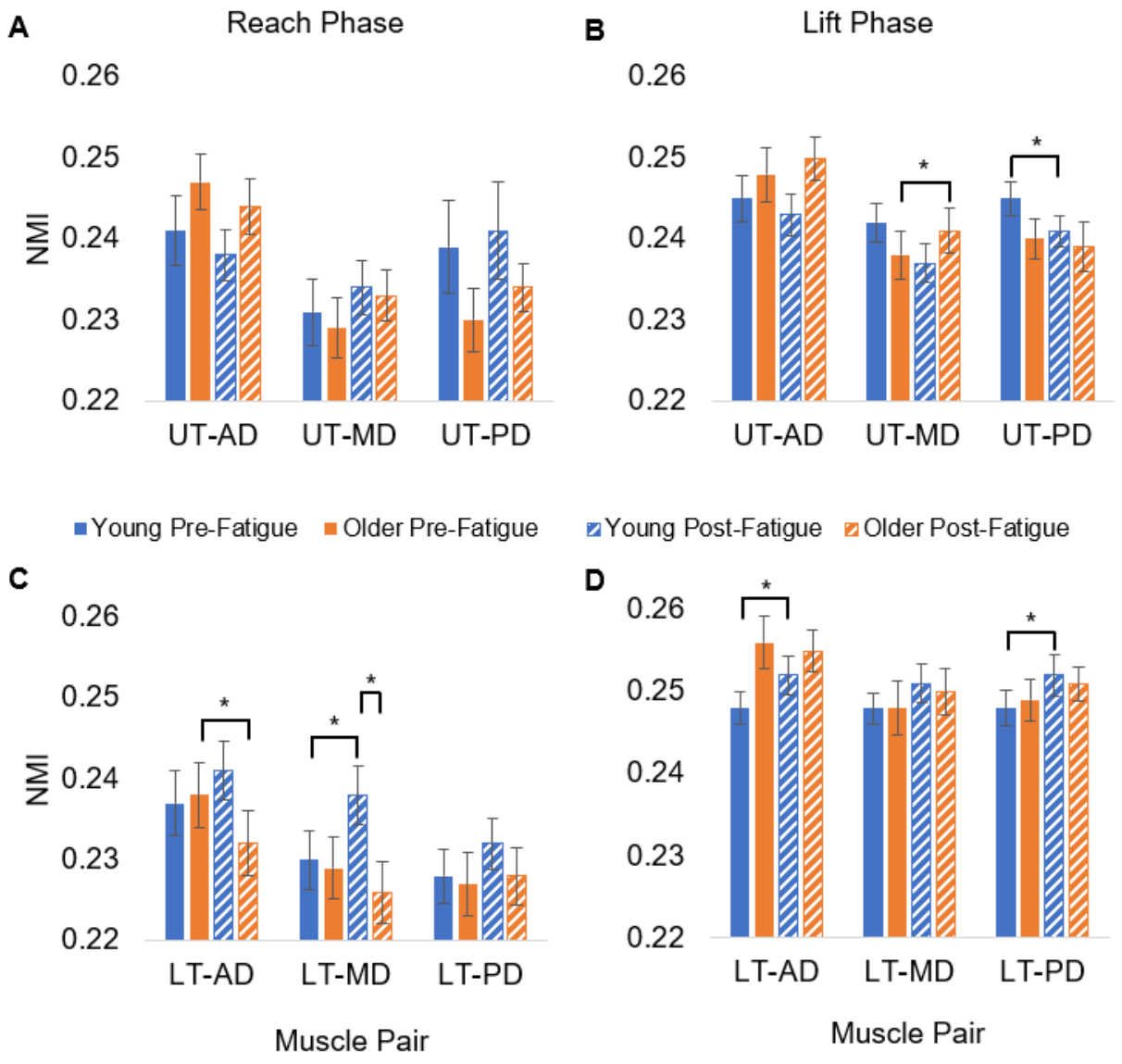

Figure 5.7. Estimated marginal means ofNMI between the trapezius and deltoid during the reach-and-lift task. Shown are the UT–deltoid NMIs at the reach (a) and lift (b) phases, and the LT–deltoid NMIs at the reach (c) and lift (d) phases. Error bars indicate the SEM. Asterisks indicate significant differences. NMI = normalized mutual information; UT = upper trapezius; MT= middle trapezius; LT = lower trapezius; AD = anterior deltoid; MD= middle deltoid; PD = posterior deltoid.

5.6 Discussion

This study is the first to investigate the impact of old age on fatigue-related changes in muscle activity, muscle pattern variability and functional connectivity in the neck/shoulder region for a movement used in activities of daily living. The main findings of our study are 1) the increases

in muscle activation variability following performance of a N/S fatiguing task were age-independent, 2) increases in within-muscle connectivity variability occurred for the deltoid following a N/S fatiguing task, but decreases in between-muscle connectivity variability occurred for trapezius-deltoid pairs, and 3) the trapezius-deltoid connectivity strategy following the N/S fatiguing task seemed to be age-dependent, such that older adults increased connectivity with the UT and young adults increased connectivity with the LT.

5.6.1 Evidence for N/S fatigue

We observed increases in trapezius and deltoid activation amplitude in the reach-and lift task following the fatiguing task, suggesting that localized muscle fatigue was present in the young and older groups. The magnitudes of these amplitude increases (6-14%) are in line with those occurring during repeated forward reaching (Fedorowich et al., 2013) and suggest that there was a small but significant increase in the physiological load of the reach-and-lift task. We acknowledge that the perceived fatigability differed by age, with a shorter time to task termination for older adults than young adults, driven by the higher number of young adults than older adults that failed to reach the RPE ≥ 8 termination criteria for the fatiguing task. However, these participants still reported high RPEs after 45 min, corresponding on average to scores of 6 or ratings just below a "very strong" exertion in young adults, to scores of 7 or a "very strong" exertion in older adults, and all adults were able to successfully complete five consecutive trials of the reach-and-lift task following the fatiguing task. Further, adjusting time to task termination with sex as a covariate (considering the higher proportion of females in our older group compared to our young group) did not alter our age result. Although others have previously shown longer endurance times in females than males (Hunter, 2016), this is in cases of isometric efforts normalized to maximal voluntary contractions; the same group, as well as ours, found no difference in more comparable, dynamic tasks (Fedorowich et al., 2013; Senefeld et al., 2017; Srinivasan et al., 2016). Moreover, there was no age influence on the fatigue-induced increases in muscle activation amplitude. This supports that localized muscle fatigue was present at a similar level in the young and older groups, and so we assume for the rest of this discussion that both groups reached the same state of N/S fatigue.

5.6.2 Age-independent effect of N/S fatigue on muscle pattern variability between self-selected speed movements

Following the fatiguing task, adults had increased muscle activation variability between successive movements of the reach-and-lift task, with increases in RMS CV across the muscles of both the young and older groups. This is in contrast with our hypothesis that there would be an aging effect on the fatigue-related increases in variability. The lack of an age difference in N/S muscle activation variability both before and after fatigue was also surprising, given that age has been associated with higher kinematic variability of the shoulder and scapula during light occupational assembly work (Qin, Lin, Faber, et al., 2014), and that the previously observed higher variability of MU firing rate with age is believed to cause higher force variability during low force isometric contractions (Hunter et al., 2016). One potential explanation is that age alters variability at the level of individual MUs but that the variations in firing behaviour from different MUs are not completely in-phase and therefore do not appreciably sum in the sEMG recording. However, we think that this might rather be related to the ability of our participant to self-select their movement speed. Indeed, Qin et al. (2014) constrained their occupational assembly work to a cycle frequency of 0.5 Hz, and Hunter et al (2016) based their MU discharge variability theory mainly on sustained isometric contractions. In fact, age and sex seemed to influence the fatigue-related changes in self-selected speed variability in our study; the increases in young adults and decreases in older adults could be partly attributable to a larger proportion of females in our older sample than our young sample. While inconclusive, the aging motor system may prioritize movement variability over muscle activation variability when adapting to N/S fatigue in self-selected speed movements, like those in activities of daily living. Activities of daily living, like drinking and feeding, are necessary to maintain independent living and tasks that mimic these activities have been recently used, with success, to objectively analyze differences in motion in both stroke and Parkinson's disease (Corona et al., 2018; Kim et al., 2014). Results from our study, however, suggest that the variations in muscle amplitudes selected by adults for reach-and-lift movements do not change with healthy aging.

The increase in activation variability with N/S fatigue agrees with several other studies of the upper extremity. After developing N/S fatigue, adults have been shown to increase their UT, AD, and supraspinatus activation variability during repetitive reaching while standing (Fedorowich et al., 2013; Srinivasan et al., 2016), and to increase their UT, LT, AD, and TRI

activation variability during seated pipetting (Samani et al., 2017). Srinivasan et al (2016) also measured variability using CV, reporting average increases of 20.1% in UT and 12.2% in AD; the amount of increased UT CV is between those observed at the reach (35.2%) and lift (6.1%) phases of the reach-and-lift task, and their increase in AD is slightly smaller, yet similar, to those seen at the reach (14.6%) and lift (26.2%) phases of our study. Therefore, increases in muscle activation variability, reasoned as the search for solutions to N/S fatigue (Côté, 2014), were similar in magnitude across constrained-speed and self-selected speed upper extremity movements in either standing or seated postures, occurring across several muscles, indicating that muscle activation variability is a robust EMG feature of adaptation to N/S fatigue in more than one type of low force tasks. However, the functional meaning of these precise N/S fatigue-induced increases (6.1-35.2%) is less clear and requires further study.

5.6.3 N/S fatigue effects on deltoid and trapezius-deltoid connectivity variability between self-selected speed movements

The fatigue-related increases in young adult AD-MD and older adult AD-PD connectivity variability and decreases in young adult MT-MD connectivity variability point towards different roles of connectivity variability within and between-muscles for adapting to N/S fatigue. Samani et al (2017) also studied connectivity variability patterns between upper extremity muscles, observing a similar decrease in connectivity variability between the trapezius and deltoid muscles in young adults performing a seated pipetting task. They interpreted this effect to be evidence of fatigue restraining the adopted motor control strategy. Our results partially agree; while fatigue also seemed to restrain the between-muscle connectivity patterns of young adults during the reach-and-lift task, this was not observed for older adults, and seemed to facilitate within-deltoid connectivity patterns in both young and older adults. Though preliminary, within-deltoid and trapezius-deltoid connectivity variabilities appear to respond differently to N/S fatigue, necessitating further studies into their functional significance.

5.6.4 Age-dependent effect of N/S fatigue on trapezius-deltoid connectivity in self-selected speed movement

Over the reach and lift phases of the reach-and-lift task, young adults responded to N/S fatigue by decreasing UT-deltoid connectivity and increasing LT-deltoid connectivity, while older adults responded in the opposite manner, pointing to age-dependent motor adaptations. The

magnitudes of these fatigue-induced changes and age differences in NMI are small in absolute (0.004-0.007) and relative (1-5%) size but statistically significant and similar to the differences reported between adults with and without chronic N/S pain (Madeleine et al., 2016). Thus, while older adults were able to perform the reach-and-lift task normally following N/S fatigue, their trapezius-deltoid connectivity patterns in self-selected speed reach and lift movements could be a potential pathway for developing N/S pain. Interestingly, the fatigue-induced changes in functional connectivity in different trapezius-deltoid muscle pairs do not fully agree with the uniform increases in between-muscle connectivity seen during repeated pipetting (Samani et al., 2017), an endurance task of isometric shoulder abduction (Kawczyński et al., 2015), and 90-min bouts of seated computer work (Farias Zuniga & Côté, 2017). These tasks are varied in that they cover dynamic, isometric, and combined (dynamic and isometric) contractions. Since measurements of muscle connectivity were made during the fatiguing tasks, unlike the pre-post measurements in our study, methodological differences may be partly responsible.

Nonetheless, the age effects on UT and LT activation are in line with the age-related fatigue effects on UT-deltoid and LT-deltoid connectivity, providing support for age-dependent adaptations in trapezius control during reach-and-lift movement. Our results suggest that there may be a cranial shift in the between-muscle connectivity and activation of the trapezius that occurs with age. Falla & Farina (2007) observed such a shift in activation during a variable force isometric contraction, but not during a constant force isometric contraction, meaning that higher force variability may cause a cranial shift in trapezius activity; as aging adults typically have higher force variability, likely due to possessing fewer MUs with more variable firing behaviour (Hunter et al., 2016), this may explain the age-related shift in trapezius control seen in this study. Another possibility is that this shift is a result of different N/S postures for young and older adults in the reach-and-lift task. Older adults have lower shoulder elevation, shoulder abduction, and trunk flexion during forward reaching at their self-selected speed (Chaffin, Faraway, Zhang, & Woolley, 2000; Chateauroux & Wang, 2008). With reduced movement at the shoulder and trunk, older adults may compensate with more movement of the scapula. A higher scapula elevation and anterior tilt would explain the age-related cranial shift in trapezius activation. Thus, future research should investigate the influence of force variability and scapula posture on trapezius control to better understand the source of the age influence.

Finally, an age-dependent connectivity strategy was not observed within subdivisions of the trapezius or deltoid muscles, showing that the within-muscle connectivity responses to N/S fatigue, in self-selected speed tasks, are not influenced by the aging process. Though Arjunan & Kumar (2015) found that connectivity within the biceps brachii is higher in older adults than young adults during a brief isometric contraction, this does not appear to carry over in dynamic movements such as the one used on our study. The increased connectivity within the deltoid in the reach phase of the reach-and-lift task matches several previous observations of within-muscle activation (Bingham, Arjunan, Jelfs, & Kumar, 2017; Farias Zuniga & Côté, 2017; Kawczyński et al., 2015; Madeleine et al., 2011; Samani et al., 2017). However, these observations contrast with the decrease in UT-MT connectivity in the lift phase of the reach-and-lift task, agreeing instead with the decreased connectivity reported by Fedorowich et al (2013). While the contrasting observation by Fedorowich et al (2013) was suggested to be due to reaching constraints in the horizontal plane (Samani et al., 2017), this constraint was not present in either the fatiguing task or the reach-and-lift task in the present study. Instead, constrained movement frequency may be responsible. Our study and that by Fedorowich et al (2013), for instance, induced fatigue during repetitive reaching according to a metronome, while other studies induced fatigue without tightly restricting movement frequency (Bingham et al., 2017; Farias Zuniga & Côté, 2017; Kawczyński et al., 2015; Madeleine et al., 2011; Samani et al., 2017). Thus, it is possible that constraints on movement frequency during the fatiguing task may influence the changes in connectivity within the trapezius.

5.6.5 Limitations

Our results are limited to repetitive motion-induced fatigue and aging effects on the muscle patterns of seated, self-selected speed, reach-and-lift movement. The age effect was based on an older adult group with a mean age of 73.9 y, mainly consisting of females. While we covaried for the influence of sex, muscle patterns depend on both age and sex (Bailey, Corona, Pilloni, et al., 2018; Bailey, Porta, et al., 2019; Fedorowich et al., 2013; Srinivasan et al., 2016). Subsequent investigations are needed to rigorously assess how these demographic factors interact to affect N/S muscle patterns. Our results are also limited by sample size and include a brief recovery during transition from the fatiguing task to the post-fatigue reach-and-lift task. Finally, the precise meaning behind specific age and fatigue-related differences in CV and NMI magnitudes remains unclear for functional upper limb movement; this was the first investigation to study how the

combination of age and fatigue alter the variability and connectivity patterns within the N/S musculature. Thus, further studies of motor adaptation are needed to better understand 1) how personal factors affect the individual's response to fatigue and 2) the functional meaning of specific changes in variability and connectivity magnitude.

5.7 Conclusions

In summary, we found age-independent and age-dependent adaptations in muscle patterns in a reach-and-lift task following N/S fatigue. Age did not alter the fatigue-induced increases in muscle activation variability and changes in within-deltoid and within-trapezius connectivity, yet age generally increased UT activation and UT-deltoid connectivity while decreasing LT activation and LT-deltoid connectivity. Thus, there appears to be age-dependent control of the scapula in reach-and-lift movements.

5.8 Declarations

5.8.1 Ethics approval and consent to participate

All participants provided informed consent to participate in the study. The study followed the Declaration of Helsinki and received ethics approval by the institutional research ethics board.

5.8.2 Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

5.8.3 Competing interests

The authors declare that they have no competing interests.

5.9 Manuscript References

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Chapter 6. Muscle activation variability, oxygenation, and thickness: Changes with dynamic low-load elbow flexion fatigue and relationships in young and old females

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6.1 Preface

Although Chapter 5 did not find an age effect on the muscle activation variability response to repetitive motion-induced fatigue in the upper limb, Chapter 5 confirmed that this gradually developing fatigue increases upper limb muscle activation variability in both young and old adults. The origin of this motor variability response to fatigue, however, is unclear. Chapter 2 identified the perfusion of oxygen into muscle as a potential regulating feature of central neural output, but the relationships between such physiological parameters of the muscle (i.e. muscle oxygenation, muscle thickness) and motor variability had not been evaluated experimentally. Muscle oxygenation and thickness measurements are highly sensitive to movement, necessitating the use of a single joint, intermittent task to model physiological and biomechanical responses to experimental fatigue in the upper limb. Therefore, Chapter 6 evaluated these responses in a repetitive and intermittent elbow flexion task. The main objectives of Chapter 6 were to determine the effects and interactions of old age and fatigue on muscle activation variability, muscle oxygenation, and muscle thickness in an elbow dominant task, as well as evaluate the relationships between the observed muscle activation variability and muscle oxygenation and thickness patterns.

