UNIVERSIDADE ESTADUAL PAULISTA
"JÚLIO DE MESQUITA FILHO"
INSTITUTO DE BIOCIÊNCIAS – RIO CLARO

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA MOTRICIDADE - INTERUNIDADES

EFFECTS OF AGE AND FATIGUE ON HUMAN GAIT

PAULO CEZAR ROCHA DOS SANTOS

Rio Claro – SP
2020

unesp
UNIVERSIDADE ESTADUAL PAULISTA
“JÚLIO DE MESQUITA FILHO”
INSTITUTO DE BIOCIÊNCIAS – RIO CLARO

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA MOTRICIDADE - INTERUNIDADES

EFFECTS OF AGE AND FATIGUE ON HUMAN GAIT

PAULO CEZAR ROCHA DOS SANTOS

Tese apresentada à University of Groningen e reconhecida pela Pró-Reitoria de Pós-Graduação da Universidade Estadual Paulista, como parte dos requisitos para obtenção do título de doutor (diploma duplo) em Ciências da Motricidade

Orientadores: Profa. Dra. Lilian Teresa Bucken Gobbi;
Prof. Dr. Tibor Hortobágyi

Coorientadores: Prof. Dr. Fabio Augusto Barbieri
Profa. Dra. Claudine Lamoth
Profa. Dra. Inge Zijdewind

Rio Claro – SP
2020

S237e

Santos, Paulo Cezar Rocha dos
Effects of age and fatigue on human gait / Paulo Cezar Rocha dos Santos. -- Rio Claro, 2020
145 p. : il., tabs., fotos

Tese (doutorado) - Universidade Estadual Paulista (Unesp), Instituto de Biociências, Rio Claro
Orientadora: Lilian Teresa Bucken Gobbi
Coorientador: Fabio Augusto Barbieri

1. Envelhecimento. 2. Fadiga. 3. Marcha humana. 4. Fadiga mental. I. Título.

Sistema de geração automática de fichas catalográficas da Unesp. Biblioteca do Instituto de Biociências, Rio Claro. Dados fornecidos pelo autor(a).

Essa ficha não pode ser modificada.

Effects of age and fatigue on human gait

PhD thesis

to obtain the degree of PhD at the
University of Groningen
on the authority of the
Rector Magnificus Prof. C. Wijmenga
and in accordance with
the decision by the College of Deans

and

to obtain the degree of PhD at the
São Paulo State University – UNESP
on the authority of the
Rector Magnificus Prof. S.R. Valentini,
and in accordance with
the decision by the Dean of UNESP.

Double PhD degree

This thesis will be defended in public on

Wednesday 7 October 2020 at 18.00 hours

by

Paulo Cezar Rocha dos Santos

born on 16 November 1985
in Osasco – SP, Brasil

UNIVERSIDADE ESTADUAL PAULISTA

Câmpus de Rio Claro

CERTIFICADO DE APROVAÇÃO

TÍTULO DA TESE: Effects of age and fatigue on human gait

AUTOR: PAULO CEZAR ROCHA DOS SANTOS
ORIENTADORA: LILIAN TERESA BUCKEN GOBBI
ORIENTADOR: TIBOR HORTOBÁGYI
COORIENTADORA: CLAUDINE LAMOTH
COORIENTADORA: INGE ZIJDEWIND
COORIENTADOR: FABIO AUGUSTO BARBIERI

Aprovado como parte das exigências para obtenção do Título de Doutor em CIÊNCIAS DA MOTRICIDADE, especialidade: Atividade Fisica e Saude pela Comissão Examinadora:

Profa. Dra. LILIAN TERESA BUCKEN GOBBI
Departamento de Educação Física / UNESP - Instituto de Biociências de Rio Claro – SP

Prof. Dr. TIBOR HORTOBÁGYI (Orientador)
Center for Human Movement Sciences, University Medical Center Groningen, University of Groningen

Prof. Dr. URS GRANACHER
Division of Training and Movement Sciences, Research Focus Cognition Sciences, University of Potsdam, Potsdam

Prof. Dr. E BERT OTTEN
Center for Human Movement Sciences, University Medical Center Groningen, University of Groningen

Profa. Dra. NATASHA MARIA MAURITS
Department of Neurology, University Medical Center Groningen, University of Groningen and Research School of Behavioural and Cognitive Neurosciences, University of Groningen

Prof. Dr. HAN HOUDIJK
Center for Human Movement Sciences, University Medical Center Groningen, University of Groningen

Prof. Dr. ALESSIO MURGIA
Center for Human Movement Sciences, University Medical Center Groningen, University of Groningen

Prof. Dr. SJOERD BRUIJN
Department of Human Movement Sciences, Faculty of Behavioural and Movement Sciences, Vrije Universiteit Amsterdam, and Amsterdam Movement Sciences

Rio Claro, 07 de outubro de 2020.

PROPOSITIONS

Belonging to the thesis

Effects of age and fatigue on human gait

Paulo Cezar Rocha dos Santos
Groningen, 7 October 2020

1. Muscle and mental fatigability minimally affected the stride outcomes of treadmill walking in younger and older adults. (this Thesis)
2. Treadmill pace may be minimizing any potential effects of fatigability on stride outcomes. (this Thesis)
3. Mental fatigability seemed to affect stride outcomes in gait conditions demanding higher cognitive involvement, such as in dual-task walking.
4. Despite several studies using repetitive sit-to-stand task to induce muscle fatigability, how this task affects muscle activation is still unexplored. (this Thesis)
5. Older adults minimized the failure in muscle activation, and voluntary force, by performing fewer repetitive sit-to-stand trials. (this Thesis)
6. Repetitive sit-to-stand provided limited scope to probe the age-effects on stride outcomes in gait and posture. (this Thesis)
7. Even with limited effect, repetitive sit-to-stand task induces age-specific adaptation in the neural drive, which could be interpreted as compensation for fatigue to maintain gait performance. (this Thesis)
8. *"It is a strange fancy to suppose that science can bring reason to an irrational world, when all it can ever do is give another twist to a normal madness."* (John Gray)
9. *"An expert is a person who has made all the mistakes that can be made in a very narrow field."* (Niels Bohr)

Ao meus pais, irmã e esposa,

Obrigado por acreditarem em mim!

Obrigado por estarem comigo neste e em outros momentos!

SUMMARY - EFFECTS OF AGE AND FATIGUE ON HUMAN GAIT

Natural aging is a degenerative process accompanied by decline, among others, in motor function, including gait and postural control, and the ability to make adjustments in these tasks when challenged by external and internal perturbations. Fatigability is a form of internal perturbation, resulting in reductions of objective measures of physical and/or mental performance and motivation over a discrete period. An intriguing question is whether and how age affects the ability to adapt gait to the state created by muscle and mental fatigability, in order to minimize a loss of daily function. Therefore, this thesis aimed to examine the effects of age and experimentally induced fatigability on human gait.

In Chapter 2, we systematically reviewed studies that examined the effects of experimentally induced mental and muscle fatigability on older adults' gait. We observed that muscle performance fatigability affects spatial and temporal features of gait and inter-stride trunk acceleration variability. In contrast, sustained mental activity tends only to affect step variability during dual-tasking. Although muscle and mental fatigability alter older adults' gait performance, the mechanisms that explain why walking changes occur are unclear.