In Chapter 6, surface electromyography data were acquired from elbow flexors and the anterior deltoid to measure muscle activity, near-infrared spectroscopy data was acquired from the biceps brachii to measure muscle oxygenation, and brightness-mode ultrasonography images were taken for the biceps brachii and brachialis to measure muscle thickness. Muscle activation variability was quantified as the repetition-to-repetition coefficient of variation.

Sections 6.2 to 6.9 are a copy of the manuscript in preparation for the *Journal of Electromyography and Kinesiology*.

6.2 Abstract

The purposes of the study were to determine, in females, the effect of old age on muscle activation variability and perfusion responses to dynamic elbow flexion fatigue, and to determine the relationships between the muscular responses and fatigability.

Fifteen young (23.3 ± 3.1 years) and ten old (62.8 ± 6.9 years) females completed a fatiguing elbow flexion task. Muscle activation variability (CV), oxygenation, and thickness

(MTH) were quantified using electromyography, near-infrared spectroscopy, and B-mode ultrasonography. Age*Time and Spearman ρ analyses were conducted.

There was no Age effect on fatigability ($p = 0.89$) or Age*Time effects on muscular measures ($p > 0.05$). With Time, there were decreases in biceps brachii ($p = 0.043$) and brachialis CV ($p = 0.005$), biceps brachii HbO_2 increased 0.9 μM ($p = 0.011$) following an initial drop of 2.6 μM ($p = 0.011$), and biceps brachii and brachialis MTH increased ($p < 0.001$). Higher initial biceps brachii CV was related to higher fatigability in young females ($\rho = -0.54$, $p = 0.038$) and higher initial brachialis CV was related to less blunted oxygenation in both age groups ($p = 0.021$). Finally, changes in oxygenation were related to altered anterior deltoid CV in young females and altered elbow flexor CV in old females.

Age did not affect fatigability or fatigue-induced changes in muscle activation variability or hemodynamics in females. However, correlations provided evidence for a link between motor variability and muscle perfusion that is more local to the site of fatigue with old age.

6.3 Introduction

Old age is a natural process associated with alterations in performance fatigability that are mainly attributed to neuromuscular adaptations (Hunter et al., 2016). At relative loads and compared to young adults, old adults are generally reported to be less fatigable in isometric tasks and more fatigable in fast dynamic tasks (Hunter et al., 2016). However, the factors responsible for these differences are not fully known.

One age-related neuromuscular adaptation that may relate to these factors is higher variability in motor unit discharge rate (Laidlaw et al., 2000). This higher variability in old adults has been shown to explain a large amount of variance in force output (Negro et al., 2009). Christou (2011) argues that more variable motor unit discharge could be responsible for lower steadiness of motor output in older age. In turn, low steadiness could reflect alterations in mechanisms of motor variability, i.e. the natural variability in repeated sensorimotor actions (Newell & Slifkin, 1998). Higher muscle activation variability with old age has been observed during gait and during repetitive forward tapping (Bailey et al., 2019; unpublished observation), but not during repeated reach-and-lift trials (Bailey, Weiss, & Côté, 2020). Interestingly, Fedorowich et al. (2013) found that, during the first minute of repetitive forward pointing, young females with higher upper trapezius and supraspinatus activation variability had higher task endurance (i.e. lower fatigability).

Since these muscles acted as shoulder stabilizers during this task, and previous research shows that old adults are fatigue-resistant when performing isometric contractions (Hunter et al., 2016), one could hypothesize that differences in fatigability between young and old adults may be related to their initial muscle activation variability.

Muscle activation variability also changes as a function of muscle fatigue, defined as the acute decrease in functional capacity associated with increased perceived difficulty (Enoka & Stuart, 1992). Studies on muscle fatigue from low-load upper extremity work report increased muscle activation variability magnitude in young adults (Fedorowich et al., 2013; Samani et al., 2017; Srinivasan et al., 2016), which can be interpreted as the voluntary search for new motor patterns to maintain task performance (Côté, 2014). We previously also observed increased muscle activation variability in older adults following repetitive motion-induced fatigue from repetitive forward reaching but found no age difference in the magnitude of observed change (Bailey, Weiss, et al., 2020; unpublished observation). These observations suggest that upper extremity muscle recruitment behaviour changes with muscle fatigue regardless of age, although the underlying mechanisms are unclear.

As there is a theorized link between oxygenation and central motor output (Amann et al., 2006), the magnitude of muscle activation variability seen initially with exercise and the change occurring with muscle fatigue may be related to how oxygen perfuses the muscle. Investigations of low-load upper extremity exercise have reported initial drops followed by a plateau or increase in oxygen saturation with muscle fatigue, indicated by tissue oxygen index (TOI) (Baudry et al., 2013; Ferguson et al., 2013; Murthy et al., 1997), and an initial decrease in total hemoglobin (THb) followed by an increase in muscle fatigue (Baudry et al., 2013; Murthy et al., 1997). The potential increase in muscle blood volume with fatigue, in addition to exercise-induced edema (Jensen et al., 1994), likely both contribute to the muscle swelling (increased muscle thickness) reported following low-load fatiguing efforts (Jensen et al., 1994; Yasuda et al., 2015). Further, old age seems to also independently influence muscle oxygenation, as Kutsuzawa et al. (2001) showed that forearm oxygen supply is slowed in old compared to young adults during low-load repeated hand gripping, and Costes et al. (1999) reported a systematically lower vastus lateralis oxygen saturation in old than young adults, but similar oxygen desaturation responses relative to oxidative capacity with incremental cycling fatigue. It remains unclear if muscle deoxygenation and swelling during fatiguing exercise are exacerbated with old age.

In sum, old age and muscle fatigue appear to affect muscle activation variability, oxygenation, and thickness in the upper extremity. To our knowledge, it is unknown whether muscle activation variability is related to the initial or fatigue-induced muscle oxygenation or thickness responses, or whether these muscular responses are associated with upper extremity fatigability in young or old adults. In addition, most studies on this topic have investigated the effects of old age only in males or did not use statistical models to identify sex-specific effects. Given the literature showing sex differences in fatigue mechanisms (Côté, 2014; Hunter, 2016), we cannot assume that results thus far apply to aging women. Thus, our objectives were to determine, as a function of old age,

1. how muscle fatigue affects muscle activity variability, oxygenation, and thickness. *Hypothesis: Old age in females will not affect the fatigue-induced changes in muscle activation variability, oxygenation, nor thickness.*
2. how fatigability is associated with the muscular responses to initial exercise and to muscle fatigue. *Hypothesis: Lower fatigability will be associated with higher initial muscle activation variability in both young and old females.*
3. how initial muscle activation variability is associated with exercise-induced changes in muscle oxygenation and thickness. *Hypothesis: Higher initial variability will be associated with less muscle deoxygenation and swelling.*
4. how fatigue-induced change in muscle activation variability is associated with fatigue-induced changes in muscle oxygenation and thickness. *Hypothesis: A larger change in variability would be associated with less muscle deoxygenation and swelling.*

6.4 Methods

6.4.1 Participants

Fifteen young adult females (mean age: 23.3 ± 3.1 years, age range: 19.3-30.5 years) and ten old females (mean age: 62.8 ± 6.9 years, age range: 55.5-76.6 years) were recruited from McGill University and the Montreal community. Participants were included if they were non-smokers, had no previous or current musculoskeletal disorders or pain in the neck and upper limbs, and had no diagnosed vascular or neurological medical condition. Participants were excluded if they consumed alcohol or exercised < 24 hours prior to their visit, however, all participants cleared

these criteria and provided their informed consent. The study followed the Declaration of Helsinki and was approved by the institutional research ethics board.

6.4.2 Instrumentation

6.4.2.1 Elbow flexion torque. Elbow flexion torque was measured using an isokinetic dynamometer (CON-TREX MJ, Physiomed Elektromedizin AG, Schnaittach, Germany). Participants sat upright on the chair of the dynamometer; at rest, their dominant upper limb was fully supported such that the hand gripped a handle in a neutral, semi-pronated wrist posture, the elbow was flexed 90° (0° = full extension), and the arm was abducted 15°. The axis of the dynamometer motor was aligned with the center of rotation of the elbow. Torques were sampled at 2000 Hz using third party motion capture software (Nexus 2.8, Vicon, Oxford, UK).

6.4.2.2 Muscle activity. Surface electromyography (EMG) sensors (Trigno Avanti, Delsys Inc, Natick, MA, USA) were positioned on six locations of the participant's dominant upper limb by the same experimenter (C.A.B.) according to SENIAM guidelines for skin preparation, sensor placement, and sensor location (Hermens et al., 2000). Briefly, the skin of each location was shaved and lightly abraded with alcohol and then EMG sensors containing double-differential Ag bar electrodes (inter-electrode distance = 10 mm) were positioned on the skin surface and oriented parallel to the muscle fibers. Sensors were positioned on the biceps brachii (BB) short head, BB long head, medial aspect of the brachialis (BRA), lateral aspect of BRA, brachioradialis (BRR), and anterior deltoid (AD) (see Table 6.1 for specific locations). EMG data were digitally sampled at 2000 Hz with a common-mode rejection ratio of 80 dB and synchronized with torque data acquisition using the motion capture software.

Table 6.1. Electrode locations and maximal voluntary isometric contraction (MVIC) postures for each muscle.

Muscle	Electrode location	MVIC posture
Biceps brachii short head	One fingerbreadth medial to the line between the acromion and cubital fossa, 1/3 proximal from the cubital fossa (Hermens et al., 2000)	Seated on chair of dynamometer, hand gripping handle, wrist semi-pronated, elbow flexed 90° in the sagittal plane, arm
Biceps brachii long head	One fingerbreadth lateral to the line between the acromion and cubital fossa, 1/3 proximal from the cubital fossa (Hermens et al., 2000)	

Brachialis medial aspect	Distal arm where the muscle becomes superficial (Staudenmann & Taube, 2015), two fingerbreadths medial to the line between the acromion and cubital fossa	abducted 15° in the frontal plane
Brachialis lateral aspect	Distal arm where the muscle becomes superficial (Staudenmann & Taube, 2015), two fingerbreadths lateral to the line between the acromion and cubital fossa	
Brachioradialis	Proximal forearm where the muscle becomes superficial (Staudenmann & Taube, 2015), two fingerbreadths from the cubital fossa	
Anterior deltoid	One fingerbreadth distal and anterior to the acromion process	Seated, holding the arm straight with the shoulder flexed 90° in the sagittal plane, hand flat

6.4.2.3 Muscle thickness. B-mode ultrasonography (Logiq S7, GE Healthcare, Chicago, IL, USA) was conducted to measure muscle thickness. Images were taken with an ultrasound probe (8 MHz, 38 mm scanning length) positioned on the distal arm immediately proximal to the elbow crease (Hodges, Pengel, Herbert, & Gandevia, 2003; Rudroff et al., 2008) while the participant was resting on the seat of the dynamometer with their arm supported, elbow flexed 90°, and forearm supinated. Images were stored for offline analysis.

6.4.2.4 Muscle oxygenation. A frequency-resolved near-infrared spectroscopy (NIRS) optode (OxiplexTS, ISS Inc., Champaign, IL, USA) was positioned over the center of BB (i.e. between the EMG sensors), one third proximally from the cubital fossa on the line between it and the acromion process, then covered with two layers of opaque black cloth to prevent exterior light intrusion. The optode contained four pairs of infrared light emitters (wavelengths of 690 nm and 830 nm) separated from one infrared light detector by 2.75 cm on average, giving an average measurement depth of 1.38 cm. Inspection of arm ultrasound images revealed that all participant

subcutaneous tissue thicknesses were less than the NIRS measurement depth, and so we assume that measurements reflect the oxygenation of the BB muscle tissue. While hemoglobin and myoglobin levels are not separated by NIRS, hemoglobin levels contribute to ~90% of the NIRS signal (Ferrari et al., 2004). Thus, oxygenation parameters derived from the frequency-resolved method included the concentrations of THb, oxygenated hemoglobin (HbO_2) and deoxygenated hemoglobin (HHb), as well as the TOI that reflects the ratio of HbO2 to THb (Ferrari et al., 2004). These parameters were sampled at 50 Hz and averaged online over 500 ms epochs.

6.4.3 Procedure

Figure 6.1 represents a schematic of the experimental and data acquisition procedures which encompassed three phases: normalization, familiarization, and the fatigue task.

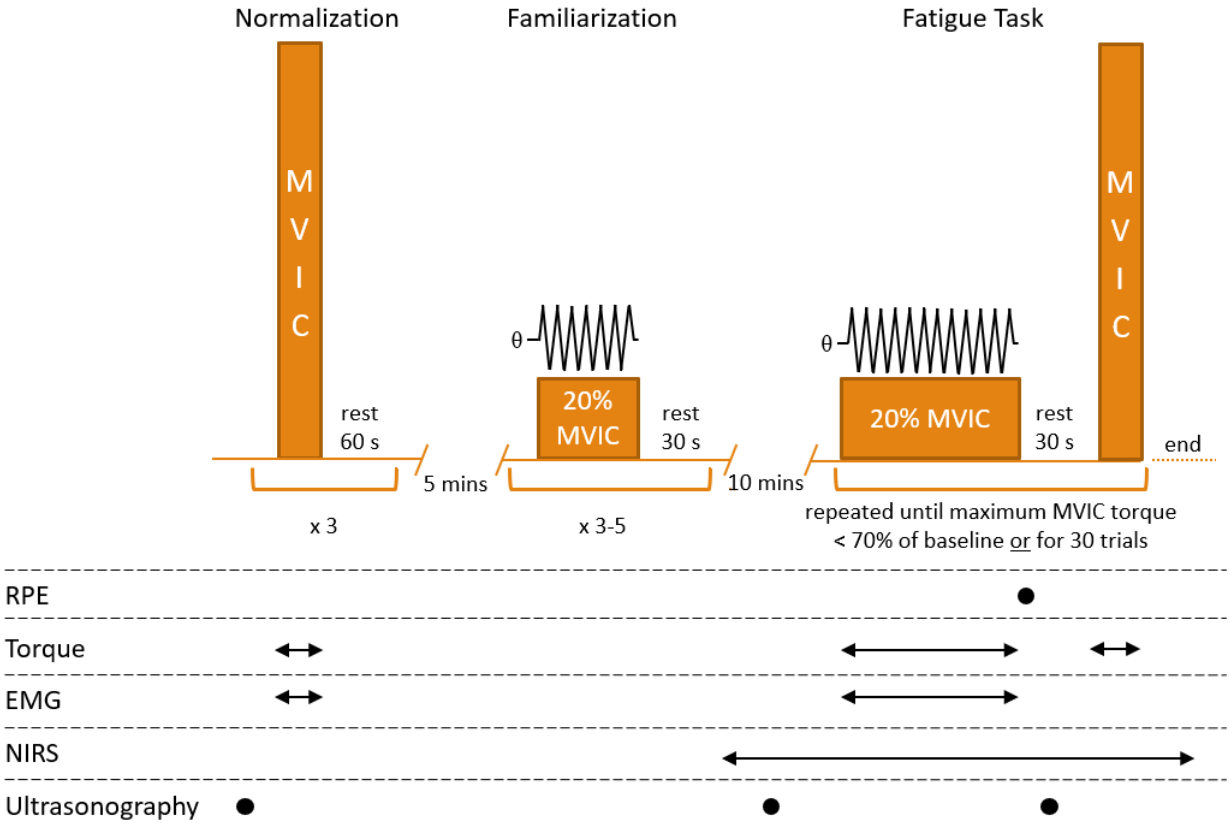

Figure 6.1. Schematic of the experimental and data acquisition procedures. Normalization: Maximal voluntary isometric contractions (MVIC) were held for five seconds. Three were performed for elbow flexion and another three for shoulder flexion, each with at least 60 seconds between efforts. Familiarization: Submaximal dynamic concentric/eccentric elbow flexions were practiced for 30 seconds at 20% of maximum elbow flexion MVIC torque, at 60°/s, and over an angle (θ) range of 60-120°. Three to five practice bouts were performed with at least 30 seconds between efforts. Fatigue task: Trials consisted of submaximal

dynamic concentric/eccentric elbow flexions for 60 seconds, followed by 30 seconds of rest and then a five-second elbow flexion MVIC. Trials were repeated until MVIC torque < 70% of maximum elbow flexion MVIC torque or 30 trials were completed. Data acquisition: Instances of discrete (dot) and continuous (arrow) data collection are identified for rating of perceived exertion (RPE), torque, electromyography (EMG), near-infrared spectroscopy (NIRS), and B-mode ultrasonography.

6.4.3.1 Normalization. Following informed consent and instrumentation, three pre-normalization ultrasound images were acquired and then the participant completed maximal voluntary isometric contractions (MVICs) to normalize their fatigue task load. The participant sat on the seat of the isokinetic dynamometer with their arm in the rest position and completed three elbow flexion MVICs (description of posture in Table 6.1). Each MVIC included a three second ramp-up from rest to maximum effort, a three second maximum effort, and finally a three second ramp down to rest. Three MVIC trials were completed with 60 s of rest between efforts, and the maximum MVIC torque ($MVIC_{max}$) was retained to normalize the fatigue task load. Shoulder flexion MVICs were also performed using the dynamometer (posture in Table 6.1). EMG was sampled during elbow and shoulder flexion MVICs to later normalize elbow flexor and anterior deltoid muscle activities, respectively. Following MVIC trials, the participant rested for five minutes before familiarization with the fatigue task.