Seeking to understand the mechanisms that explain how age and fatigability would affect gait, we experimentally induced muscle and mental fatigability and examined these fatigue effects on treadmill walking in 12 older and 12 younger adults. Muscle fatigability was induced by participants repeatedly performing the sit-to-stand task (rSTS). Mental fatigability was induced by participants performing demanding mental tasks for 30 minutes.

In chapter 3, we verified that the rSTS and demanding mental tasks minimally affected the stride variables and the dynamics of walking on the treadmill in the two age groups. Regarding the mental fatigability, we interpreted that demanding mental tasks indicate to induce adaptation on gait only in dual-task conditions. We also speculated that age-specific modulations on neuromuscular control due to fatigability might have compensated for the effects of fatigue to maintain the gait performance. In addition, the effects of rSTS were perhaps not specific enough to induce changes in key elements of gait.

In chapter 4, we examined the effects of age and exhaustive rSTS on muscle activation during ascent and descent phases of the STS task. We found that by performing remarkably fewer STS trials, older adults had minimized fatigability effects on muscle activation, voluntary force, and motor function, producing minimal changes in stride outcomes and gait dynamics after rSTS, as seen in Chapter 3. In chapter 5, we examined if there was an age-specific modulation in the common neural drive to muscles to compensate for muscle fatigability and spare gait function. We found that rSTS produced an age-specific compensatory strategy in the neural control of muscles to maintain the gait performance.

Chapter 6 summarizes the main findings. We discussed the data from the perspective that: 1) the effects of age and fatigability may be more evident during real-life, overground walking situations involving cognitive and motor dual-tasking compared to walking on a treadmill and 2) perhaps, a fatigue-induction model that involved walking tasks and/or focused on specific aspects of the task (such as fatigue induced by long distances walking over level and/or inclined surfaces, or stairs ascent protocols) could be more effective in examining the effect of aging on gait adaptability. However, even with limited effects, rSTS produced age-specific changes in the neural drive for synergistic ankle muscles, which can be interpreted as compensation for fatigue that healthy older adults develop to maintain walking performance.

Key words: Aging; fatigability; mental fatigue; walking

SAMENVATTING - EFFECTEN VAN LEEFTIJD EN VERMOEIDHEID OP HET LOPEN VAN DE MENS

Gezond ouder worden gaat samen met functionele achteruitgang, waaronder die van het lopen, balans en het vermogen om deze aan te passen aan allerei interne en externe verstoringen. Vermoeidheid kan beschouwd worden als een interne verstoring welke resulteert in een afname van fysieke en /of mentale prestaties en een afname in de motivatie om fysieke taken uit te voren. Een belangrijke vraag is, of en hoe leeftijd het vermogen beindvloed om het lopen aan te passen aan spier en mentale vermoeidheid en op wat voor wijze dit effect heeft op dagelijkse activiteiten.

Hoofdstuk 2 presenteert een systematisch literatuuronderzoek waarbij studies zijn geanalyseerd die de effecten van experimenteel veroorzaakte spier- en mentale vermoeidheid op het lopen van ouderen onderzochten. Uit het review komt naar voren dat spatiële en temporele kenmerken van het lopen en de en de variabiliteit van de rompversnellingen beinvloed worden door spiervermoeidheid. Daarentegen heeft aanhoudende mentale activiteit alleen invloed op de stapvariabiliteit van het lopen als er tegelijkertijd een cognitieve taak wordt uitgevoerd, zgn. dubbeltaken. Ondanks dat het review heeft aangetoond dat spier- en mentale vermoeidheid de loopprestaties veranderen, blijven de mechanismen die ten grondlag liggen aan de gerapporteerde loopveranderingen onduidelijk.

Om meer inzicht te krijgen op welke wijze leeftijd en vermoeidheid het lopen beïnvloeden, hebben we een experiment ontworpen om spiervermoeidheid en mentale vermoeidheid te veroorzaken, en de effecten ervan op het lopen op een loopband te onderzoeken bij 12 ouderen en 12 jongvolwassenen. Spiervermoeidheid werd veroorzaakt door de deelnemers herhaaldelijk een zit-staan taak te laten uitvoeren (repetitive sit-to-stand, rSTS) en mentale vermoeidheid werd veroorzaakt door de deelnemers 30 minuten lang veeleisende mentale taken op een computer te laten uitvoeren. In hoofdstuk 3 laten we zien dat zowel bij ouderen als jongvolwassenen, de rSTS taak en mentale taken, schrede variabelen en de dynamica van het lopen nauwelijks beïnvloedden. Wat betreft de mentale vermoeidheid, kan het zijn dat, aanpassingen in het looppatroon alleen optreden wanneer tegelijkertijd complexere, dubbeltaken worden uitgevoerd. Daarnaast kan het zijn dat leeftijdsspecifieke aanpassingen in de neuromusculaire controle, als gevolg van vermoeidheid, mogelijk de effecten van vermoeidheid hebben gecompenseerd om de loopprestaties te behouden. Bovendien waren de effecten van rSTS taak mogelijk te algemeen om veranderingen in de belangrijkste elementen van het lopen teweeg te brengen.

In hoofdstuk 4 onderzochten we de effecten van leeftijd en rSTS taak op spieractivatie tijdens specifieke fases van STS-taak (fasen opstaan en zitten). We vonden dat ouderen in vergelijking met jongevolwassenen opmerkelijk minder STS-herhalingen uitvoerden. Door minder STS-herhalingen uit te voeren, bleven vermoeidheidseffecten op spieractivatie, kracht en de uitvoering van de taak vrijwillige kracht en motoriek tot een minimum beperkt bij oudere volwassenen. Daarom werden minimale veranderingen gevonde loopvariabelen. In hoofdstuk 5 hebben we onderzocht of er een leeftijdsspecifieke aanpassing was in de gemeenschappelijke neurale aansturing van spieren om de spiervermoeidheid tijdens het lopen te compenseren. We vonden dat rSTS een leeftijdsspecifieke compensatiestrategie veroorzaakte in de neurale aansturing van spieren met als doel de loopprestaties te behouden.

Hoofdstuk 6 vat de belangrijkste bevindingen samen. De resultaten worden besproken vanuit het perspectief dat: 1) de effecten van leeftijd en vermoeidheid waarschijnlijk meer optreden tijdens looptaken die lijken op het lopen in het dagelijks leven, loopsituaties met cognitieve en motorische dubbeltaken. 2) een vermoeidheid inducerend model dat looptaken omvat en/ of gericht is op specifieke aspecten van het lopen (zoals, vermoeidheid veroorzaakt door lange afstanden te lopen op vlakke en / of hellende oppervlakken, of protocollen voor het) wellicht duidelijker verschillend tussen jong en oud laten zien in het aanpassingsvermogen van het looppatroon. Echter, al zijn de algemene effecten klein, rSTS taak geeft leeftijdsspecifieke veranderingen in de neurale aansturing van synergetische enkelspieren, wat kan worden geïnterpreteerd als een compensatie voor vermoeidheid die gezonde oudere volwassenen ontwikkelen.

Sleutelwoorden: Veroudering; vermoeidheid; mentale moeheid; wandelen

RESUMO – EFEITO DO ENVELHECIMENTO E DA FADIGA NO ANDAR NO HUMANO

O envelhecimento é um processo degenerativo que resulta em declínios funcionais, como aqueles observados na performance do andar, no controle postural e na habilidade de adaptação destas tarefas para com perturbações internas e externas. Perturbações internas surgem devido à uma redução na disponibilidade dos recursos biológicos, podendo ser atribuídas como consequência da fadiga. Uma questão intrigante é quando e como o envelhecimento afeta a capacidade de adaptação à perturbação criada pela fadiga para minimizar a perda da funcionalidade. Portanto, esta tese teve como objetivo examinar os efeitos do envelhecimento e da fadiga induzida experimentalmente no andar.

No capítulo 2, nós revisamos sistematicamente estudos que examinaram o efeito da fadiga muscular e mental no andar de idosos. Nós identificamos que, embora as fadigas muscular e mental alterem o desempenho do andar, os mecanismos que explicam o porquê das alterações no andar ocorrem não estão claros. Em conclusão, fadiga muscular afeta parâmetros espaço-temporais do andar e a variabilidade da aceleração do tronco. Em contrapartida, fadiga mental parece afetar a variabilidade do andar somente em condições de tarefa dupla.

Buscando entender os mecanismos que explicam como a fadiga afeta o andar, nós induzimos as fadigas muscular e mental experimentalmente e verificamos seus efeitos no andar na esteira de 12 adultos e 12 idosos. A fadiga muscular foi induzida pela repetitiva tarefa do sentar e levantar (rSTS). A fadiga mental foi induzida por tarefas de demanda mental por 30 minutos. No capítulo 3, nos verificamos que o envelhecimento, a rSTS e a tarefa de demanda mental afetaram minimamente as variáveis da passada e a dinamicidade do andar na esteira de idosos e adultos saudáveis. Nós interpretamos que a fadiga mental parece induzir efeitos somente na condição de tarefa dupla; modulações neuromusculares especificas para cada grupo podem ter compensado os efeitos da fadiga para a manutenção do desempenho do padrão do andar induzido pela esteira; e que os efeitos da rSTS talvez não foram específicos o suficiente para induzir mudanças em elementos chaves do andar.

No capítulo 4, nós examinamos os efeitos do envelhecimento e da rSTS na ativação muscular durante as fases de levantar e sentar da cadeira, e no nível de força. Nós indicamos que por realizar um substancial menor número de repetições, idosos tiveram minimizados os efeitos da fadiga muscular na atividade do músculo e na produção de força máxima. Isto provavelmente explica as mínimas alterações observadas nas variáveis do passada e na dinamicidade do andar vistas no capítulo 3. No capítulo 5, nós testamos se existiam modulações específicas do envelhecimento no controle neuromuscular para compensar os efeitos da fadiga no andar em esteira. Nós indicamos que apesar de idosos tentarem minimizar os efeitos da fadiga muscular por diminuir o desempenho na rSTS, esta elicitou estratégias específicas da idade no comando neural para os músculos para manter a performance do andar em esteira.

O capítulo 6 resume as principais descobertas desta tese. Discutimos os dados na perspectiva de que 1) os efeitos da idade e da fadiga podem ser mais evidentes durante as tarefas do andar quando este é avaliado próximo às condições de vida real, ou em situações de tarefa-dupla em comparação com a caminhada na esteira; 2) talvez, um modelo de indução à fadiga que envolvesse tarefas de andar e/ou que focasse em aspectos específicos da locomoção (como o andar por longa distância em superfícies planas e/ou inclinadas, e subir e descer escadas), pudesse ser mais eficaz para examinar o efeito do envelhecimento nas adaptações do andar. No entanto, mesmo com efeitos limitados, a rSTS provoca alterações específicas da idade no 'drive' neural para músculos sinergistas do tornozelo, que podem ser interpretadas como compensação à fadiga para que idosos mantenham o desempenho do andar.

Palavras-chave: Envelhecimento; fadiga; fadiga mental; marcha humana

TABLE OF CONTENTS

1

General introduction

Epidemiological data suggest that the age of the population has been growing substantially. World Health Organization projections indicate that from 2010 to 2050, the segment of the population aged over 65 years old will almost triple (from 524 million to 1.5 billion) [1]. Aging is a natural degenerative process of the cardiorespiratory, musculoskeletal, and neuronal systems [2]. It is not surprising that the physiological and biomechanical processes associated with aging are in the forefront of health and life sciences.

Natural aging is associated with a visible 40% decline in the capacity to produce maximal voluntary force, accompanied by a substantial reduction in type II muscle fiber, in the number and diameter of myelinated motoneuron axons, in the velocity of peripheral nerve conduction, impairing functions of sensory fiber, resulting in an altered motor units function [3,4]. Aging also affects the central nervous system, as older compared with younger adults have ~15% lower white and grey matter volume, which necessitates overactivation to perform the same motor task [5,6]. Aging affects not only focal activation of selected brain areas during motor actions but the activation of networks, with some networks increasing and others decreasing the strength of functional connectivity, with a net effect of decreases in cognitive and motor function [7–9].

Age-related degenerative processes result in functional decline, including walking speed, postural control, and the ability to adapt these tasks to environmental or self-imposed perturbations [10,11]. An impaired ability to adapt to environmental stimuli is interpreted as compromised evolutionary survival [12]. An intriguing question in health and life science is whether and how age affects the ability to adapt to a perturbation created by fatigue in order to minimize a loss of daily function.

1. AGE-RELATED ADAPTABILITY IN GAIT

The term "Adaptability" reflects the ability of an individual (or system) to adjust to or deal with changing circumstances [12]. In motor control, adaptability can be a marker of the ability to cope with environmental, task and individual perturbations [13,14]. In the context of gait, adaptability ensures that the task can be completed notwithstanding internal (as a biological reduction in the availability of resources, i.e., fatigue) and external disturbances (e.g., slip, trip) in daily life. Because gait is a dynamic and complex interface between the individual and the environment, adaptability in the systems controlling gait is needed. However, age-related reductions in neuromuscular, sensorimotor, and cognitive function could interfere with adaptability to perturbations [15,16], with reductions in the ability to adapt gait to perturbations [13]. The reduced adaptability of gait increases instability, and the risk of trips, slips, and falls [17–19].

The most visible changes in old adults' gait are slower habitual walking speed, accompanied by shortened and wide steps, longer double support time, and a higher cadence [11,20]. Age-related gait changes also include changes in the variability characteristics of several gait features [21], such as a decline of local dynamic stability of about 50% as quantified by the maximal Lyapunov exponent in anteroposterior and mediolateral accelerations during treadmill walking [22]. Such changes in stability and variability features of gait have been associated with cognitive health and predict daily function, independence, mobility, falls, and mortality [18,23–26].

A decline in gait performance, stability, and complexity features of gait in older adults are likely related to the age-related alteration in neuromuscular control. Older vs. younger adults walk with ~50% higher knee agonist-antagonist coactivation [27,28]. The mechanisms for increased coactivation might be related to age-specific reductions in inhibitory control [29]. Combined with altered inhibitory control, old age also involves reduced cortico-muscular communication and intermuscular common drive during gait [30,31] that may underlie the lack of adaptation in gait in response to a perturbation.