6.4.3.2 Familiarization. The participant performed several 30-second practice bouts of precise low-load dynamic elbow flexions with the dynamometer. Each repetition required concentric followed by eccentric elbow flexion between 60° and 120°, moving at a velocity of 60°/s and maintaining a target torque equal to 20% of $MVIC_{max}$. The participant received real-time visual feedback about their torque output on a computer screen, displayed as a window equal to 20 ± 5% of $MVIC_{max}$. Following a demonstration by the experimenter, the participant practiced only the concentric contractions (Bout 1), then only the eccentric contractions (Bout 2), then both concentric and eccentric efforts (Bout 3). The participant rested 30 seconds between practice bouts and practiced until mean torque output was between 15% and 25% of $MVIC_{max}$, which was achieved by all participants within five bouts. Following familiarization, the participant underwent final instrumentation for NIRS (lasting about five minutes) and then rested for 10 minutes. NIRS data were continuously sampled during rest and post-familiarization ultrasound images were acquired mid-way through rest.

6.4.3.3 Fatigue task. The fatigue task required repeated trials of dynamic elbow flexions using the dynamometer. Each trial had three parts: a 60 second work bout of 60°/s concentric/eccentric repetitions from 60-120° elbow flexion with a target torque of 20% $MVIC_{max}$, a 30 second rest period, and an elbow flexion MVIC. Immediately following the work bout, the participant reported their rating of perceived exertion (RPE) in the arm region using the Borg CR-10 scale (G. A. Borg, 1982). The participant repeated trials until MVIC torque < 70% $MVIC_{max}$, matching the ~ 30% decline in $MVIC_{max}$ reported in a prior dynamic fatiguing task (Dalton et al., 2015) or they completed their 30^{th} trial. Participants were unaware of these stoppage criteria. Torque and EMG data were sampled during work bouts, NIRS data were continuously sampled, and ultrasound images were acquired during rest periods.

6.4.4 Data Analyses

Motor variability was quantified by the repetition-to-repetition variability of torque and muscle activity during the first and final trials of the fatigue task. For each participant, concentric and eccentric phases of repetitions were partitioned according to peaks of the dynamometer angle signal and the mean torque of each concentric repetition was calculated. The coefficient of variation of the middle ten mean torque values (Torque CV) was determined to quantify torque variability. EMG data were bandpass filtered with a dual pass Butterworth filter (10-450 Hz, fourth order), smoothed using a root mean square moving average (100-ms windows overlapping by 1 ms), normalized to the maximum root mean square value recorded during the corresponding MVICs, then partitioned into the concentric and eccentric phases. Root mean square magnitude of each concentric repetition was calculated and the coefficient of variation of the middle ten values (EMG CV) was determined to quantify muscle activation variability. Upon inspection of muscles with two EMG sensors (BB and BRA), there were no significant differences in EMG CV between sensors and so these values were averaged to give one value per muscle.

BB and BRA muscle thicknesses (MTH) were measured 5 cm proximal to the distal edge of the ultrasound image as the vertical distance between the echogenic fascial layers (Hodges et al., 2003). Test-retest reliability, quantified using intraclass correlation coefficients, was excellent for both pre-normalization MTHs (BB: 0.98, BRA: 0.98) and post-familiarization MTHs (BB: 0.99, BRA: 0.96), with no significant difference between these conditions. Therefore, Baseline

MTHs were calculated as the means of the three pre-normalization measurements, and MTHs were calculated from images taken immediately following the first and final trials.

BB muscle oxygenation parameters (THb, HbO_2, HHb, TOI) were low-pass filtered offline using a 1 Hz, fourth order Butterworth filter. Mean values were calculated for the first five minutes following familiarization to identify baseline oxygenation and for the final 30 seconds of the first and final work bouts.

The final dataset obtained for statistical analysis of the fatigue task included participant characteristics, the # of trials completed, RPE and Torque CV at two times (First, Final), EMG CV of four muscles (BB, BRA, BRR, AD) at two times (First, Final), MTH of two muscles (BB, BRA) at three times (Baseline, First, Final), and oxygenation parameters at three times (Baseline, First, Final).

6.4.5 Statistical Analyses

Independent t-tests were conducted to test for Age effects (young females, old females) on height, mass, BMI, $MVIC_{max}$, and # of trials. Non-parametric tests (Mann-Whitney U) were used if data were not normally distributed. General estimating equations were computed to test for main effects and interactions of Age and Time (Baseline where applicable, First, Final) on RPE, Torque CV, EMG CV, MTH, and oxygenation parameters (THb, HbO_2, HHb, TOI). Muscle was also modeled as a within-group fixed factor for EMG CV and MTH. Standardized effect sizes (Cohen's d) were computed for pairwise comparisons and values of 0.20-0.59, 0.60-1.19, and ≥ 1.20 were interpreted as small, medium, and large effect sizes respectively (Rice & Harris, 2005). Finally, Spearman's ρ correlation analyses were conducted separately for young females and old females to test for age-specific relationships among three sets of measures comparing initial values (First Trial), initial responses (Baseline → First Trial), and fatigue-induced responses (First → Final Trial):

1) Fatigability (# of trials) with initial muscle activation variability and fatigue-induced muscle thickness and oxygenation responses.
2) Initial muscle activation variability with the initial and fatigue-induced muscle thickness and oxygenation responses.
3) Fatigue-induced muscle activation variability response with the fatigue-induced muscle thickness and oxygenation responses.

Statistical significance for all analyses was set at $p < 0.05$.

6.5 Results

6.5.1 Group characteristics

Table 6.2 summarizes characteristics of the young and old female groups. Young females were taller ($z = 2.08$, $p = 0.036$, $d = 1.40$) and had higher MVIC torque ($t = 2.77$, $p = 0.011$, $d = 1.13$) than old females, but did not differ in mass ($t = 0.30$, $p = 0.76$, $d = 0.12$), BMI ($t = 1.26$, $p = 0.23$, $d = 0.54$), or # of trials to fatigue ($z = 0.14$, $p = 0.89$, $d = 0.14$). Range in # of trials was high, from 4-30 trials in young females and from 4-27 trials in old females. Task termination in 24 of 25 participants was determined by reaching MVIC < 70% $MVIC_{max}$; the one young female who completed all 30 trials reached a MVIC of 78.6% $MVIC_{max}$.

Table 6.2. Characteristics of the young and old female groups and p-values for Age differences. Means (SD) are reported for normally distributed characteristics (mass, BMI, MVIC torque) and medians (SD) are reported for non-normally distributed characteristics (height, # of trials). Significant p-values ($p < 0.05$) are bolded.

Characteristic	Young females (n = 15)	Old females (n = 10)	Age p-value
Height (m)	1.67 (0.07)	1.59 (0.04)	**0.036**
Mass (kg)	65.4 (8.7)	66.7 (13.0)	0.76
BMI ($kg*m^{-2}$)	23.5 (2.8)	25.7 (5.0)	0.23
MVIC torque (Nm)	45.3 (6.6)	37.7 (6.9)	**0.011**
# of trials completed	7 (8)	8 (6)	0.89

6.5.2 Age and Fatigue effects on perceived exertion and muscle parameters

6.5.2.1 Perceived exertion. There was significantly increased RPE during the fatigue task in both young and old females (Time effect: $\chi_1^2 = 64.69$, $p < .001$). For both age groups, RPE increased on the Borg CR-10 scale by 4 points ($d = 1.6$, $CI_{95\%}$: 3-5). Young females also reported significantly higher RPE scores (Age effect: $\chi_1^2 = 4.89$, $p = .027$), with a mean difference of 1 point ($d = 0.62$, $CI_{95\%}$: 0-2). RPE scores after the Final Trial corresponded to “very hard” on average in young females (mean: 7; $CI_{95\%}$: 6-8) and to “hard” on average in old females (mean: 5; $CI_{95\%}$: 4-7).

6.5.2.2 Muscle activation variability. There was a significant Time*Muscle effect on EMG CV (χ^2_3 = 8.76, p = .033), where, for young and old females, BB CV and BRA CV decreased from the First to the Final Trial by 3.1% (p = 0.043, d = 0.40, $CI_{95\%}$: 0.1-6.1%) and 4.8% (p = 0.005, d = 0.56, $CI_{95\%}$: 1.4-8.1%) respectively (Figure 6.2). There were no significant Age-based effects on EMG CV (p > 0.05).

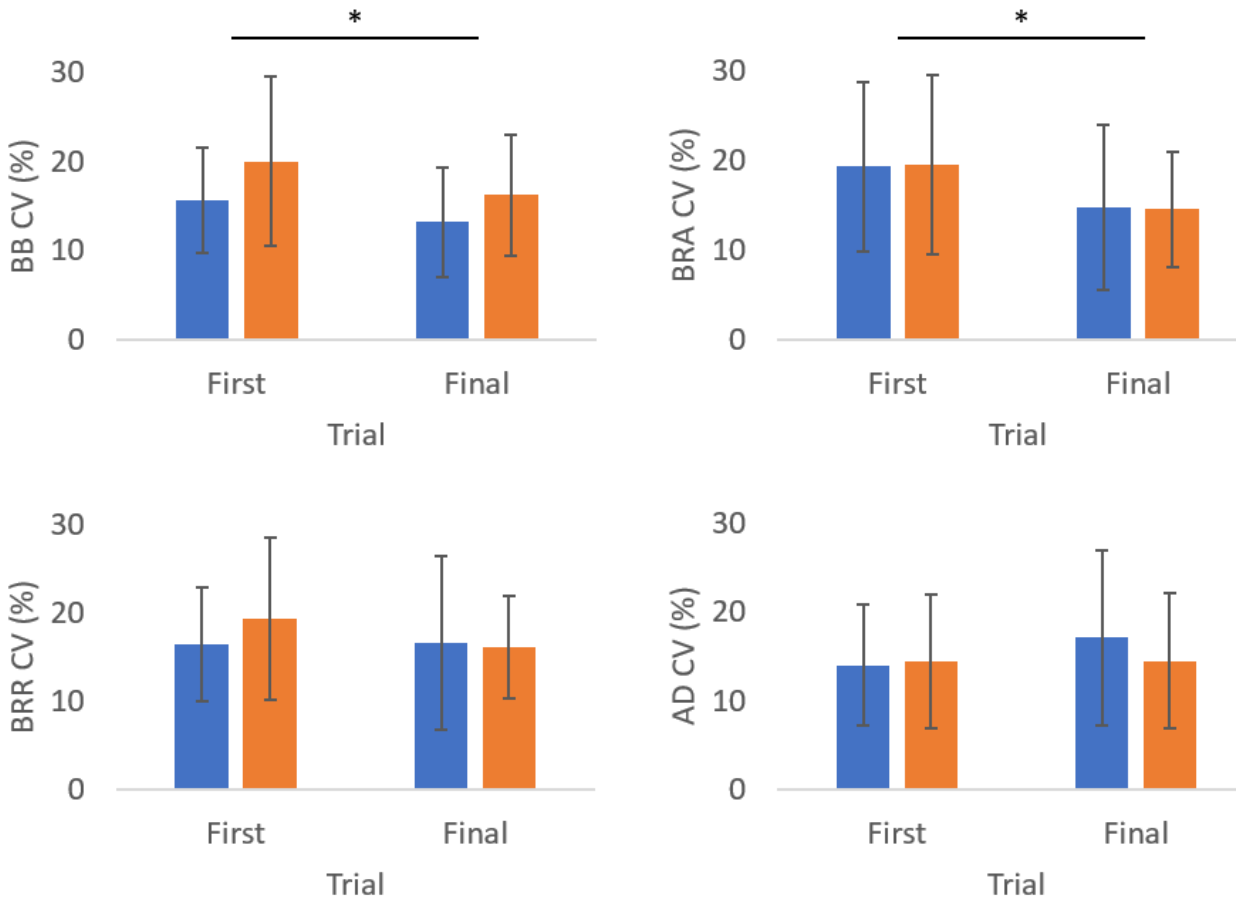

Figure 6.2. Repetition-to-repetition variability of muscle activity during the first and final exercise bouts of the fatigue task in young (blue) and old females (orange). Variability in biceps brachii (BB CV, top left), brachialis (BRA CV, top right), brachioradialis (BRR CV, bottom left), and anterior deltoid activity (AD CV, bottom right) are displayed. * indicates a significant main time effect (p < 0.05).

6.5.2.3 Torque variability. There were no significant Time, Age, or interaction effects on Torque CV (p > 0.05).

6.5.2.4 Muscle oxygenation. There were significant effects of Time on TOI (χ^2_2 = 7.97, p = 0.019) and HbO_2 (χ^2_2 = 12.00, p = 0.002) (Figure 6.3). Pairwise comparisons revealed that, for

young and old females, TOI decreased Baseline→First by 2.0% (p = 0.027, d = 0.52, $CI_{95\%}$: 0.2-3.8) and absolute HbO_2 decreased Baseline→First by 2.6 μM (p = 0.011, d = 0.57, $CI_{95\%}$: 0.5-4.7 μM) then increased First→Final by 0.9 μM (p = 0.011, d = 0.58, $CI_{95\%}$: 0.2-1.7 μM). There were also significant effects of Age on THb (χ_1^2 = 7.01, d = 0.63, p = 0.008), HbO_2 (χ_1^2 = 6.34, d = 0.61, p = 0.012), and HHb (χ_1^2 = 6.10, d = 0.58, p = 0.014), where young females had larger hemoglobin concentrations than old females. However, there were no interactions between Time and Age on any oxygenation measures.

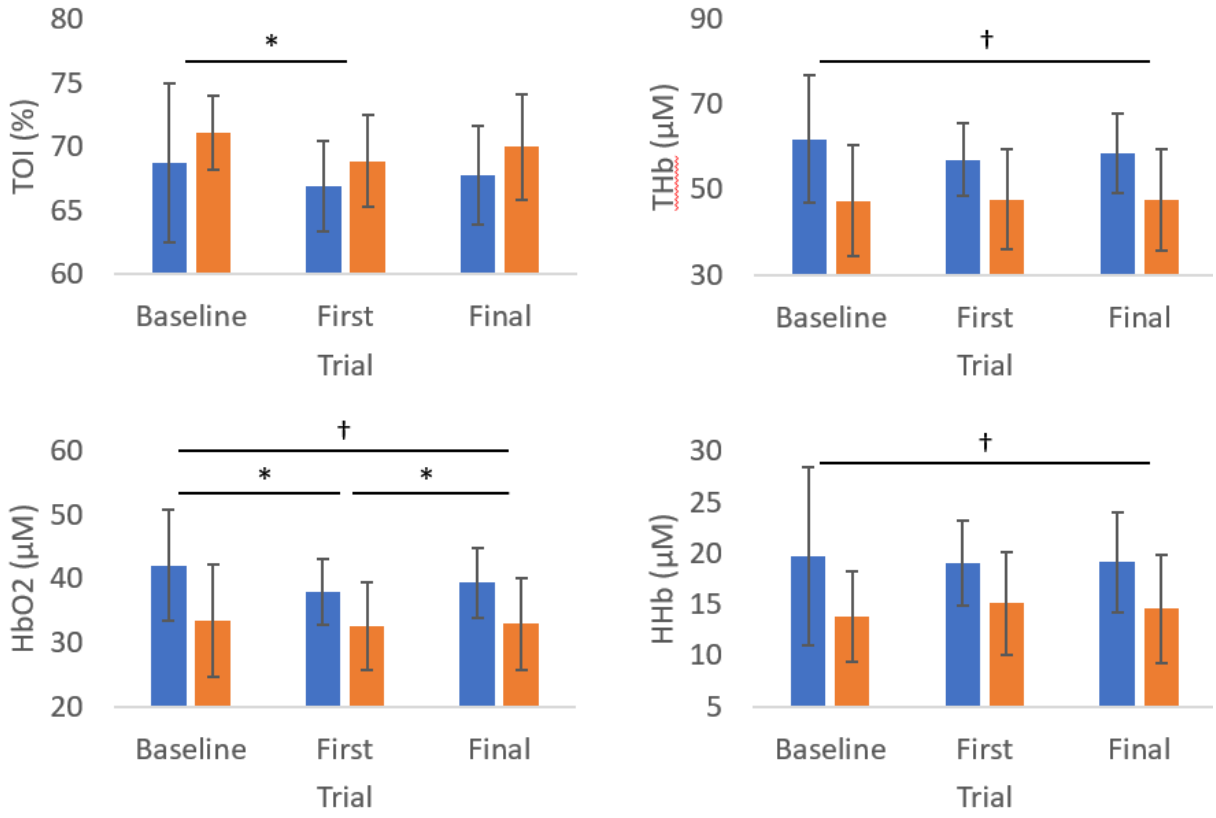

Figure 6.3. Biceps brachii muscle oxygenation at baseline and during the first and final exercise bouts of the fatigue task in young (blue) and old females (orange). Oxygen saturation (TOI, top left), total hemoglobin concentration (THb, top right), oxygenated hemoglobin concentration (HbO_2, bottom left), and deoxygenated hemoglobin concentration (HHb, bottom right) are displayed. * indicates a significant main Time effect and † indicates a significant main Age effect (p < 0.05).

6.5.2.5 Muscle swelling. There was a significant Time*Muscle interaction on MTH (χ_2^2 = 9.87, p = 0.007) where, for young and old females, BRA MTH increased First→Final by 0.12 cm (p < 0.001, d = 1.45, $CI_{95\%}$: 0.09-0.16 cm) and BB MTH increased First→Final by 0.06 cm (p <

0.001, d = 0.57, $CI_{95\%}$: 0.01-0.10 cm) (Figure 6.4). Expressed relative to baseline values, average MTH increases were 4.3% for BRA and 7.4% for BB. There were no significant Age-based effects on MTH ($p > 0.05$).