Adaptability can be examined through the evaluation of responses to experimental perturbations. There are a number of perturbation models to examine human motor adaptability, including mechanical/external and internal disturbances. Mechanical/external perturbation models include: sudden changes in surface stability, slip induction [32], and split-belt treadmill walking [33]. Older adults can cope and adapt to these perturbations in an age-specific manner, i.e., older vs. younger revealed faster horizontal heel contact velocity after slip induction and greater swing speed of the fast leg during split-belt treadmill walking [33,34]. Internal perturbations, on the other hand, include the state induced by fatigue that can interfere with gait control [35,36].

2. FATIGABILITY AS A PERTURBATION MODEL IN OLDER ADULTS

Fatigue has a diverse set of definitions. Herein, we are considering the taxonomy proposed by Kluger et al. [37] and Enoka et al. [38] in which fatigue can be assessed as a trait (i.e., the average amount of fatigue sensations experienced during consecutive days, weeks, or months) and/or a state (i.e., the rate of change in key outcomes and/or increased feelings of exertion during a fatiguing task). Although it is possible to assess the trait of fatigue by reporting tools, this type of fatigue cannot be experimentally manipulated. Therefore, in laboratory environments, the experimental set-up usually induces a state of fatigue in "trait fatigue-free" healthy older adults to examine somehow if this population can adapt motor performance with the interference induced by prolonged muscle and mental exertion [39–41].

The state of fatigue derives from the interaction between perceived (i.e., increased in self-reported exertion) and performance (i.e., reduction of performance over time) fatigability [37,38,40]. While prolonged low-force activity or motor task at a high percentage of the available maximal mechanical output can lead to muscle performance fatigability, performing prolonged demanding mental activities interfere with cognitive functions leading to mental performance fatigability state [22,40–42]. Muscle performance fatigability is a complex phenomenon involving neural and physiological alterations at the peripherical and central levels [43]. At the peripherical level, muscle performance fatigability increases the accumulation of metabolites in the intramuscular milieu [43,44]. Such increases activate groups III and IV muscle afferents that inhibit part of the motoneurons pools, decreasing motor unit firing [43,44]. One observed effect of muscle fatigability on the central level is that the central nervous system increases the strength of neural drive as an attempt to compensate for the effects of fatigue on muscle properties [45–47]. Alteration in muscle control is also observed as a ~10 to 30% increase in electromyography amplitude due to fatiguing muscle exercise in older adults [46,48]. Muscle fatigability is also characterized by a reduction in the capacity to produce maximal voluntary torque or to sustain a motor task [44].

Mental performance fatigability is a psychobiological state experienced during and after prolonged periods of demanding cognitive activity, marked by feelings of tiredness and lack of energy and deterioration in cognitive performance [41,49–51]. For instance, demanding mental tasks decreased motivation, and processing speed (i.e., 7 to 15% higher reaction time) and performance (i.e., 5 to 30 of increase in errors) [22,51]. The transient decline in cognitive functions is also accompanied by impairments in the top-down control of movement [50]. Therefore, it is reasonable to assume that behavioral mental fatigability would affect motor performance, mainly in tasks that require higher cognitive resources and for older adults due to the reduced capacity to allocate such resources [49,52].

Altogether, the effects of muscle and mental performance fatigability in both peripherical and central levels accompanied by changes/reductions in behavioral data can justify fatigue as a unique niche to examine age-related adaptation to internal perturbation [53]. Although in the laboratory environment, several tasks exist to induce muscle and mental performance fatigue, we particularly used repetitive sit-to-stand and cognitive demanding computer tasks.

2.1. Repetitive sit-to-stand

Protocols to induce muscle performance fatigability usually involve a single joint, such as isolated knee or ankle joint exercise vs. multi-joint and/or large muscle mass involved exercises [39]. To induce muscle performance fatigability, we choose repetitive sit-to-stand as a demanding functional task that requires relatively higher muscle effort compared to level and inclined walking [54]. Repetitive sit-to-stand not only induces changes in muscle activations in knee extensor but also in the ankle and hip muscles [48] (see details in chapter 4). After repetitive sit-to-stand, maximal voluntary force declines by 8 to 16% and these changes are accompanied by reductions in muscle activation. Rate of perceived exertion also increases due to repetitive sit-to-stand independent of age [40,55]. During repetitive sit-to-stand, older adults' relative muscle activation was 50 to 100% of the maximum knee muscular activation capacity, twice as high as compared with younger adults [48,54]. Because the muscle groups involved in sit-to-stand are also active during gait [56] and repetitive sit-to-stand evokes peripherical and central changes in muscle control (Figure 1), the repetitive sit-to-stand might be a feasible protocol to induce muscle performance fatigability to examine age-related gait adaptability.

2.2. Computer tasks to induce mental performance fatigability

The general concept suggests that due to age-related decline in the availability and capacity to allocate cognitive resources [8], and the association between cognitive function and gait [15], interference with attention and executive function would augment the age differences in gait performance. While several tasks have been used to induce mental performance fatigability (i.e., simulating drive, long-time exposure to visual stimuli, dual-task) [57], cognitive reaction time and inhibitory tasks are particularly interesting because these tasks interfere with attention and executive functions [51]. Such tasks increase the perception of fatigue and are associated with changes in brain activation [51]. Targeting mental performance fatigability, three different computational tests were proposed previously (Psychomotor Vigilant Test, Stroop, and AX-continuous performance task) with similar effects on reported fatigue and task-specific outcomes [51,58]. Therefore, a protocol that combines all tests might induce a decline in a large range of cognitive functions, such as attention, processing speed, executive function, and motivation. It is also reasonable that using protocols that target more cognitive functions would augment the sensibility to induce changes in gait because declines in those functions are related to a decline in walking performance in older adults (Figure 1) [15].

3. OBJECTIVES AND OUTLINE OF THIS THESIS

This thesis aimed to examine the effects of age and experimentally induced fatigability on gait. In chapter 2, we systematically reviewed studies that examined the effects of experimentally induced mental and muscle fatigability on gait in older adults. We observed that if studies move from descriptive to mechanistic applications, the viability of the fatigability protocols might increase. Such applications would also strengthen our understanding of the underlying mechanism of age-related gait adaptability to muscle and mental fatigability. We, thus, induced states of fatigue by using repetitive sit-to-stand (muscle performance fatigability) and three computer demanding mental tasks (mental performance fatigability) to examine age-related adaptation in gait (Figure 1). In chapter 3, we aimed to examine the effects of age and fatigue-type on gait performance. Therefore, we determined the effects of age, repetitive sit-to-stand, and demanding mental tasks on gait stride related outcomes and gait dynamics during treadmill walking. Having observed minimal effects of repetitive sit-to-stand and demanding mental tasks on stride outcomes during treadmill walking, to better understand this null result, we examine the effects of fatigue perturbation on muscle activation. As such, in Chapter 4, we tested the repetitive sit-to-stand as a model to examine age-related adaptability in functional tasks, by assessing the effects of repetitive sit-to-stand on muscle activation and maximal voluntary contraction in lower limb muscles in healthy younger and older adults. In Chapter 5, we examined if there was an age-specific modulation in the common neural drive to muscles to compensate the muscle fatigability during gait. To that aim, we determine the effects of age and experimentally induced muscle fatigability on intermuscular coherence during treadmill walking.