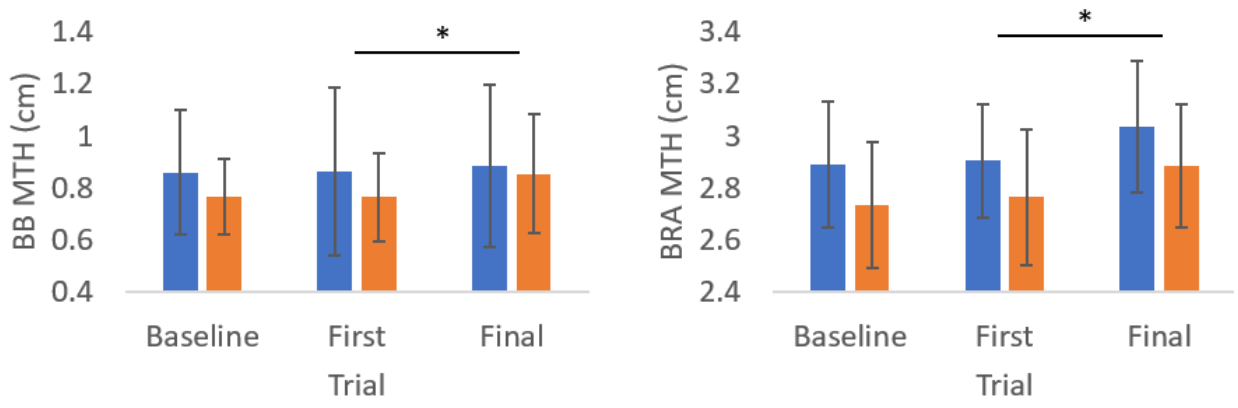

Figure 6.4. Muscle thickness at baseline and after the first and final exercise bouts of the fatigue task in young (blue) and old females (orange). Muscle thickness of biceps brachii (BB MTH, left) and brachialis (BRA MTH, right) are displayed. * indicates a significant main Time effect ($p < 0.05$).

6.5.3 Relationships between fatigability and muscle parameters

In young females, a higher # of trials was related to lower initial BB CV ($\rho = -0.54$, $p = 0.038$) and in old females, a higher # of trials was related to a larger fatigue-induced increase in THb ($\rho = 0.64$, $p = 0.047$).

6.5.4 Relationships between muscle activation variability, oxygenation, and thickness

Correlation results are summarized in Supplemental Tables 6.1 and 6.2. Few correlations were seen with initial muscle activation variability in either young or old females. In young females, higher initial BRA CV was related to having a smaller initial decrease in TOI ($\rho = 0.59$, $p = 0.021$), and higher initial AD CV was related to having a smaller fatigue-induced increase in HHb ($\rho = -0.53$, $p = 0.049$). In old females, higher initial BRA CV was related to having a smaller fatigue-induced increase in THb ($\rho = -0.68$, $p = 0.032$).

Correlations with fatigue-induced changes in muscle activation variability were found in the AD of young females (Figure 6.5) and in the elbow flexors of old females (Figure 6.6). For young females, larger increases in AD CV were related to having larger increases in THb ($\rho = 0.69$,

p = 0.007) and HHb (ρ = 0.59, p = 0.026). For old females, larger decreases in BB CV and BRA CV were related to having larger increases in HbO_2 (ρ = -0.67, p = 0.033) and having larger decreases in THb (ρ = 0.73, p = 0.019), respectively. Smaller increases in BRA MTH (i.e. less BRA swelling) was related to having greater decreases in BB CV (ρ = 0.70, p = 0.026) and BRR CV (ρ = 0.68, p = 0.032).

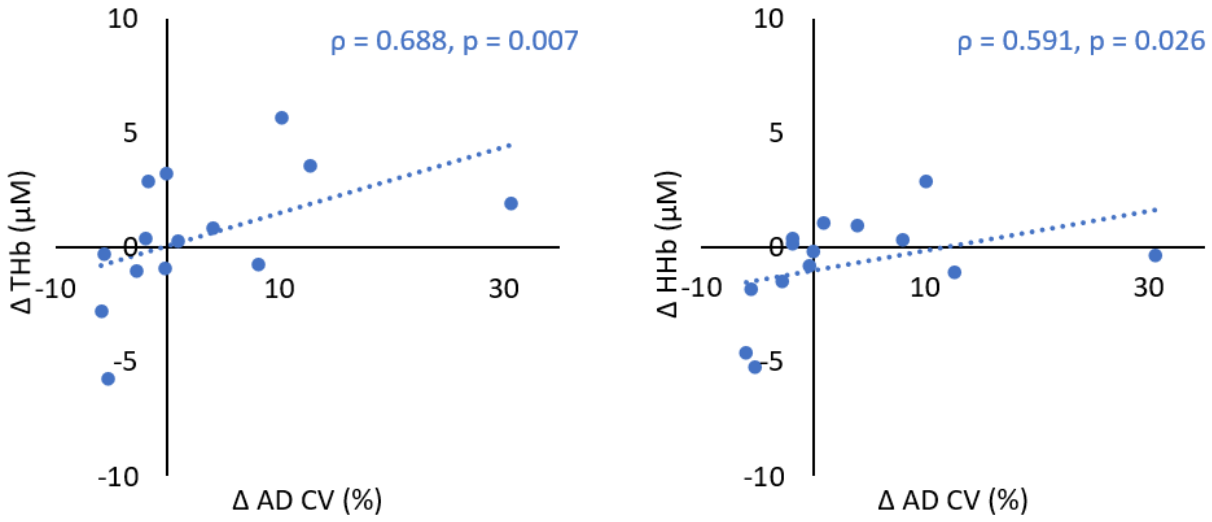

Figure 6.5. Relationships in young females between fatigue-induced changes in anterior deltoid activation variability (Δ AD CV) and changes in total hemoglobin concentration (ΔTHb, left) and in deoxygenated hemoglobin concentration (ΔHHb, right).

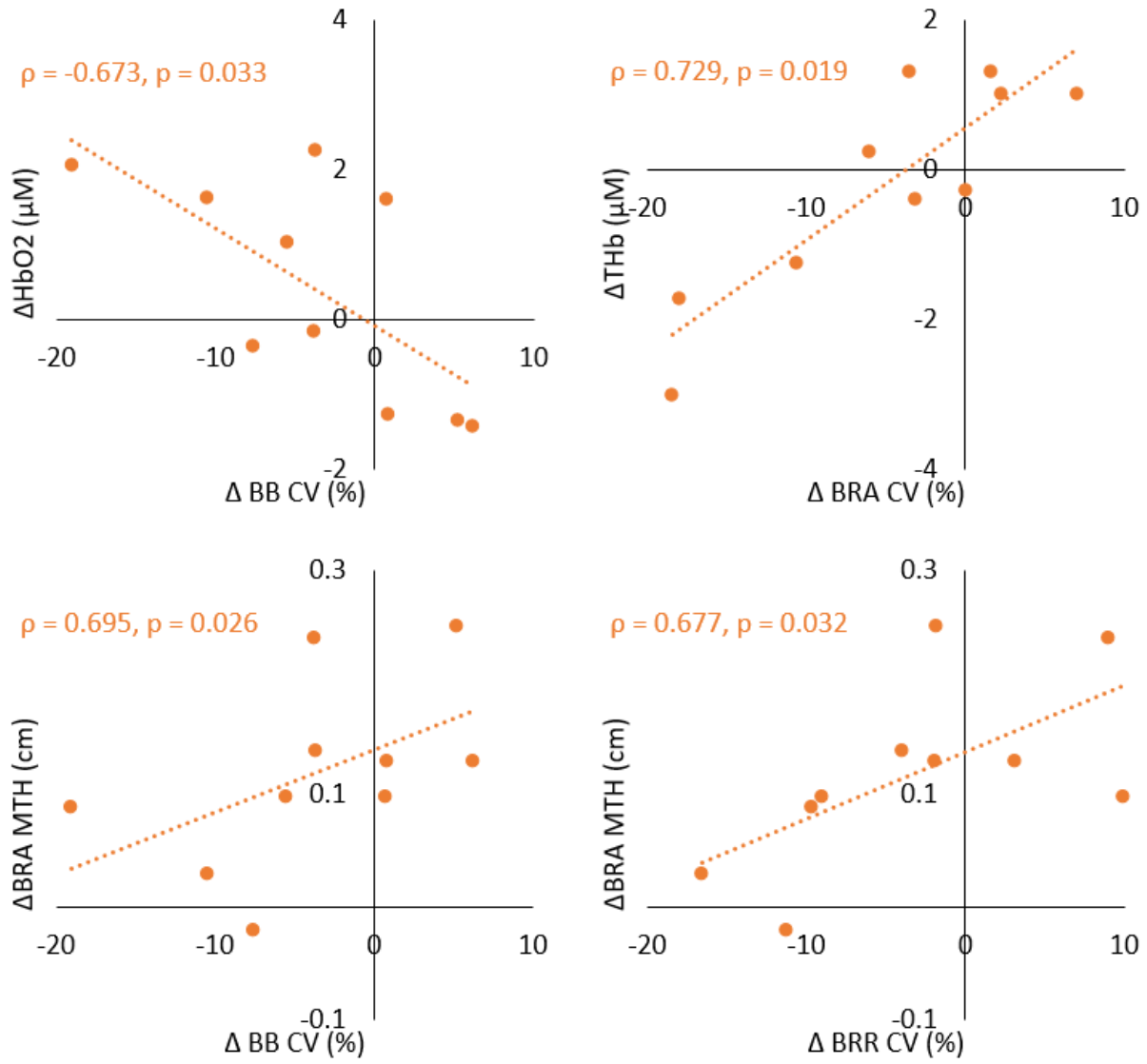

Figure 6.6. Relationships in old females between fatigue-induced changes in biceps brachii (Δ BB CV), brachialis (Δ BRA CV) and brachioradialis activation variability (Δ BRR CV), and changes in oxygenated hemoglobin concentration (ΔHbO_2, top left), in total hemoglobin concentration (ΔTHb, top right), and in brachialis muscle thickness (ΔBRA MTH, bottom left and right).

6.6 Discussion

This is the first study to investigate the influences of old age and upper limb fatigue on alterations in muscle activation variability, oxygenation, and thickness in females. This study is also the first to investigate relationships between motor variability and hemodynamics. Our main findings were 1) the fatigue-induced changes in muscle activation variability, oxygenation, and

thickness did not differ with old age; 2) lower fatigability was related to lower initial muscle activation variability in young but not old females; 3) higher initial muscle activation variability was related to a more blunted muscle oxygenation response with exercise; 4) relationships between the fatigue-induced changes in muscle activation variability and the oxygenation and swelling responses differed with old age.

6.6.1 Fatigue-induced changes in muscle parameters did not differ with old age

The lack of an age difference in how elbow flexion fatigue influenced the magnitude of activation variability within a single muscle agrees with our findings following myoelectric fatigue in the shoulder (Bailey, Weiss, et al., 2020; unpublished observation). However, the magnitudes of the young and old female elbow flexor responses in the current study were small decreases (-3.1% for BB, -4.8% for BRA), contrasting with the larger increases (6.1-35.2%) we previously reported in shoulder muscles. Other studies reported similarly sized increases in shoulder muscle and joint movement-to-movement variability following shoulder fatigue (Qin, Lin, Faber, et al., 2014; Srinivasan et al., 2016), suggesting that the changes in motor variability due to muscle fatigue differ between elbow and shoulder-based tasks. A likely reason for this difference is the reduced degrees of freedom available at the elbow compared to the shoulder. The high degrees of freedom and muscular redundancy available at the shoulder allow individuals to search for new motor patterns to effectively prolong performance as fatigue develops (Côté, 2014). Despite possessing elbow flexor redundancy between BB, BRA, and BRR, it seems that females used fewer muscle recruitment strategies as fatigue developed, perhaps reflecting the use of fewer and more energy efficient muscle recruitment strategies.

There was also no main effect of old age on muscle activation variability, agreeing with observations during repeated trials of reaching and lifting (Bailey, Weiss, et al., 2020) but disagreeing with observations of gait and repetitive forward reaching (Bailey, Porta, et al., 2019; unpublished findings). Even in studies when muscle activation variability differed with old age, observations were not consistent across all muscles. Assuming that the higher motor unit discharge rate variability seen with old age (Laidlaw et al., 2000) is somewhat consistent across motor unit pools, it appears that the age differences in muscle activation variability are reflective more of differences in the flexibility of the selected motor strategies than differences in motor unit physiology.

The magnitudes of the muscle deoxygenation and swelling responses also did not differ with old age, agreeing with previous muscle oxygenation findings in the lower extremity (Costes et al., 1999; Hart et al., 2015) and extending this finding for the first time to fatiguing exercise in the upper extremity. Unlike in the lower extremity, however, we found no systematic effect of old age on muscle oxygenation at rest, initial exercise, or muscle fatigue. Reasons for these study differences are not fully clear but could reflect age differences that are limb-dependent (upper vs. lower extremity) and/or sex-dependent (females only in the present study) (Mantooth et al., 2018). The age-independent exercise-induced changes were seen in TOI, HbO_2, BB MTH, and BRA MTH. The initial drop in BB oxygen saturation (2.0% decrease in TOI) was likely a result of the decreased oxygen supply (2.6 μM decrease in HbO_2) and, as previously reported in a study of repeated elbow flexions at 20% of maximum effort to fatigue (Baudry et al., 2013), neither oxygen saturation nor supply fully recovered to resting levels before fatigue developed. Thus, the rest intervals included in our task did not appear to affect the muscle oxygenation response. The swelling of the elbow flexors in response to low-load dynamic exercise agrees with prior findings (Rudroff et al., 2008; Yasuda et al., 2015), although the reported relative changes (10-20%) were larger than those we observed (4-7%). These larger relative changes may be due to studying males and/or the lack of a rest interval prior to exercise failure. Taken together, these prior studies and the present study suggest that although old age does not affect the muscle oxygenation and swelling responses to low-load fatiguing exercise, these responses are likely both task (extremity, presence of rest) and sex-dependent.

6.6.2 Relationships between fatigability, initial muscle activation variability, and change in oxygenation

In contrast with our second hypothesis, lower performance fatigability was related to *lower* initial BB activation variability and only in young females. We expected that having higher initial variability would reflect having flexibility in the available motor strategies to mitigate development of muscle fatigue as suggested previously (Fedorowich et al., 2013; van Dieën, Oude Vrielink, & Toussaint, 1993). However, like with the observed decreases in elbow flexor activation variability, it seems that the constraints of elbow flexion led to young females adopting a more stereotypical pattern, perhaps to be more energy efficient. Lower fatigability in old females was instead related to having larger fatigue-induced increase in THb, which reflects more accumulation of hematocrit and blood in the elbow flexors with a longer task duration. The lack of relationships

with changes in oxygen saturation (TOI) or oxygen availability (HbO_2, HHb), alongside previous evidence of BB myoelectric fatigue in the absence of altered BB oxygen saturation (Blangsted et al., 2005), suggest that the muscle oxygenation response during low-load elbow flexions is not a key factor in the development of fatigue nor in fatigability.

6.6.3 Relationships between muscle activation variability, oxygenation, and thickness

There were few relationships between the initial or fatigue-induced changes in muscle oxygenation or thickness and initial muscle activation variability (2/48 comparisons significant in young females and 1/48 comparisons significant in old females). An individual's initial motor variability has been recently suggested to represent a personal trait. Sandlund et al. (2017) found that the cycle-to-cycle variability in elbow and shoulder kinematics during repetitive pipetting differed significantly between individuals and that these individual differences were repeatable across days. While further studies are needed to confirm these findings for muscle activation variability, our results point towards a more blunted oxygenation response (i.e. smaller decrease in TOI, smaller increase in HHb and THb) during low-load dynamic elbow flexion exercise in females that possess higher initial muscle activation variability, which agreed with our third hypothesis.

Again, relatively few correlations were observed between the fatigue-induced changes in muscle activation variability and the changes in muscle oxygenation and thickness (2/24 comparisons in young females and 4/24 comparisons in old females). While BB and BRA CV decreased with fatigue in both age groups, there was considerable inter-individual variability in the decrease and even cases of increases (Figure 6). There were also similar numbers of individuals with increased AD CV vs. decreased AD CV following fatigue (Figure 5), so we will interpret individual responses in both directions for the remainder of this discussion. Currently, there is limited evidence available for comparing links between motor variability and muscle physiology. As decreases in variability were typically associated with decreased THb, and vice-versa, it appears that an individual's muscle activation variability response with low-load elbow flexion fatigue relates directly to accumulation/dispersal of muscle blood volume. Relationships with hematocrit may reflect the blood volume-related accumulation/dispersion of metabolites that are known to alter activation of group III/IV afferents, changing motor unit output (Barry & Enoka,

2007). As metabolite content does not appear to affect oxygen availability (Flodgren et al., 2006), relationships of decreased variability with decreased HHb and increased HbO_2, reflecting a reduction in motor variability with increased oxygen availability and vice-versa for opposite responses, are likely a result of different neural mechanisms. Indeed, a relationship was recently reported between individual-specific changes in BB motor unit firing rates and sensitivity to oxygen availability during low-load isometric elbow flexions, with the authors attributing the link to competing influences of oxygen availability on neuromodulators, autonomic tone, and afferent feedback (McKeown et al., 2019). While cause-and-effect mechanisms remain to be confirmed, fatigue-related adjustments in muscle activation variability in females appear to be linked to changes in metabolite content and oxygen availability within the muscle.

Interestingly, relationships with variability in young and old females seemed to differ by muscle, as there were relationships with AD activity variability in young females and with elbow flexor activity variability in old females. As fatigue developed during repetitive movement alters motor variability local and non-local to the fatigue site (Fuller et al., 2011; McDonald, Tse, & Keir, 2016), and the young and old females had similar BB oxygenation responses to the same relative level of muscle fatigue, it seems that these responses are associated with adjustments in muscle recruitment patterns that are non-local in young females and local (at the fatigue site) in old females. Associations with elbow control in young adults and with shoulder control in old adults parallel the sex differences reported by Srinivasan et al (2016). In response to a fatiguing neck/shoulder task, the authors reported larger trapezius variability increases in males and larger biceps brachii variability increases in females, interpreting this as evidence of shoulder-based and elbow-based control strategies in males and females respectively. Differences may reflect a shift in motor control to more distal patterns in individuals with lower strength, which is also an interpretation that could apply to the results of this study, although other aging-related factors may also play roles.

6.6.4 Limitations

There are several limitations of note for this study. We report on results in females only; as sex affects responses during fatiguing upper extremity tasks in muscle activation variability (Srinivasan et al., 2016) and in muscle oxygenation (Mantooth et al., 2018; Takagi et al., 2016), results from this study are not generalizable to young and old males. We also did not perform an

a-priori power analysis for evaluating Age*Time effects and post-hoc achieved power was unable to be computed for the general estimating equations using G*Power, as general estimating equations differ from conventional statistical models (e.g. ANOVAs). We used general estimating equations since they have been shown to achieve higher statistical power with smaller sample size compared to repeated measures ANOVAs (Ma, Mazumdar, & Memtsoudis, 2012). We also chose to study muscle oxygenation non-invasively using NIRS due to the theorized relationship between oxygenation and motor control (Amann et al., 2006); future studies may wish to investigate the relationship between arterial oxygenation and muscle activation variability and/or investigate microvascular blood flow directly (Hildebrandt et al., 2017) using more invasive methods. Finally, the associations between fatigue-induced changes in muscle activation variability and oxygenation resulting from our cumulative sample of 25 participants should be interpreted cautiously and as preliminary results. These preliminary associations should be studied further in larger sample sizes of males and females and in experiments that directly manipulate muscle oxygenation (e.g. blood flow restriction or occlusion) to investigate causal mechanisms of muscle activation variability.

6.7 Conclusion

For the first time in females and in the upper limb, we investigated how old age affected the concurrent motor variability and hemodynamic fatigue responses. Our results show that old age did not affect changes in the magnitudes of muscle activation variability, oxygenation, or thickness occurring in females due to dynamic, intermittent, low-load elbow flexion fatigue. Higher initial muscle activation variability was related to higher fatigability in young females and a blunted change in muscle oxygenation with exercise. Changes in muscle blood volume and oxygen availability were linked to alterations in non-local muscle activation variability for young females and in local muscle activation variability for old females. Therefore, in the absence of age-related differences in development of low-load elbow flexion muscle fatigue and in fatigability, we found preliminary and novel evidence for a link between muscle hemodynamics and motor variability that varies in locality to the site of fatigue with old age.

6.8 Declarations

6.8.1 Funding

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6.8.2 Conflicts of interest/competing interests

The authors have no conflicting or competing interests to declare.

6.8.3 Ethics approval

The informed consent form and experimental protocol were approved by the Research Ethics Board of McGill University.

6.8.4 Consent to participate

Informed consent was provided by all participants signing the consent forms.

6.8.5 Consent for publication

Not applicable.

6.8.6 Availability of data and material

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

6.8.7 Code availability

Not applicable.

6.8.8 Authors' contributions

Conception and design of the experiment was performed by C.A.B. and J.N.C. Data was acquired by C.A.B and S.Y., data was processed and analyzed by C.A.B, and data was interpreted by all authors. C.A.B wrote the first draft of the manuscript which was critiqued by J.N.C. and S.Y. All persons designated as authors qualify for authorship and approved the final manuscript.

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Chapter 7. Comprehensive discussion

7.1 Key findings of this dissertation

Chapters 3-6 report findings based on joint (kinematic) and muscle (EMG) metrics measured in male and female gait across the lifespan, EMG metrics measured in repetitive, fatiguing shoulder work in samples of young and old adults, and EMG metrics measured concurrently with other physiological outcomes in repetitive, fatiguing elbow work in samples of young and old females.

Major findings from Chapters 3-6 can be summarized as follows:

1. The influence of old age on motor variability of individual joint outputs in gait was specific to the degree of freedom and, to a lesser extent, the sex of the individual. Older age was associated with lower ankle variability in the sagittal plane, higher ankle variability in the frontal plane, higher pelvic variability in the frontal and transverse planes, and higher knee variability in the sagittal plane for males only. *(Chapter 3)*
2. Higher motor variability in the spatiotemporal output of gait was related to and independently predicted by having higher sagittal and frontal plane ankle variability as well as higher sagittal plane hip variability. *(Chapter 3)*
3. The influence of old age on motor variability of individual muscle outputs in gait was specific to the sex of the individual. Older age was associated with higher variability in rectus femoris activation for both males and females but was associated with lower variability in gastrocnemius lateralis activation for females only. *(Chapter 4)*
4. Higher motor variability in the spatiotemporal output of gait was only weakly related to variability in rectus femoris activation and showed no association with any other muscle activity variability metric. *(Chapter 4)*
5. There was no influence of old age on motor variability of muscle outputs in the absence or presence of fatigue from repetitive shoulder work. Regardless of age, fatigue led to increased variability in trapezius and deltoid muscle activation variability and increased variability in within-deltoid connectivity, but decreased variability in trapezius-deltoid connectivity. *(Chapter 5)*
6. Old age influenced fatigue-related changes in trapezius-deltoid connectivity following repetitive shoulder work, with old adults strengthening connectivity with the upper

trapezius and young adults strengthening connectivity with the lower trapezius. *(Chapter 5)*

7. There was no influence of old age on motor variability of muscle outputs in the absence or presence of fatigue from repetitive elbow exercise. Regardless of age, fatigue led to decreased variability in elbow flexor activation variability. *(Chapter 6)*
8. Higher initial motor variability in muscle outputs during elbow exercise was related to having more blunted biceps brachii oxygenation in both young and old females and to higher fatigability in only young females. *(Chapter 6)*
9. Elbow fatigue-related changes in biceps brachii oxygenation were related to a fatigue-induced motor variability response at the anterior deltoid in young females and at the elbow flexors in old females. *(Chapter 6)*

7.2 Effects of old age on variability of lower and upper limb joint and muscle outputs

7.2.1 Limb-dependent influences of age-related motor variability

Significant alterations in the variability of joint kinematic and muscle activation outputs were found in gait with older age. Chapter 3's report of higher variability in frontal plane ankle motion and in both frontal and transverse plane pelvic motion with older age (Bailey et al., 2020), agrees with the higher variability with older age observed previously in spatiotemporal measures (Beauchet et al., 2017; Callisaya, Blizzard, Schmidt, et al., 2010) and extending these to non-sagittal planes of joint motion. Further, Chapter 4 investigated neuromuscular variability patterns in gait for the first time, finding higher variability in rectus femoris activity during several subphases of stance and swing (Bailey, Porta, et al., 2019). Together, these findings suggest that old age amplifies the variability of select joint and muscle outputs in the lower limb.

The influence of old age, however, was not fully consistent across joints and muscles. In Chapters 3 and 4 respectively, it was reported that sagittal plane ankle variability and gastrocnemius lateralis activation variability were *lower* with older age (Bailey et al., 2020; Bailey, Porta, et al., 2019), suggesting that older age is accompanied by a reduction in motor flexibility at the ankle. This contrasts prior studies that found *higher* sagittal plane ankle variability with old age (Buzzi et al., 2003; Kurz & Stergiou, 2003). Differences may be explained by the selection of different metrics of motor variability, with the metrics reported in Chapters 3 and 4 (standard

deviation, coefficient of variation) indicative of magnitude while those evaluated previously in gait (Lyapunov exponent, entropy) were indicative of local dynamic stability and complexity (Buzzi et al., 2003; Kurz & Stergiou, 2003). Thus, variability of sagittal plane ankle motion in aging gait may feature a decrease in the magnitude of variability with increased local dynamic instability and complexity.

In contrast to the lower limb, there was no evidence of an age effect on variability of muscle activity during repetitive upper limb movements executed mainly by shoulder agonists (Chapter 5) or by the elbow flexors (Chapter 6) (Bailey, Weiss, and Côté, 2020; Bailey, Yoon, and Côté, in preparation). This came as a surprise, as higher variability in shoulder and scapula kinematics was previously reported in old age (Qin, Lin, Faber, et al., 2014) and higher variability in force output is well documented in both the upper and lower limbs (Hunter et al., 2016). In Chapter 5, the lack of an age difference was attributed to our task being performed at the participant's self-selected pace compared to the set paces used in previous literature, such that individuals may prioritize variability in spatiotemporal output over variability in the underlying individual motor patterns. However, the age differences in variability of muscle activity observed in self-selected speed gait (Bailey, Porta, et al., 2019) refute this interpretation. Collectively, the findings of this dissertation rather suggest that the healthy aging process preferentially affects the variability of individual muscle outputs during repetitive lower limb activities but not repetitive upper limb activities.

7.2.2 Mechanisms contributing to age-related differences in motor variability

The complex effects of old age on variability of motor outputs found in this dissertation help provide insight into the theories of motor variability in aging adults. From the literature reviewed in Chapter 2, one potential theory that emerged is that of "neuromotor noise" (Dingwell et al., 2017), where increases in motor variability in healthy aging are a consequence of the motor unit remodeling process that features structural (e.g. fewer and more clustered motor units) and physiological changes (e.g. higher variability in discharge rates) to the peripheral nervous system (Christou, 2011; Enoka et al., 2003; Hunter et al., 2016). Assuming that the remodeling of motor units is systemic and not local, i.e. that old adults possess lower numbers of motor units than young adults across motor unit pools of the entire body (Piasecki, Ireland, Jones, & McPhee, 2016), there should be higher variability in the muscle and joint outputs produced downstream and, consequently, higher variability in spatiotemporal output. Chapters 3 and 4 appear at first glance

to provide evidence for this theory, as old age was associated with higher ankle inversion/eversion variability and rectus femoris activation variability, with each related to variability in stride time (Bailey et al., 2020; Bailey, Porta, et al., 2019). In the same studies however, old age was associated with *lower* variability of certain motor outputs (ankle flexion/extension, gastrocnemius lateralis activation), with variability of ankle flexion/extension being an independent predictor of stride time variability. These findings are not in full agreement with the neuromotor noise theory of motor variability.

Alternatively, motor variability responses in aging adults may represent more centrally mediated control strategies. The prefrontal, parietal, and sensorimotor regions of the brain are well known to be involved in motor control and also undergo more atrophy relative to other brain regions with old age (Seidler et al., 2010). Studies of dual tasking support this central mechanism of motor control, as an added cognitive task deteriorates motor control more in old than in young adults (Li & Lindenberger, 2002). This central mechanism may help explain the opposing age effects on sagittal and frontal plane ankle variability that were reported in Chapter 3, such that the results may represent a centrally-mediated shift from sagittal to frontal plane ankle variability with old age that could reflect a strategy to preserve balance during gait. The collective results of this dissertation, featuring age differences in movement-to-movement variability that were dependent on the degree of freedom and the muscle in gait, but non-existent in the upper limb, tend to agree more with a central rather than a peripheral origin to motor variability in repetitive movement tasks.

7.3 Influences of sex and fatigue on variability of motor outputs as a function of age

7.3.1 Sex influenced age differences in variability of lower limb joint and muscle outputs

Findings from Chapters 3 and 4 show for the first time that age-related changes in gait motor variability are not the same in males and females. Sex-dependent age differences in gait have been previously observed in ensemble averaged motor patterns, with older age being associated with longer dorsiflexion duration, rising more rapidly in women (Ko et al., 2011), higher hip absorptive work in women only (Ko et al., 2011), and higher mid-swing gastrocnemius lateralis activity in women but higher mid-swing rectus femoris activity in men (Bailey, Corona,

Pilloni, et al., 2018; also see Appendix A). Independent of age, older women are reported to have more frequent, shorter, and narrower steps, and higher range of motion at the ankle but lower range of motion at the hip in comparison with older men (Ko et al., 2011). Collectively, these sex-specific age effect findings suggest that aging women tend to rely more on ankle joint and muscle patterns while aging men rely more on hip patterns to produce gait. This dissertation supports the sex-specific control of the ankle in aging women, with Chapter 4 showing that older age was associated with lower stride-to-stride variability in gastrocnemius lateralis activation only in females (Bailey, Porta, et al., 2019). Thus, aging females may produce more stereotyped muscle recruitment patterns at the ankle. Meanwhile, Chapter 3 identified higher stride-to-stride variability in knee flexion/extension with age only in males (Bailey et al., 2020), indicating that aging males may utilize a more flexible series of knee patterns, perhaps to mitigate cumulative knee joint loads that are associated with chronic conditions like knee osteoarthritis (Ezzat, Cibere, Koehoorn, & Li, 2013). Collectively, these results support the idea that the adjustments in average and movement-to-movement joint and muscle patterns in the gait of aging males and females are distinct. Given the highly rhythmic nature of gait production, it can be hypothesized that sex-dependent changes in motor variability with old age may be observed in other rhythmic tasks of the lower limb (e.g. running, stair ascent/descent). Investigating sex differences in other lower limb tasks could help better contextualize the factors responsible for motor variability in aging men and women.

7.3.2 Fatigue did not influence age differences in variability of upper limb muscle outputs

In contrast to the sex differences seen with age, there was no evidence in Chapters 5 and 6 for an age effect on changes in muscle activation variability with low-load repetitive motion-induced fatigue in the upper limb. Therefore, young and old adults seem to possess similar movement-to-movement muscle strategies to adapt to fatigue from repetitive upper limb motion. The increased muscle activation variability seen with fatigue in Chapter 5 (Bailey, Weiss, et al., 2020) agrees with prior observations in a standing repetitive pointing task (Fedorowich et al., 2013; Srinivasan et al., 2016) and in a seated pipetting task (Samani et al., 2017), extending these findings for the first time to old adults. Thus, Chapter 5 supports the hypothesis that fatigue in the neck and shoulder leads to a search for more flexible muscle patterns to mitigate fatigue development and prolong task performance (Côté, 2014), such that initially high variability (i.e. flexibility) in muscle patterns may protect against fatigue development (Fedorowich et al., 2013). This was,

however, not seen in Chapter 6, where elbow flexor activation variability decreased following fatigue in young and old females and lower initial muscle activation variability in young females was related to less fatigability. This suggests that individuals selectively restrict their muscle recruitment strategies as fatigue develops, where strategies are optimized to be energy efficient. Differences in the fatigue-related motor variability responses reported in this dissertation are likely due to the different tasks studied, which included a multi-joint, shoulder dominant task (Chapter 5) and a single-joint, elbow dominant task (Chapter 6). While these tasks each possessed muscular redundancy for achieving the required performance, the shoulder dominant task possessed a significantly higher number of available degrees of freedom. Therefore, as fatigue develops, it seems that young and old adults similarly search for flexible muscle patterns when degrees of freedom are high and constrain their muscle patterns when degrees of freedom are low. Low motor variability may lead to cumulative tissue loads, discomfort, pain, and injury, meaning these results could have implications for the prevention of work-related musculoskeletal disorders in young and old adults.

While age did not affect the fatigue-related changes in movement-to-movement muscle patterns, age did affect the changes in muscular connectivity patterns. Results from Chapter 5 showed a shift from lower trapezius-deltoid connectivity to upper trapezius-deltoid connectivity in old adults and the reverse in young adults (Bailey, Weiss, et al., 2020). This apparent cranial shift in trapezius-deltoid connectivity in old age may represent compensation by the scapula for the age-related reductions in shoulder and trunk movement reported previously in reaching-based tasks (Chaffin et al., 2000; Chateauroux & Wang, 2008). This strategy could be a result of poorer seated reaching posture, including less shoulder abduction and trunk flexion (Chaffin et al., 2000; Chateauroux & Wang, 2008). The smaller neck musculature could be more susceptible to overloading during repetitive reaching compared to the larger thoracic musculature, potentially leading to neck discomfort, pain, and eventually musculoskeletal disorders. Thus, our results indicate that motor adaptations to fatigue do differ with age, albeit in how muscles are connected functionally and not in their variability from movement to movement.

7.4 Muscle oxygenation is a potential physiological determinant of motor variability

Findings from Chapters 3-5 provide evidence for independent influences of age and fatigue on motor variability patterns, but with no interaction between these factors. As both age and fatigue are marked by clear physiological alterations in the muscle, we explored whether these physiological alterations relate to the motor variability response. Chapter 6 showed that the biceps brachii oxygenation and muscle activation variability responses were related (Bailey et al., in preparation), providing the first evidence that neuromuscular variability in fatiguing tasks may be regulated by how oxygen is supplied to and used by the muscle. This finding agrees with previous literature that suggests that oxygenation is a central regulator of motor behaviour (Amann et al., 2006; McKeown et al., 2019), extending to oxygenation within the muscle and behaviour of gross muscle patterns for the first time. Together, these findings suggest that neuromuscular variability is a centrally mediated control strategy, supporting our interpretation in Section 7.2.2.

7.5 A brief note on implications for preventing age-related injuries

7.5.1 Preventing age-related falls

This dissertation found that higher stride time variability in aging adults, a key risk factor for falling, was tied to alterations in the variability of ankle and hip motor patterns. This provides new insights for clinicians to design new fall prevention and rehabilitation gait interventions. Traditional interventions aim to achieve more normative joint and muscle patterns, with stride-to-stride control approaches (e.g. gait adaptability and reactive step training) to fall prevention only recently becoming more recognized (Lord & Close, 2018). While the investigation of neuromuscular variability patterns in gait rehabilitation has begun, e.g. for persons with Parkinson's disease (Bailey, Corona, Murgia, et al., 2018), normative motor variability patterns remain to be established. Results from this dissertation suggest that the mitigation of old age-related ankle inversion/eversion variability, in favour of ankle dorsiflexion/plantar flexion variability, is a potential intervention target to reduce excess stride time variability and fall risk in old adults. This could be achieved, for instance, through interventions using real-time feedback from Inertial Measurement Units (IMUs) specifically targeting these kinematic variables.