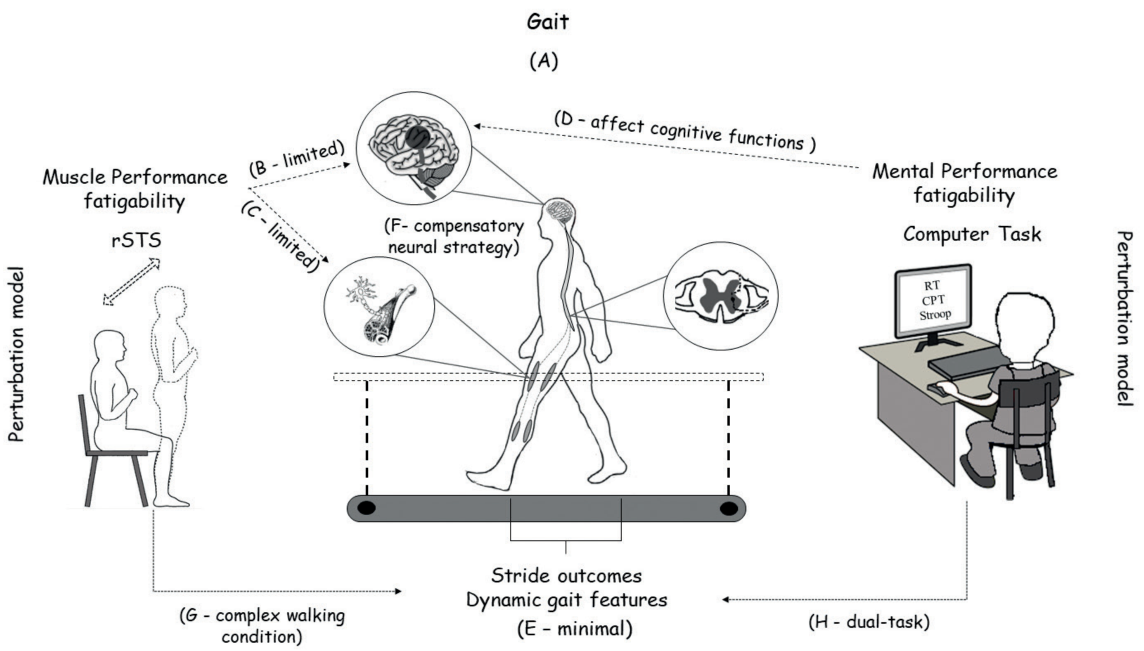


Figure 1. Schematic representation of the experimental set-up. Gait is a dynamic and complex task in which the central nervous system sends coordinated commands via the spinal cord to activate muscles that generate gait and its constituent outcomes (stride outcomes, dynamic gait features) (A). Experimentally induced fatigue perturbs motor control and interferes with available internal resources. Muscle performance fatigability, induced by repetitive sit-to-stand (rSTS), arises from changes at the central level (i.e., increase in central drives inputs) (B) to compensate for alterations in muscles (i.e., declines in voluntary force) (C). Performing a demanding mental task (Mental performance fatigability) for a prolonged period can reduce intrinsic motivation, executive function, and attention (D) (parameter associated with gait performance). Although we expect that both types of fatigue may induce changes in stride outcomes and dynamic features (E), greater effects on Muscle than Mental performance fatigability are expected because rSTS evokes changes at both central and peripherical levels.

REFERENCES

[1] WHO WHO-. Preface Overview Humanity's Aging Living Longer New Disease Patterns Longer Lives and Disability New Data on Aging and Health Assessing the Cost of Aging and Health Care Changing Role of the Family Suggested Resources. 2011.

[2] López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell 2013;153:1194. doi:10.1016/j.cell.2013.05.039.

[3] Vandervoort AA. Aging of the human neuromuscular system. Muscle Nerve 2002;25:17–25. doi:10.1002/mus.1215.

[4] Aagaard P, Suetta C, Caserotti P, Magnusson SP, Kjaer M. Role of the nervous system in sarcopenia and muscle atrophy with aging: strength training as a countermeasure. Scand J Med Sci Sports 2010;20:49–64. doi:10.1111/j.1600-0838.2009.01084.x.

[5] Mattay VS, Fera F, Tessitore A, Hariri AR, Das S, Callicott JH, et al. Neurophysiological correlates of age-related changes in human motor function. Neurology 2002;58:630–5. doi:10.1212/WNL.58.4.630.

[6] Heuninckx S, Wenderoth N, Swinnen SP. Systems neuroplasticity in the aging brain: Recruiting additional neural resources for successful motor performance in elderly persons. J Neurosci 2008;28:91–9. doi:10.1523/JNEUROSCI.3300-07.2008.

[7] Geerligs L, Renken RJ, Saliasi E, Maurits NM, Lorist MM. A Brain-Wide Study of Age-Related Changes in Functional Connectivity. Cereb Cortex 2015;25:1987–99. doi:10.1093/cercor/bhu012.

[8] Grady C. The cognitive neuroscience of ageing. Nat Rev Neurosci 2012;13:491–505. doi:10.1038/nrn3256.

[9] Li Q, Dong C, Liu T, Chen X, Perry A, Jiang J, et al. Longitudinal Changes in Whole-Brain Functional Connectivity Strength Patterns and the Relationship With the Global Cognitive Decline in Older Adults. Front Aging Neurosci 2020;12:71. doi:10.3389/fnagi.2020.00071.

[10] Caetano MJD, Lord SR, Schoene D, Pelicioni PHS, Sturnieks DL, Menant JC. Age-related changes in gait adaptability in response to unpredictable obstacles and stepping targets. Gait Posture 2016;46:35–41. doi:10.1016/J.GAITPOST.2016.02.003.

[11] Aboutorabi A, Arazpour M, Bahramizadeh M, Hutchins SW, Fadayevatan R. The effect of aging on gait parameters in able-bodied older subjects: a literature review. Aging Clin Exp Res 2016;28:393–405. doi:10.1007/s40520-015-0420-6.

[12] Birren J.E., Schroots J.J.F. History, concepts, and theory in the psychology of aging. In: Birren J.E., Schaie K.W., editors. Handb. Psychol. aging. 4th ed., San Diego: San Diego, USA: Academic Press; 1996, p. 3–23.

[13] McCrum C, Epro G, Meijer K, Zijlstra W, Brüggemann GP, Karamanidis K. Locomotor stability and adaptation during perturbed walking across the adult female lifespan. J Biomech 2016;49:1244–7. doi:10.1016/j.jbiomech.2016.02.051.

[14] Greve C, Zijlstra W, Hortobágyi T, Bongers RM. Not All Is Lost: Old Adults Retain Flexibility in Motor Behaviour during Sit-to-Stand. PLoS One 2013;8:e77760. doi:10.1371/journal.pone.0077760.

[15] Morris R, Lord S, Bunce J, Burn D, Rochester L. Gait and cognition: Mapping the global and discrete relationships in ageing and neurodegenerative disease. Neurosci Biobehav Rev 2016;64:326–45. doi:10.1016/j.neubiorev.2016.02.012.

[16] Prince F, Corriveau H, Hébert R, Winter DA. Gait in the elderly. Gait Posture 1997;5:128–35. doi:10.1016/S0966-6362(97)01118-1.