7.5.2 Preventing age-related upper limb musculoskeletal disorders

The lack of an effect of old age on muscle activation variability in fatiguing upper limb tasks indicates that movement-to-movement variability in neuromuscular patterns does not explain why old adults incur more neck/shoulder musculoskeletal disorders. Instead, findings from Chapter 5 indicate that the functional connectivity between muscles is a more likely neuromuscular control feature to explaining age-related musculoskeletal disorders. As we observed a cranial shift in trapezius-deltoid connectivity with fatigue from repetitive reaching in old adults, and a caudal shift in this connectivity in young adults, old adults may support deltoid activity by increasing recruitment of neck musculature to elevate the scapula while young adults support deltoid activity with thoracic musculature to retract the scapula. Therefore, rather than targeting neuromuscular variability patterns to prevent age-related neck/shoulder disorders, the results of this dissertation suggest targeting how other muscles support the fatiguing deltoid, as aging adults seem to recruit more easily overloaded neck musculature. This serves as a recommendation to account for inter-muscle functional connectivity in EMG-based rehabilitation approaches.

7.6 Future research

7.6.1 Evaluating repetitive movement control using advanced computational approaches

The review of motor variability literature (see Chapter 2) highlights the variety of metrics available, where each quantifies a distinct feature of variability. This dissertation investigated the size of variability using the standard deviation and coefficient of variation of the discrete variable of interest measured from movement to movement. This measure satisfied the aims of this dissertation but, on its own, does not provide a full understanding of movement-to-movement variability. Dynamical systems analyses, such as dynamic stability analyses and detrended fluctuation analysis, can provide insight on the temporal regulation of movement-to-movement variability. The uncontrolled manifold and goal equivalent manifold approaches can quantify whether the variability observed is beneficial or detrimental to the performance or goal of movement. These more complex motor variability approaches have previously been used to study movement in young adults and in males, meaning there is a need for new studies with sex- and age-balanced samples to better understand the dynamics and structure of motor variability as a function of old age and sex. Quantifying all of these features of variability across several joints

and muscles unfortunately leads to numerous parameters that are difficult to simultaneously interpret. Machine learning techniques, such as those used to identify participant clusters from large numbers of variables, may provide a useful novel way to study motor variability. Indeed, k-means clustering has been used to identify several distinct spinal flexion/extension movement strategies in young males (Beaudette, Zwambag, Graham, & Brown, 2019) and could be similarly applied to understand the variability strategies present in repetitive movement tasks across the lifespan of men and women.

7.6.2 Evaluating longitudinal aging data

A major limitation of most aging research, including the studies that form this dissertation, are that hypotheses on aging in biomechanics and motor control are commonly tested using cross-sectional datasets. While these cross-sectional studies provide insights into how an average individual may respond with old age, they do not monitor how biomechanics and motor control change within an aging individual. Such longitudinal studies are rare due to their methodological challenges. The Canadian Longitudinal Study on Aging (CLSA) and Baltimore Longitudinal Study of Aging (BLSA) are the two major ongoing longitudinal investigations occurring in Canada and the U.S.A, respectively. Aside from measuring physical function, such as grip strength, the CLSA and BLSA do not conduct any biomechanical analyses since acquiring these data typically requires more specialized instrumentation. Monitoring the longitudinal changes in motor patterns with age is likely to help better prevent musculoskeletal injuries in the rapidly aging Canadian and American populations but will require the formation of a dedicated and sustainable research program.

7.7 Conclusions

This dissertation aimed to 1) determine how old age affects the motor variability of joint and muscle outputs during repetitive movements, comparing effects between the lower and upper limb, 2) examine how age differences in motor variability patterns varied by sex and with fatigue, and 3) explore the physiological origin of motor variability. Results from this dissertation reveal that 1) old age affects the variability of motor outputs in the lower limb in a sex-specific way, but not in the upper limb, 2) age-related changes in variability patterns differ by sex in the lower limb but not with fatigue in the upper limb, and 3) muscle oxygenation is a potential physiological regulator of neuromuscular variability. Together, these findings demonstrate that men and women

undergo fundamental changes in movement-to-movement control of joint and muscle patterns as part of the healthy aging process.

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Appendix A: Sex-dependent and sex-independent muscle activation patterns in adult gait as a function of age

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A.1. Preface

Appendix A presents a study completed prior to the studies presented in this dissertation. This preceding study investigated sex-dependent and independent muscle activity patterns in gait as a function of old age, focusing on patterns averaged across several strides. The findings of this study motivated the evaluation of male and female age-related motor variability responses in Chapters 3 and 4 of this dissertation.

Sections A.2 to A.11 are a copy of the manuscript published by *Experimental Gerontology*. Formatting has been altered to allow insertion as an appendix to this thesis.

A.2. Abstract

Introduction: Aging leads to poorer neuromuscular control that may impact mobility. However, the specific decades when these changes occur, and whether these time-based changes are sex-specific, is unclear.

Methods: Adults aged 20-82 y (N = 93, 51 females) walked six gait trials at their preferred speed over a 10-m platform. Electromyography (EMG) of the rectus femoris (RF), tibialis anterior (TA), and gastrocnemius lateralis (GL) were measured using wireless surface sensors. Root mean square (RMS) and within-cycle coefficient of variation (CV) values were calculated for several phases of gait. Mixed effect models were conducted to test for Age, Sex, Muscle, and interaction effects, covarying for gait speed and stride length.

Results: A significant Age x Sex x Muscle interaction on RMS at the mid-swing phase was found ($p = .036$), showing 4.2% lower RF RMS for males ($\beta = -.42$, $p = .008$) and 3.3% higher GL RMS for females ($\beta = .33$, $p = .038$) with each of the three decades investigated. Significant Age x Muscle interactions on GL RMS were found at loading, mid-stance, and over the full gait cycle ($ps < .05$), with 2.0-4.3% higher values per decade ($\beta = .20$-$.43$, $ps < .05$). There was generally higher CV with higher age at mid-swing and over the full gait cycle (significant Age effects, $ps < .05$). Females showed higher CV at loading, mid-stance, and terminal stance (significant Age x Sex effects, $ps < .05$).

Discussion/Conclusion: Results suggest sex-dependent influences of age on muscle recruitment during a few specific phases of gait, and sex-independent influences of age on the recruitment of

the ankle musculature, and on the overall gait cycle. These influences may help explain overall increased instability and fall risk in older adults.

Keywords: EMG activation, EMG signal variability, aging, sex differences, gait

A.3. Introduction

Normal aging is a gradual process that impacts strength and gait stability. Each year after 40 years of age, adults may lose as much as 1.5% of their maximal strength (Vandervoort, 2002). Strength deficits are also present during dynamic contractions (Vandervoort, 2002; Deschenes, 2004; Kirkendall and Garrett, 1998), such as those during gait. These decreases in strength can have functional consequences. For instance, lower limb strength is correlated to gait stability (Moxley Scarborough et al., 1999) and is predictive of falls (Pijnappels et al., 2008), which lead to some of the most common injuries suffered by older adults. One consequence of falls can be functional dependence, which has also been shown to be independently associated to gait function (Gill et al., 1995). Although gait function seems to be directly linked to age-related changes in lower limb strength, older adults remain more unstable than young adults after controlling for strength, suggesting that other physiological changes have a role in age-related gait instability (Kang and Dingwell, 2008).

Age-related differences in mobility and fall risk occur alongside other changes in gait patterns. Generally, older adults have slower preferred gait speeds than young adults (Smith et al., 2002; Ko et al., 2011; Kobayashi et al., 2016) and longer stance and double support durations (Beauchet et al., 2017), which together could be interpreted as reflecting age-related adaptation strategies to optimize gait stability. Moreover, DeVita and Hortobagyi (2000) found that older adults have higher hip extensor torque and power, and lower ankle plantar flexor torque and power compared to younger adults, and interpreted this as a redistribution of joint loads from the ankle to the hip due to joint-specific effects of aging on musculoskeletal structures of these joints.

The previously observed age-related redistribution of joint torque and power at the ankle and hip suggests that there may be changes in how muscles are recruited during gait. Schmitz et al. (2009) explored these muscle activations during the gait cycle using electromyography (EMG),

and found that older adults had higher normalized muscle activation than young adults at preferred speed, citing differences at the gastrocnemius lateralis (GL) during loading, and at the vastus lateralis, soleus, tibialis anterior (TA), and rectus femoris (RF) during mid-stance. While higher RF and vastus lateralis activation may be expected in an ankle-to-hip change in joint loading, the higher TA, soleus and GL are not, and could instead be interpreted as higher co-activation during gait, a common stabilizing feature of older adults (Hortobágyi and Devita, 2006; Hortobágyi et al., 2009) that could result in both higher ankle joint stiffness and lower ankle joint power. Schmitz et al. (2009) concluded that the age effect was more prominent for uniarticular than biarticular muscles; however, this conclusion was based on a comparison of the soleus and GL at mid-stance in a fast gait speed condition, and may not reflect observations across all phases during preferred speed gait. In fact, the age effect on soleus activation during mid-stance was smaller in magnitude than the age effect on GL activation during loading (Schmitz et al., 2009), meaning biarticular muscles could see larger age-related changes at preferred speed gait. Marques et al. (2016) also observed a higher TA activation during stance in older adults, however, they also found lower RF activation, contrasting with Schmitz et al. (2009). Since the study from Marques et al. (2016) assessed only females, this suggests that sex may be an influencing factor in the effect of age on gait muscle activity.

Indeed, an individual's sex seems to affect their motion and joint loading during gait. While some studies of young and old adults have found that females walk at a slower preferred speed than males (Callisaya et al., 2010; Cho et al., 2004), the majority report equal gait speeds (Smith et al., 2002; Ko et al., 2011; Kobayashi et al., 2016; Mengarelli et al., 2017; Di Nardo et al., 2015; Kerrigan et al., 1998; Bruening et al., 2015) with shorter stride lengths (Smith et al., 2002; Ko et al., 2011; Kobayashi et al., 2016; Kerrigan et al., 1998; Bruening et al., 2015) and higher cadences (Smith et al., 2002; Ko et al., 2011; Kobayashi et al., 2016; Mengarelli et al., 2017; Di Nardo et al., 2015; Kerrigan et al., 1998; Frimenko et al., 2015). These shorter and faster strides for females, once factoring in sex differences in height, occur with proportionally larger hip, knee, and ankle range of motion during the gait cycle (Ko et al., 2011; Røislien et al., 2009), and with less positive work performed by the knee and more negative work performed by the hip and knee (Ko et al., 2011). This seems to show that sex, like age, could also affect joint load distribution during gait. At mid-stance, for instance, lower knee and ankle joint loads were found in females compared to males, independent of height and mass (Cho et al., 2004). At terminal stance, however, females

have higher magnitudes and longer durations of knee flexion and ankle plantar flexion (Ko et al., 2011; Kerrigan et al., 1998; Røislien et al., 2009), as well as higher knee extension torque (Cho et al., 2004), suggesting that females transition from double to single-leg stance with more motion amplitude than males. Moreover, sex differences in gait kinematics can be age-dependent (Kobayashi et al., 2016). Ko et al. (2011) reported that the duration of ankle dorsiflexion during initial swing increased with age more steeply for females than for males, meaning that sex may affect the age-related changes in ankle motion. With epidemiological evidence that falls occur more frequently and are more serious in older females than in older males (O'Loughlin et al., 1993; Stevens and Sogolow, 2005), an investigation of how sex affects age-related changes in gait motion is needed.

These sex-dependent changes in knee and ankle motion and loading are likely due in part to sex differences in muscle recruitment. Young female adults tend to activate their TA and GL to a greater extent than males within a single gait stride (Di Nardo et al., 2015), which the authors suggest demonstrates a more complex gait activation pattern for females. Moreover, this same group recently demonstrated that this sex difference in TA and GL activation profile was absent in children aged 6–8 but appeared in those aged 10–12, where sex-related motor control features may start to appear (Di Nardo et al., 2017). However, while sex seems to influence the shape of EMG in gait in young adults, little is known about its influence in older adults.

Further, the experimental design of previous muscle activation studies can limit the interpretation of the "age" effect. A statistical approach that groups participants into a young group and an older group (Schmitz et al., 2009; Marques et al., 2016; Theou et al., 2013) has typically been used, although age itself is a continuous measure. The older groups in these studies had a mean age > 70 years (Schmitz et al., 2009; Theou et al., 2013), limiting the interpretation of the "age" effect to adults > 70 years, or an age range > 20 years (Marques et al., 2016), requiring an assumption that older adults at the top (82 years) and bottom (60 years) of the range respond with the same "age" effect. Using regression models that treat age as a continuous variable, and/or more than a single group of older adults may more robustly capture the effects of aging and provide an estimate of the amount of change associated with the aging process.

To our knowledge, no study has assessed the effects of older age as a continuous variable on gait muscle activation separately for males and females. Therefore, the objective of this study

was to assess the interaction between age and sex on lower limb muscle activation during gait. Since Ko et al. (2011) reported an Age × Sex interaction on duration of ankle dorsiflexion, we hypothesized that aging would affect TA and GL activation differently for males and females. We also hypothesized that, due to a belief that females have more complex activation of lower limb muscles during gait (Di Nardo et al., 2015), females would have more variable EMG signal shapes than males, regardless of age.

A.4. Methods

A.4.1. Participants

From 2014 to 2017, 93 healthy adults aged 20 years and over were recruited among students and staff of University of Cagliari (Italy) and among people attending the University of the Third Age of Quartu S. Elena (Italy) on a voluntary basis. Participants were recruited following group meetings that detailed the purposes of the study and the experimental procedures. An exclusion criterion was the existence of any neurologic or orthopedic condition severely impairing gait, balance and muscular strength. A physician was consulted to examine borderline cases. Participants provided informed consent to participate in this study, which was given ethics clearance from the institutional ethics board.

A.4.2. Gait Analysis

Upon arrival, participants were instrumented for EMG gait analysis. EMG data were collected using wireless surface bipolar electrode sensors (FreeEMG, BTS Bioengineering, Italy) that sampled at 1000 Hz. Sensor dimensions were 41.5×24.8×14mm and 17×8mm for the mother and satellite sensors, each containing 17mm electrodes that were placed at an interelectrode distance of 20mm (gain: 1065.4; range ± 1.5 mV; input impedance:>10 GΩ; CMRR:>110 dB at 50–60 Hz). Using SENIAM guidelines for the lower limb (Hermens et al., 2000), the RF sensor was placed halfway on the line between the anterior superior iliac spine and the superior aspect of the patella, the TA sensor was placed one third of the distance from the fibular head on the line to the medial malleolus, and the GL sensor was placed one third of the distance from the fibular head on the line to the heel. These muscles were selected due to contrasting results on the effect of age on RF activation (Schmitz et al., 2009; Marques et al., 2016), age- and sex-specific effects on dorsiflexion kinematics (Ko et al., 2011) that may emerge in part from altered TA recruitment, and evidence that age differences in GL activation may be more substantial than differences in soleus

activation during preferred speed gait (Schmitz et al., 2009). An 8-camera optoelectronic motion capture system (120 Hz; Smart-D, BTS Bioengineering, Italy) sampled markers placed on several landmarks of the foot and shank according to the Davis model (Davis et al., 1991). EMG sensors and markers were placed bilaterally on each participant. After placement, participants practiced walking at their preferred speed over a 10m platform, and then data were sampled from six trials of gait, with 30 s of rest between each trial. Only data from straight-walking strides were analyzed.

A.4.3. Data Reduction

A gait analysis software program (Smart-Analyzer, BTS Bioengineering, Italy) was used to identify the first and second heel contact events during constant-speed walking, and these heel contact events were used to locate the gait cycle with respect to the EMG signal. Five gait cycles for each leg were identified from the six trials. These data were filtered to remove the DC bias, and bandpass filtered from 20 to 450 Hz using a 2nd order, dual-pass Butterworth filter. Data were then low-pass filtered at a 6 Hz cutoff (4th order, dual-pass Butterworth filter) to linear envelope the EMG signals (Schmitz et al., 2009). The enveloped EMG cycles were then time-normalized to 101 points from 0 to 100%, and amplitude-normalized to their peak value (Yang and Winter, 1984; Sousa and Tavares, 2012).

The enveloped and normalized EMG cycles were then divided into several phases according to a previous evaluation of muscle activation (Schmitz et al., 2009). The phases that were explored were the loading response (0–10%), mid-stance (10–30%), terminal stance (30–60%), initial swing (60–73%), mid-swing (73–87%), and terminal swing (87–100%). The root mean square (RMS) and within-cycle coefficient of variation (CV) were extracted from each phase and from the full cycle (0–100%), to quantify the magnitude and within-gait phase variability of muscle activation, respectively. Within a single EMG signal X, RMS was calculated using Eq. (1), and the CV was calculated using Eq. (2). RMS and CV values were averaged across five trials, for each participant.

$$RMS_X = \sqrt{\frac{1}{n}\sum({x_1}^2 + {x_2}^2 \dots {x_n}^2)} \qquad \text{(Equation 1)}$$

$$CV_X = \frac{sd(X)}{mean(X)} \qquad \text{(Equation 2)}$$

A.4.4. Statistical Analyses

All statistical analyses were completed using SPSS (v23, IBM, USA). Independent t-tests were first conducted on age, height, mass, gait speed, and stride length to test for between-group effects of sex. These gait parameters were entered as covariates in all further statistical models based on prior evidence that gait speed and stride length are dependent on age and sex (Smith et al., 2002; Ko et al., 2011; Kobayashi et al., 2016; DeVita and Hortobagyi, 2000; Cho et al., 2004; Kerrigan et al., 1998; Bruening et al., 2015). Mixed effects models, with compound symmetry covariance structures, were then conducted on the RMS and CV at each phase of the gait cycle to test for a within- group effect of Muscle (RF, TA, GL), a between-group effect of Sex (male, female), the influence of Age (as a continuous variable), and for any interactions. Three-way and two-way interaction effects with age were subsequently explored using linear regression models, modeling muscles independently for Age x Muscle effects and both muscles and sex independently for Age x Sex x Muscle effects. β-Coefficients were extracted to estimate the rate of change in muscle outcomes with each year of age. Statistical significance for mixed effects models and regression analyses was set at $p < .050$.

Finally, adults were stratified into three sub-groups (20–29 years, 60–69 years, and 70–79 years) for post-hoc ANOVA analyses on RMS values with a significant Age-based effect, following the aforementioned procedures for analyzing three-way and two-way interaction effects. Group-by-group comparisons were made using Bonferroni adjustments for multiple comparisons, by setting the level of significance at $p < .017$ (0.050/3). These group-wise comparisons on RMS values were made to better isolate the age where the quantity of gait muscle activation begins to differ.

A.5. Results

Participant age ranged from 20 years to 82 years, with a mean (standard deviation) of 57 (18) years. No differences in mean age ($p = .236$) or gait speed ($p = .199$) were found between males and females, however females were shorter ($p < .001$), lighter ($p < .001$), and had shorter stride lengths ($p = .001$) than males (Table A.1). A more detailed breakdown of sample sizes per decade can be found in Table A.2.

Table A.1. Group characteristics of males and females. Values are means (SD) and sex effect p-values are presented. Bolded values are statistically significant.

	Male	Female	Sex Effect
Age (years)	52 (20)	60 (16)	.236
Height (cm)	173 (6)	158 (7)	**< .001**
Mass (kg)	73.3 (9.4)	57.8 (10.9)	**< .001**
Gait speed (m/s)	1.19 (0.21)	1.14 (0.17)	.199
Stride length (m)	1.31 (0.15)	1.21 (0.13)	**.001**

Table A.2. Decade-by-decade sample sizes of males and females.

Age Bin	Male (n)	Female (n)	Total (n)
20-29 y	13	6	19
30-39 y	1	0	1
40-49 y	3	0	3
50-59 y	2	4	6
60-69 y	13	30	43
70-79 y	10	9	19
80-89 y	0	2	2

Several age-related effects and interactions were observed on RMS and CV (see Tables A.3 and A.4 for male and female means) and can be seen in visualizations of the average RF (Fig. A.1), TA (Fig. A.2), and GL (Fig. A.3) curves over the gait cycle.

A.5.1. Loading

For RMS, there was a significant Age x Muscle interaction ($p < .001$) where higher age was associated with higher GL RMS ($\beta = 0.41$, $p < .001$). Age groups significantly differed for GL RMS, with differences even evident between the 60–69 year and 70–79 year groups (20–29 years < 60–69 years < 70–79 years, $ps < .017$). For CV, there was a significant Age x Sex interaction ($p=.012$) where higher age was associated with lower CV in males ($\beta = -0.34$, $p < .001$).

A.5.2. Mid-Stance

For RMS, there was a significant Muscle x Age interaction ($p < .001$) where higher age was associated with higher GL RMS ($\beta = 0.20$, $p = .048$). Age group comparisons for GL RMS, however, did not reach statistical significance (ps > .017).

For CV, a significant Age x Muscle interaction ($p = .001$) revealed associations between higher age and both lower RF CV ($\beta = -0.26$, $p = .017$), and lower TA CV ($\beta = 0.46$, $p < .001$). There was also a significant Age x Sex interaction ($p = .019$) where higher age was associated with lower female CV ($\beta = -0.29$, $p < .001$).

A.5.3. Terminal Stance

For RMS, there were no significant age effects or age-related interactions (ps > .050).

For CV, there was a significant Age x Sex effect ($p = .005$), where higher age was associated with higher CV in females ($\beta = 0.23$, $p = .010$).

A.5.4. Initial Swing

For RMS, there was a significant Age x Muscle interaction ($p = .002$) where higher age was associated with lower RF RMS ($\beta = -0.37$, $p = .001$). This was corroborated by age group differences in RF RMS (20-29 y > 60-69 y and 70-79 y, ps < .017).

For CV, there was a significant Age x Muscle effect ($p = .017$), where higher age was associated with lower TA CV ($\beta = -0.48$, $p < .001$).

A.5.5. Mid-Swing

For RMS, there was a significant Age x Sex x Muscle interaction ($p = .016$) where higher age was associated with lower TA RMS in both males and females ($\beta = -0.62$, $p < .001$; $\beta = -0.67$, $p < .001$ respectively), but with higher RF RMS in males ($\beta = 0.42$, $p = .008$) and higher GL RMS in females ($\beta = 0.33$, $p = .038$) (Fig. A.4). Age group comparisons revealed differences for TA RMS in males and females (20-29 y > 60-69 y and 70-79 y, ps < .017), but not for male RF RMS or female GL RMS (ps > .017).

For CV, there was a significant age effect ($p < .001$) where higher age was associated with higher CV ($\beta = .25$, $p < .001$).

A.5.6. Terminal Swing

For RMS, there were no significant age effects or age-related interactions (ps > .050).

For CV, a significant Age x Muscle effect ($p < .001$) revealed associations between higher age and both lower RF CV ($\beta = -0.27$, $p = .013$) and higher GL CV ($\beta = 0.27$, $p = .019$).

A.5.7. Gait Cycle

For RMS, there was a significant Muscle x Age interaction ($p < .001$) where higher age was associated with lower RF RMS ($\beta = -0.25$, $p = .029$) and higher GL RMS ($\beta = 0.31$, $p = .005$), and trended towards lower TA RMS ($\beta = -0.23$, $p = .055$). Age group comparisons revealed that GL RMS was higher for 70–79 years than 20–29 years ($p = .006$), but no significant group differences for RF RMS or TA RMS (ps > .017).

For CV, there was a significant Age effect ($p = .038$) where higher age was associated with higher CV ($\beta = 0.17$, $p = .011$).

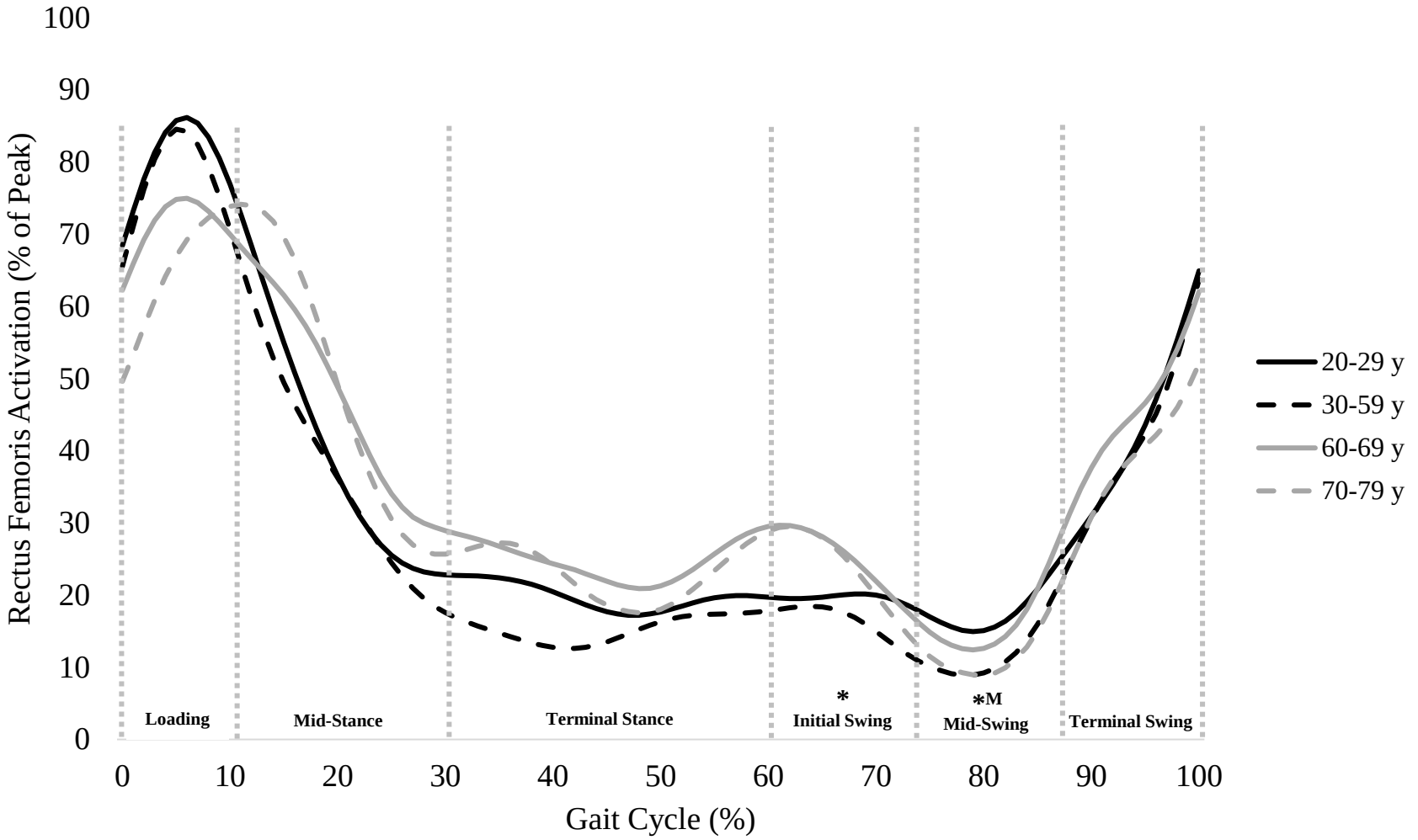

Figure A.1. Mean rectus femoris activation of participants during the gait cycle. To visualize age effects, mean curves were calculated for adults aged 20-29 y (N = 19; solid black line), 30-59 y (N = 10; dashed black line), 60-69 y (N = 43; solid grey line), and 70-79 y (N = 19; dashed grey line). Vertical dashed lines identify specific phases. Significant Age effects (*) and male-specific Age effects (*M) on activation amplitude are shown.

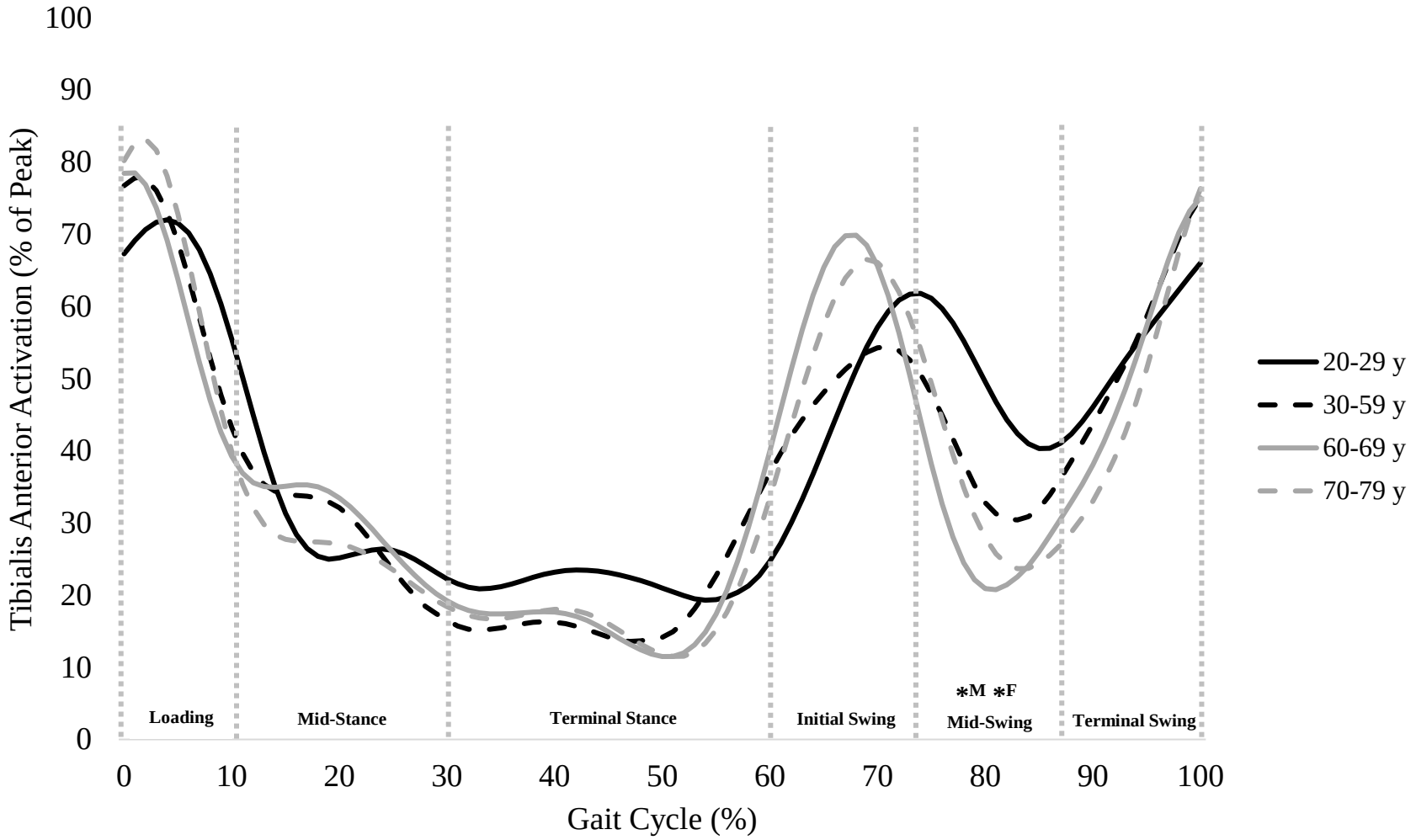

Figure A.2. Mean tibialis anterior activation of participants during the gait cycle. To visualize age effects, mean curves were calculated for adults aged 20-29 y (N = 19; solid black line), 30-59 y (N = 10; dashed black line), 60-69 y (N = 43; solid grey line), and 70-79 y (N = 19; dashed grey line). Vertical grey lines identify specific phases. Significant male-specific Age effects (*M) and female-specific Age effects (*F) on activation amplitude are shown.

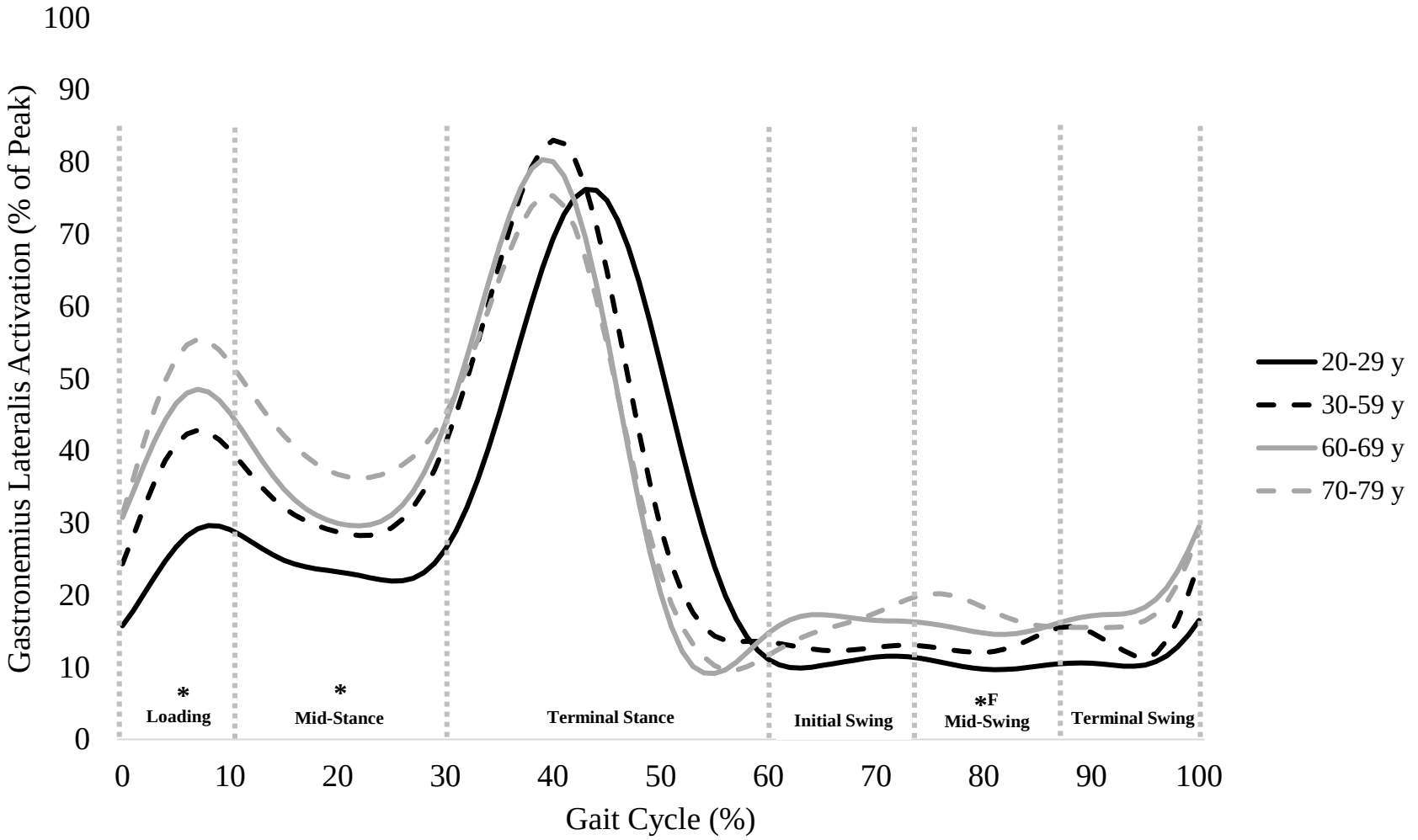

Figure A.3. Mean gastrocnemius lateralis activation of participants during the gait cycle. To visualize age effects, mean curves were calculated for adults aged 20-29 y (N = 19; solid black line), 30-59 y (N = 10; dashed black line), 60-69 y (N = 43; solid grey line), and 70-79 y (N = 19; dashed grey line). Vertical grey lines identify specific phases. Significant Age effects (*) and female-specific Age effects (*F) on activation amplitude are shown.