[17] Morrison S, Colberg SR, Parson HK, Neumann S, Handel R, Vinik EJ, et al. Walking-Induced Fatigue Leads to Increased Falls Risk in Older Adults. J Am Med Dir Assoc 2016;17:402–9. doi:10.1016/j.jamda.2015.12.013.

[18] Hausdorff JM, Rios DA, Edelberg HK. Gait variability and fall risk in community-living older adults: a 1-year prospective study. Arch Phys Med Rehabil 2001;82:1050–6. doi:10.1053/apmr.2001.24893.

[19] Parijat P, Lockhart TE. Effects of lower extremity muscle fatigue on the outcomes of slip-induced falls. Ergonomics 2008;51:1873–84. doi:10.1080/00140130802567087.

[20] Hortobágyi T, Lesinski M, Gäbler M, VanSwearingen JM, Malatesta D, Granacher U. Effects of Three Types of Exercise Interventions on Healthy Old Adults' Gait Speed: A Systematic Review and Meta-Analysis. Sport Med 2015;45:1627–43. doi:10.1007/s40279-015-0371-2.

[21] Kobsar D, Olson C, Paranjape R, Hadjistavropoulos T, Barden JM. Evaluation of age-related differences in the stride-to-stride fluctuations, regularity and symmetry of gait using a waist-mounted tri-axial accelerometer. Gait Posture 2014;39:553–7. doi:10.1016/j.gaitpost.2013.09.008.

[22] Santos PCR, Hortobágyi T, Zijdewind I, Bucken Gobbi LT, Barbieri FA, Lamoth C. Minimal effects of age and prolonged physical and mental exercise on healthy adults' gait. Gait Posture 2019;74:205–11. doi:10.1016/j.gaitpost.2019.09.017.

[23] Kikkert LHJ, Vuillerme N, van Campen JP, Appels BA, Hortobágyi T, Lamoth CJC. Gait characteristics and their discriminative power in geriatric patients with and without cognitive impairment. J Neuroeng Rehabil 2017;14:84. doi:10.1186/s12984-017-0297-z.

[24] Lamoth CJ, van Deudekom FJ, van Campen JP, Appels BA, de Vries OJ, Pijnappels M. Gait stability and variability measures show effects of impaired cognition and dual tasking in frail people. J Neuroeng Rehabil 2011;8:2. doi:10.1186/1743-0003-8-2.

[25] Cesari M, Kritchevsky SB, Penninx BWHJ, Nicklas BJ, Simonsick EM, Newman AB, et al. Prognostic Value of Usual Gait Speed in Well-Functioning Older People - Results from the Health, Aging and Body Composition Study. J Am Geriatr Soc 2005;53:1675–80. doi:10.1111/j.1532-5415.2005.53501.x.

[26] Woo J, Ho SC, Yu ALM. Walking speed and stride length predicts 36 months dependency, mortality, and institutionalization in chinese aged 70 and older. J Am Geriatr Soc 1999;47:1257–60. doi:10.1111/j.1532-5415.1999.tb05209.x.

[27] Hortobagyi T, Finch A, Solnik S, Rider P, DeVita P. Association Between Muscle Activation and Metabolic Cost of Walking in Young and Old Adults. Journals Gerontol Ser A Biol Sci Med Sci 2011;66A:541–7. doi:10.1093/gerona/glr008.

[28] Lee H-J, Chang WH, Choi B-O, Ryu G-H, Kim Y-H. Age-related differences in muscle co-activation during locomotion and their relationship with gait speed: a pilot study. BMC Geriatr 2017;17:44. doi:10.1186/s12877-017-0417-4.

[29] Hortobágyi T, Devita P. Mechanisms responsible for the age-associated increase in coactivation of antagonist muscles. Exerc Sport Sci Rev 2006;34:29–35.

[30] Gennaro F, Bruin ED. A pilot study assessing reliability and age-related differences in corticomuscular and intramuscular coherence in ankle dorsiflexors during walking. Physiol Rep 2020;8. doi:10.14814/phy2.14378.

[31] Spedden ME, Choi JT, Nielsen JB, Geertsen SS. Corticospinal control of normal and visually guided gait in healthy older and younger adults. Neurobiol Aging 2019;78:29–41. doi:10.1016/j.neurobiolaging.2019.02.005.

[32] McCrum C, Gerards MHG, Karamanidis K, Zijlstra W, Meijer K. A systematic review of gait perturbation paradigms for improving reactive stepping responses and falls risk among healthy older adults. Eur Rev Aging Phys Act 2017;14. doi:10.1186/S11556-017-0173-7.

[33] Vervoort D, den Otter AR, Buurke TJW, Vuillerme N, Hortobágyi T, Lamoth CJC. Effects of Aging and Task Prioritization on Split-Belt Gait Adaptation. Front Aging Neurosci 2019;11:10. doi:10.3389/fnagi.2019.00010.

[34] Lockhart TE, Woldstad JC, Smith JL, Lockhart{ TE, Woldstad{ JC, Smith} JL. Effects of age-related gait changes on the biomechanics of slips and falls n.d. doi:10.1080/00 14013031000139491.

[35] Monjo F, Terrier R, Forestier N. Muscle fatigue as an investigative tool in motor control: A review with new insights on internal models and posture-movement coordination. Hum Mov Sci 2015;44:225–33. doi:10.1016/j.humov.2015.09.006.

[36] Granacher U, Gruber M, Förderer D, Strass D, Gollhofer A. Effects of ankle fatigue on functional reflex activity during gait perturbations in young and elderly men. Gait Posture 2010;32:107–12. doi:10.1016/j.gaitpost.2010.03.016.

[37] Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses: Proposal for a unified taxonomy. Neurology 2013;80:409–16. doi:10.1212/ WNL.0b013e31827f07be.

[38] Enoka RM, Duchateau J. Translating Fatigue to Human Performance. Med Sci Sport Exerc 2016;48:2228–38. doi:10.1249/MSS.0000000000000929.

[39] Place N, Millet GY. Quantifcation of Neuromuscular Fatigue: What Do We Do Wrong and Why? Sport Med 2020;50:439–47. doi:10.1007/s40279-019-01203-9.

[40] Santos PCR, Barbieri FA, Zijdewind I, Gobbi LTB, Lamoth C, Hortobágyi T. Effects of experimentally induced fatigue on healthy older adults’ gait: A systematic review. PLoS One 2019;14:e0226939. doi:10.1371/journal.pone.0226939.

[41] Van Cutsem J, Marcora S, De Pauw K, Bailey S, Meeusen R, Roelands B. The Effects of Mental Fatigue on Physical Performance: A Systematic Review. Sport Med 2017;47:1569–88. doi:10.1007/s40279-016-0672-0.

[42] Marcora SM, Staiano W, Manning V. Mental fatigue impairs physical performance in humans. J Appl Physiol (Bethesda, Md 1985) 2009;106:857–64. doi:10.1152/ japplphysiol.91324.2008.

[43] Taylor JL, Amann M, Duchateau J, Meeusen R, Rice CL. Neural Contributions to Muscle Fatigue: From the Brain to the Muscle and Back Again. Med Sci Sports Exerc 2016;48:2294–306. doi:10.1249/MSS.0000000000000923.

[44] Taylor JL, Butler JE, Gandevia SC. Changes in muscle afferents, motoneurons and motor drive during muscle fatigue. Eur J Appl Physiol 2000;83:106–15. doi:10.1007/ s004210000269.