Table A.3. Mean root mean squares (SD) of the rectus femoris (RF), tibialis anterior (TA), and gastrocnemius lateralis (GL) at each gait cycle phase for males and females. Sex effect p-values from the mixed effect models are also presented.

Gait Cycle Phase	Muscle	Male	Female	Sex Effect
Loading (0-10%)	RF	72.3 (11.3)	69.4 (13.7)	
	TA	69.1 (10.6)	68.7 (9.0)	.546
	GL	40.5 (19.8)	41.4 (18.5)	
Mid-stance (10-30%)	RF	49.5 (14.7)	52.9 (11.4)	
	TA	27.3 (8.6)	36.5 (13.1)	.311
	GL	37.8 (15.7)	36.0 (11.5)	
Terminal Stance (30-60%)	RF	16.2 (6.5)	28.1 (8.3)	
	TA	19.5 (10.9)	22.5 (7.9)	.088
	GL	53.9 (6.6)	53.9 (7.7)	
Initial Swing (60-73%)	RF	23.5 (18.0)	28.4 (11.6)	
	TA	55.3 (12.3)	55.6 (14.0)	.240
	GL	16.5 (9.5)	18.0 (9.3)	
Mid-swing (73-87%)	RF	23.5 (8.3)	21.5 (9.0)	
	TA	27.7 (10.9)	30.2 (12.8)	.128
	GL	12.7 (5.0)	17.3 (9.6)	
Terminal Swing (87-100%)	RF	42.7 (17.9)	47.5 (15.3)	
	TA	56.1 (11.3)	51.2 (11.2)	.217
	GL	17.2 (8.7)	19.6 (8.7)	
Gait (0-100%)	RF	41.2 (8.9)	44.9 (5.3)	
	TA	45.4 (4.2)	45.7 (4.6)	.706
	GL	40.5 (6.4)	40.7 (5.6)	

Table A.4. Mean within-cycle coefficient of variation (SD) of the rectus femoris (RF), tibialis anterior (TA), and gastrocnemius lateralis (GL) at each gait cycle phase for males and females. Sex effect p-values from the mixed effect models are also presented. Bolded values are statistically significant.

Gait Cycle Phase	Muscle	Male	Female	Sex Effect
Loading (0-10%)	RF	25.3 (15.1)	15.4 (7.8)	
	TA	37.1 (23.1)	24.3 (11.2)	**<.001**
	GL	22.0 (9.8)	18.2 (8.4)	
Mid-stance (10-30%)	RF	56.7 (18.7)	34.6 (10.6)	
	TA	38.7 (19.6)	31.4 (14.9)	**.001**
	GL	32.4 (14.9)	31.6 (15.7)	
Terminal Stance (30-60%)	RF	36.0 (20.0)	26.8 (14.5)	
	TA	55.7 (17.5)	49.4 (21.2)	**.001**
	GL	64.5 (16.3)	64.9 (13.6)	
Initial Swing (60-73%)	RF	28.6 (20.7)	23.8 (15.4)	
	TA	32.1 (19.1)	28.6 (13.8)	.132
	GL	26.4 (15.7)	22.7 (12.9)	
Mid-swing (73-87%)	RF	40.5 (17.6)	37.7 (20.6)	
	TA	33.0 (15.2)	34.1 (16.1)	.301
	GL	33.9 (16.7)	24.8 (14.9)	
Terminal Swing (87-100%)	RF	39.4 (16.9)	29.2 (11.7)	
	TA	34.0 (14.9)	35.7 (21.1)	**.013**
	GL	41.8 (25.1)	33.8 (17.9)	
Gait (0-100%)	RF	93.0 (25.4)	69.7 (15.6)	.582
	TA	77.8 (12.0)	71.6 (12.1)	

GL	84.7 (28.2)	87.6 (21.2)

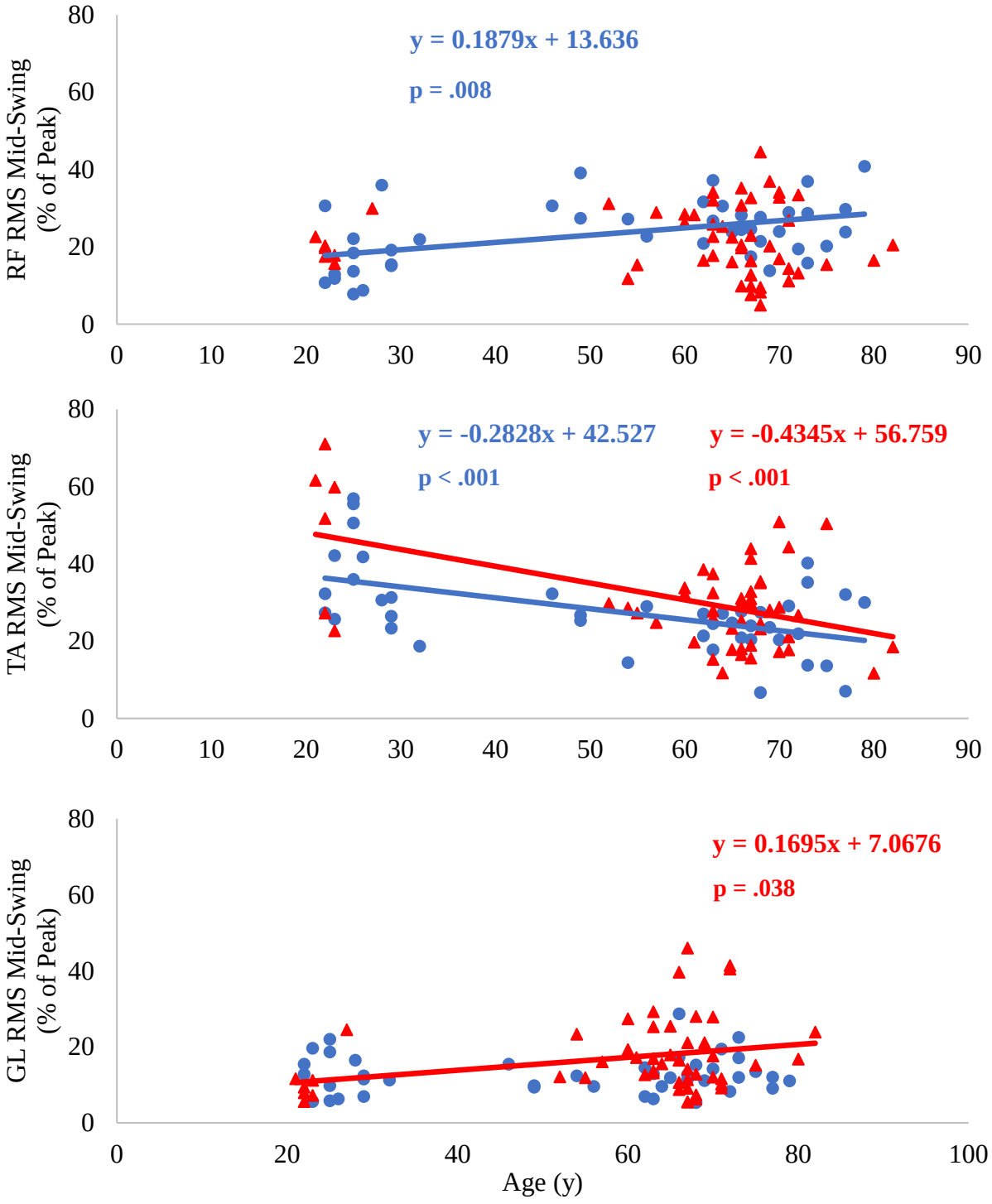

Figure A.4. Muscle- and sex-specific age regressions of mean root mean squares at the mid-swing phase. Male (blue circles) and female (red triangles) values are displayed for the

rectus femoris (RF; top), tibialis anterior (TA; middle), and gastrocnemius lateralis (GL; bottom). Linear best fits are shown for the significant male Age effects (solid blue lines) and female Age effects (solid red lines).

A.6. Discussion

To our knowledge, this study is the first to assess the effects of older adult age, as a continuous variable, and sex on muscle activation and EMG signal variability within key phases of the gait cycle. The results can be summarized into five main findings: 1) older age had significant effects on EMG amplitude, increasing GL mainly at stance, decreasing TA mainly at swing, and generally decreasing RF amplitude; 2) older age generally increased EMG signal variability; 3) females displayed greater increases in EMG signal variability with age at loading, mid- stance, and terminal stance; 4) sex-dependent effects were mainly observed at mid-swing for EMG amplitude (with increasing age resulting in lower TA amplitude, but males' increasing age resulting in higher RF amplitude, and females' increasing age resulting in higher GL amplitude), and at stance for EMG signal variability (see conclusion 3 above); and 5) aside from 3 and 4 above, when considering the entire gait cycle, as well as the ankle muscles for the majority of the gait cycle, many age effects were independent of sex.

A.6.1. Overall effects of old age

Over the gait cycle, increasing age was consistently associated with lower RF and higher GL activation amplitudes, with a trend towards lower TA activation amplitude. Each decade was associated with 2.5% lower RF activation and 3.1% higher GL activation. These results agree with the previously observed higher GL activation during loading (Schmitz et al., 2009), lending further support that higher recruitment of the GL is an age-related adjustment important to gait immediately following heel strike. In Schmitz et al. (2009), the young and older groups' mean ages (26 and 73 years) and their gastrocnemius activations during loading (32 and 47% of mean activation) suggest that their equivalent decade rate of change was 3.2%, lower than what we observed for the loading phase (4.3%). The present study also observed age effects on muscle activation during other phases of gait (ex. initial swing) that were previously not seen (Schmitz et al., 2009; Marques et al., 2016). These may have emerged due to differences in the structure of the statistical models, as we treated age as a continuous variable, sampled a larger size of both males and females, and con- trolled for effects of gait speed, and stride length in the age models.

Although the precise reasons for these between-study differences is unclear, lower recruitment of the RF and higher recruitment of the GL during gait of aging adults suggests that the age-related joint load redistribution from the ankle to the hip likely does not coincide with a shift away from ankle muscle recruitment. The theory that age causes a distal to proximal joint load redistribution originates from DeVita and Hortobagyi (2000), who observed higher hip extensor and lower ankle plantar flexion loads in older adults than in young adults. However, this association between age and lower ankle plantar flexion load may not arise from lower plantar flexion activation. The current study shows associations between higher GL activation and age at loading, mid-stance, and the full gait cycle, suggesting that plantar flexor recruitment generally increases with age. Additionally, RF activation was lower with higher age during loading as observed by Marques et al. (2016), and lower over the full gait cycle, meaning muscle activation seemed to shift from the hip to the ankle, opposite of joint load observations. However, the age effect on RF activation disagrees with previous studies (Schmitz et al., 2009; Franz and Kram, 2013), with Franz and Kram (2013) finding that gluteus maximum activity approached maximum isometric values in older adults. A more comprehensive study of how age affects recruitment of the hip musculature during gait is needed, especially given the potential effects on biceps femoris (Schmitz et al., 2009) and gluteus maximus (Franz and Kram, 2013), as well as the suggestion that iliacus and psoas may be the main contributors to active hip flexion work (Schmitz et al., 2009).

In addition, the RMS differences between the 20–29 year, 60–69 year, and 70–79 year age groups of our study suggest that different neuromuscular adaptations of gait can occur in different decades for older adults. Compared to adults 20–29 years, GL RMS at loading, RF RMS at initial swing, and TA RMS at mid-swing were different for adults 60–69 years, yet GL RMS over the gait cycle was different only for adults 70–79 years. It seems that age-related changes in the quantity of neuromuscular activation occur earlier in specific phases of stance and swing than over the full gait cycle. Further, the GL RMS at loading was also higher for adults 70–79 years than those 60–69 years, suggesting that recruitment of the GL may change significantly over a single decade in older adults.

A.6.2. Are there sex-specific effects of aging on ankle muscle EMG?

According to our first hypothesis, we expected to find evidence for sex-specific effects of old age on ankle muscle activity. However, we did not find strong support for this. For one, the

age association with GL activation at the mid-swing phase was indeed different between males and females. While male and female age were both associated with lower TA activation (6.2–6.7% per decade), only female age was associated with GL activation amplitude, with each decade approximately corresponding to 3.3% higher GL activation. These associations were independent of gait speed (Smith et al., 2002; Ko et al., 2011; Kobayashi et al., 2016) and stride length (Smith et al., 2002; Ko et al., 2011; Kobayashi et al., 2016; DeVita and Hortobagyi, 2000; Cho et al., 2004; Kerrigan et al., 1998; Bruening et al., 2015). Aging females have been shown to have steeper rises in dorsiflexion duration than aging males (Ko et al., 2011), suggesting that lower TA and higher GL activations could lengthen the period of dorsiflexion. Kirkwood et al. (2011) associated the timing of GL activation in older females with a recurring history of falls, however the amount of activation was not analyzed. Interestingly, their mean activation curves appear to show a lower GL activation amplitude for females with recurring falls, compared to older females without a history of recurring falls. Moreover, higher gastrocnemius activation has been interpreted as a strategy to maintain postural stability at the expense of energy efficiency (Nagai et al., 2011; Hortobagyi et al., 2011). While this link requires further study, it suggests a neuromuscular origin to the aging effects on dorsiflexion that could be sex-specific. However, our results do not provide clear support for this sex-specific effect on dorsiflexion control mechanisms, and the higher GL activation during mid-swing for aging females is worth further investigation.

A.6.3. Are there sex differences in EMG signal variability?

Our results show that old age was also associated with higher variability of muscle activation patterns during the overall gait cycle and at mid-swing. This higher EMG signal fluctuation with age could reflect an overcompensation of neuromuscular activation when performing gait. Reasons for this age-related overcompensation could include both peripheral and central mechanisms; increased motor unit sizes (Vandervoort, 2002) and, as discussed in Seidler et al. (2010), excessive recruitment in the brain, may both lead to more imprecise and therefore more variable muscle activation. Mechanistic studies are needed to fully understand the specific reasons for the higher and more variable muscle activation patterns observed with age.

In accordance with our second hypothesis, we show some evidence for a sex difference in variability of activation signals. Indeed, at loading, older males had lower CV than younger males. Conversely, at terminal stance, older females displayed higher CV than younger females. This

suggests that with old age, female patterns become more complex and less stable than male gait activation (Di Nardo et al., 2015). However, the limited use of EMG signal CV in the literature suggests that it may be an unsuitable indicator of activation complexity, and therefore that different computational methods used in this limited literature may actually capture different neuromuscular activation phenomena. These differences between studies could also be due to methodological differences in the gait data acquisition protocols. In our study, single strides were analyzed from short distance gait, and it is possible that patterns may differ when comparing consecutive strides from longer distance and more continuous gait. Indeed, Di Nardo et al. (2017) assessed hundreds of TA and GL gait cycles, finding higher EMG complexity in female adolescents and adults than males, but no sex differences in younger children. Accordingly, the authors suggested that sex differences in recruitment emerge in adolescence and develop in adulthood. Though their recent study did not examine older adults, it provides support for recording many EMG cycles during continuous gait to evaluate muscle activation modulation and complexity, and so the interpretation from our study is limited to short distance gait.

We also note a limitation inherent to our sample. The participants, while a fairly numerous sample (N=93) that ranges largely in age (20–82 years), were mostly 20–29 years and 60 years+, resulting in an under-sample of males and females aged 30–59 years. Adults in this age range seem to follow a linear age effect with spatiotemporal parameters of gait (Beauchet et al., 2017), agreeing with the linear relationships in this study, however there is some evidence to suggest a non-linear age effect on certain kinematic parameters of gait (Monda et al., 2015). The sample in this study was also cross-sectional in design, and so we caution that longitudinal studies are needed to better understand the individual effects of aging on gait, particularly during the middle-age period.

A.7. Conclusions

As a whole, our study provides evidence to support that the influence of healthy aging on muscle activation is sex-dependent, but only in some phases of gait. This is the case at mid-swing, with higher RF activation for males and higher GL activation for females. Further, the influence of aging on the variability of within-cycle EMG signals is sex-dependent during stance, with lower signal variability with age in males at loading, and conversely, higher signal variability with age in females at terminal stance. Independent of sex, age generally affects the recruitment of ankle

muscles during gait, primarily through higher GL activation. These results suggest that the neuromuscular mechanism of ankle instability in aging adults shares both sex-dependent and sex-independent characteristics, encouraging future studies to include sex as a factor when studying the influence of age on the neuromuscular control of gait.

A.8. Acknowledgements

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A.9. Author Contributions

CB and JC were responsible for study conception, while FC, GP, MP, MF, PH, MPP, and MP were responsible for the study organization and execution. CB and JC designed and executed the statistical analyses. CB wrote the first draft of this manuscript, which was reviewed and critiqued by MP and JC. All authors read and approved the final manuscript.

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