[45] Semmler JG, Ebert SA, Amarasena J. Eccentric muscle damage increases intermuscular coherence during a fatiguing isometric contraction. Acta Physiol 2013;208:362–75. doi:10.1111/apha.12111.

[46] Boonstra TW, Daffertshofer A, van Ditshuizen JC, van den Heuvel MRC, Hofman C, Willigenburg NW, et al. Fatigue-related changes in motor-unit synchronization of quadriceps muscles within and across legs. J Electromyogr Kinesiol 2008;18:717–31. doi:10.1016/j.jelekin.2007.03.005.

[47] Danna-Dos Santos A, Poston B, Jesunathadas M, Bobich LR, Hamm TM, Santello M. Influence of fatigue on hand muscle coordination and EMG-EMG coherence during three-digit grasping. J Neurophysiol 2010;104:3576–87. doi:10.1152/jn.00583.2010.

[48] Bryanton MA, Bilodeau M. The influence of knee extensor fatigue on lower extremity muscle activity during chair rise in young and older adults. Eur J Appl Physiol 2019;119:61–71. doi:10.1007/s00421-018-3999-4.

[49] de Jong M, Jolij J, Pimenta A, Lorist MM. Age Modulates the Effects of Mental Fatigue on Typewriting. Front Psychol 2018;9:1113. doi:10.3389/fpsyg.2018.01113.

[50] Lorist MM. Impact of top-down control during mental fatigue. Brain Res 2008;1232:113–23. doi:10.1016/j.brainres.2008.07.053.

[51] Smith MR, Chai R, Nguyen HT, Marcora SM, Coutts AJ. Comparing the Effects of Three Cognitive Tasks on Indicators of Mental Fatigue. J Psychol Interdiscip Appl 2019;153:759–83. doi:10.1080/00223980.2019.1611530.

[52] Behrens M, Mau-Moeller A, Lischke A, Katlun F, Gube M, Zschorlich V, et al. Mental Fatigue Increases Gait Variability During Dual-task Walking in Old Adults. J Gerontol A Biol Sci Med Sci 2018;73:792–7. doi:10.1093/gerona/glx210.

[53] Monjo F, Forestier N. The postural control can be optimized by the first movement initiation condition encountered when submitted to muscle fatigue. Hum Mov Sci 2017;54:1–12. doi:10.1016/j.humov.2017.03.001.

[54] Hortobágyi T, Mizelle C, Beam S, DeVita P. Old adults perform activities of daily living near their maximal capabilities. J Gerontol A Biol Sci Med Sci 2003;58:M453-60.

[55] Bryanton M, Bilodeau M. The role of thigh muscular efforts in limiting sit-to-stand capacity in healthy young and older adults. Aging Clin Exp Res 2017;29:1211–9. doi:10.1007/s40520-016-0702-7.

[56] Buurke TJW, Lamoth CJC, van der Woude LH V., Rob den Otter A. Synergistic Structure in the Speed Dependent Modulation of Muscle Activity in Human Walking. PLoS One 2016;11:e0152784. doi:10.1371/journal.pone.0152784.

[57] Tran Y, Craig A, Craig R, Chai R, Nguyen H. The influence of mental fatigue on brain activity: Evidence from a systematic review with meta-analyses. Psychophysiology 2020. doi:10.1111/psyp.13554.

[58] Chai R, Smith MR, Nguyen TN, Ling SH, Coutts AJ, Nguyen HT. Comparing features extractors in EEG-based cognitive fatigue detection of demanding computer tasks. 2015 37th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc., 2015, p. 7594–7. doi:10.1109/EMBC.2015.7320150.

2

Effects of experimentally induced fatigue on healthy older adults' gait: a systematic review

P. C. Rocha dos Santos[1,2]
F. A. Barbieri[3]
I. Zijdewind[4]
L.T.B. Gobbi[2]
C. Lamoth[1]
T. Hortobágyi[1]

[1]Department of Human Movement Sciences, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands,
[2]Posture and Gait Studies Laboratory (LEPLO), Graduate Program in Movement Sciences, Institute of Biosciences, São Paulo State University (UNESP), Rio Claro, Brazil,
[3]Human Movement Research Laboratory (MOVI-LAB), Graduate Program in Movement Sciences, Department of Physical Education, São Paulo State University (UNESP), Bauru, Brazil.
[4]Department of Biomedical Sciences of Cells and Systems, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.

Adapted from: PLoS ONE 14 (12): e0226939, 2019

ABSTRACT

Introduction: While fatigue is ubiquitous in old age and visibly interferes with mobility, studies have not yet examined the effects of self-reported fatigue on healthy older adults' gait. As a model that simulates this daily phenomenon, we systematically reviewed eleven studies that compared the effects of experimentally induced muscle and mental performance fatigability on gait kinematics, variability, kinetics, and muscle activity in healthy older adults.

Methods: We searched for studies in databases (PubMed and Web of Science) using Fatigue, Gait, and Clinical conditions as the main terms and extracted the data only from studies that experimentally induced fatigue by sustained muscle or mental activities in healthy older adults.

Results: Eleven studies were included. After muscle performance fatigability, six of nine studies observed increases in stride length, width, gait velocity (Effect Size [ES] range: 0.30 to 1.22), inter-stride trunk acceleration variability (ES: 2.06), and ankle muscle coactivation during gait (ES: 0.59, n = 1 study). After sustained mental activity, the coefficient of variation of stride outcomes increased (ES: 0.59 to 0.67, n = 1 study) during dual-task but not single task walking.

Conclusion: Muscle performance fatigability affects spatial and temporal features of gait and, mainly, inter-stride trunk acceleration variability. In contrast, sustained mental activity tends only to affect step variability during dual tasking. A critical and immediate step for future studies is to determine the effects of self-reported fatigue on gait biomechanics and variability in healthy older adults to verify the viability of experimentally induced fatigue as a model for the study of gait adaptability in old age.

Key Words: Fatigability, Sustained activity, Walking, Aging, Mental fatigue, Muscle Fatigue

List of abbreviations: Abd, Abduction; acc, acceleration; AP, Anteroposterior; CAD, Cadence; CG, Control Group; CoV, Coefficient of variation; DT, Dual-Task; DsT, Double support Time; Effect sizes, ES; FG, Fatigue Group; FRA, Functional Reflex Activity; IK, Isokinetic; LDS, Local Dynamic Stability; LW, Overground level walking; LyE, Lyapunov Exponent; ML, Medial-lateral; Motiv, Motivation; Mov, Movement; n/m, not mentioned; OW, Obstacle walking; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; Prop, Proprioception; RMS, root mean square; RPE, Rating of Perceived Exertion; RT, Reaction Time; RW, Regular Walking; SD, Step Duration; SdD, Stride Duration; SdL, Stride Length; SdW, Stride Width; SL, Step Length; Sp, Speed; ST, Single-Task; STS, Sit-to-Stand; StT, Stance Time; SW, Step Width; SwT, Swing Time; UL, Unilateral; V, Vertical; var, Variability; vel, Velocity.

1. INTRODUCTION

Population studies and primary care data show that ~46% of older adults complain about being tired [1–3]. Tiredness is the sensation of exhaustion, a reduction of physical and mental energy, and a diminished interest in the surrounding world. Prolonged physical or mental exertion can reduce motor performance (performance fatigability) [4–6] or reduce the capacity to allocate cognitive resources to perform a task [7] and increase self-reported fatigue (perceived fatigability) [8]. Performing a low-force activity for a prolonged period, such as a long high-paced walk, can lead to a sensation of muscle performance fatigability. Performing a motor task at a high percentage of the available maximal mechanical output, i.e., at a high relative effort, can also lead to muscle performance fatigability, a state that is associated with reduced contractile force and a sub-optimal neural activation of muscles [6,8,9]. The decline in force due to sustained muscle effort can interfere with the quality of motor acts such as carrying an object, maintaining bodily postures, and gait [10–12].

While prolonged low force and short-term high force motor acts can directly reduce motor performance due to impairment in force and muscle activation, demanding mental activities can also create a psychobiological state characterized by a perception of tiredness and a lack of motivation [8,13,14]. Sustaining attention or a mental effort for a prolonged period puts older adults in a fatigued mental state [7,15,16] that slows cognitive processes often quantified by slowed reaction times [13,14,17]. Sustained mental activity is also associated with alteration of cortical brain areas and decreases in neurotransmitter levels [14,18]. Such modifications may impair top-down cognitive control and the execution of motor tasks indirectly, even in the absence of demonstrable muscle weakness [19,20]. Sustained mental activities can also decrease parasympathetic and increase sympathetic activity, reducing motivation and pre-frontal brain activation [7,20].

While both fatigue types are prevalent in old age and visibly interfere with gait, studies have not yet examined the effects of trait of fatigue on healthy older adults' gait. To minimize interference and maintain gait quality, older adults are expected to adopt strategies that help to compensate for the mal-effects of fatigue on gait. The unanswered question is whether and how those healthy older adults who report no trait of fatigue can adapt their gait when either kind of fatigue is induced by experimental protocols in a laboratory environment. Such paradigms are thought to simulate performance or perceived fatigued states often reported by older adults. It is important because the after-effects of sustained activities can destabilize gait and posture, increasing the risks for slips, trips, and falls [21–24]. The picture emerging from the systematically not yet reviewed studies is that fatigue-free healthy older adults are able somehow to adjust their gait kinematics, kinetics, variability, and muscle activation to states created by performance or perceived fatigue induced in a laboratory environment [25–27]. It seems likely that experimentally induced muscle fatigability by prolonged physical activity affects the generation of mechanical work and power at the ankle, knee, and hip joints during gait [28]. Such changes are reasonable because the cellular mechanisms of fatigue impair voluntary force generation and the neural drive of muscles [4,6,29] that generate torques and powers during gait. Specifically, it is likely that older adults would in compensation for the force loss increase stride width and muscle activity to increase gait stability [25]. Subtler mechanisms could involve increases in the activity of antagonist muscles and distribute effort by recruiting less affected muscles at adjacent joints [28,30,31]. Concerning mental fatigability, we expect that interference with attention, arousal, executive function, mood, and motivation would primarily affect gait variability [32,33]. Indeed, brain areas underlying these cognitive functions are also active during imagined walking [34] and are related to temporal step outcomes and gait variability [35–37]. We thus hypothesized that gait adaptations might be fatigue-type specific. The purpose of this paper was to systematically review studies that compared the effects of experimentally induced muscle and mental performance fatigability on gait kinematics, variability, kinetics, and muscle activity in healthy older adults. A comprehensive review of these adaptations is timely and needed because it would increase our understanding of how old age affects the capacity to adapt gait to sustained muscle or mental activities.

2. METHODS

We performed a computerized systematic literature search, following PRISMA (S1 Checklist) and Cochrane Handbook for Systematic Reviews guidelines [38,39], in PubMed and Web of Science for the period between January 1987 to August 2019 (last 30 years from the beginning of the search (2017) and updated for the 2 following years). The search consisted of four terms: Term 1 was the population by using the keywords ‘old’, ‘elderly’ and ‘adults’; Term 2 was the intervention ‘Fatigue’ probed with the keywords ‘fatigue’, ‘fatigability’, ‘tiredness’, and its variants (e.g., mental fatigue, physical fatigue, motor fatigue, cognitive fatigue, performance fatigability, and perceived fatigability). Term 3 was the outcomes ‘Gait’ and ‘Walking’ with the outcomes of gait adaptability concerning gait biomechanics, kinetics, kinematics, muscle activity, spatial-temporal parameters, inverse dynamics, gait stability, and gait variability. Term 4 included the exclusion criteria and clinical conditions, such as neurological and orthopaedical diseases. Although the Cochrane Handbook for Systematic Reviews suggest that the 'NOT' operator should be avoided as exclusion where possible [39], in our case, exclusion terms were necessary as a search strategy to remove from the initial screening the substantial number of papers in diseased populations. Filters were set to include English language (S1 Table). The PubMed syntax was adapted to the Web of Science search. We also identified studies missed by the search from the list of references of relevant individual papers.

2.1. Eligibility, Study Selection and Exclusion criteria

We used the Population, Intervention, Comparison, Outcome, and Study design as the criterion for inclusion of papers in this review [38]. Population: older human adults. Intervention: fatigue induced by prolonged physical/muscle and mental tasks. Comparison: gait in fatigue and non-fatigued state. Outcomes: gait kinematics (e.g., spatial and temporal stride parameters, joint angle, joint angular, acceleration outcomes), kinetics (e.g., force outcomes as momentum, work and power, ground reaction force), electromyography (e.g., amplitude and temporal parameters used to assess muscle activation). For the analysis of gait variability and stability, we considered the standard deviation, coefficient of variation, and measures of variability regarding gait dynamics, such as root means square (RMS), sample and multi-scale entropy methods, detrended fluctuation analysis, and local dynamic stability and margin of stability, respectively. We also considered gait performed under different conditions such as obstructed gait, level surface walking, and treadmill walking. Finally, randomized controlled trials, non-randomized controlled trials, and non-randomized non-controlled trials were included.

From the initial yield, obtained by combining original articles from electronic databases and targeted searches, titles and abstracts were screened. When a study was potentially eligible and relevant, it was selected for a full-text analysis and then subjected to a quality analysis. Studies that analyzed the effects of fatigue on gait in age groups other than only in older adults were included, but we considered the data only for older adults (over 63 years). When the information was considered insufficient based on title and abstract alone, the full text was analyzed to decide on inclusion.

We had excluded studies that examined running and stair climbing. In addition, studies unrelated to induced fatigue (decline in performance and/or increase in self-reported fatigue) by sustained physical and mental activities or that could not indicate a measurement of induced fatigue, a lack of quantitative gait outcomes and/or a lack of older adults in the sample were excluded at the initial screening of titles and abstracts.

2.2. Quality assessment

Two of the authors (PCRS, FAB) screened candidate papers and worked based on a set of guidelines to improve inter-rater reliability. Both authors analyzed the methodological quality of the included studies by using a quality appraisal tool [40]. This appraisal tool relates to the internal and external validity of the measurement and the generalizability of the results. For each question, '1' is rated when the criterion was met, '0.5' when information is lacking detail or clarity, and '0' if the criterion was missing. A higher total score represents a higher quality of the study. In case of discrepancies between the two authors, a third author (TH) was consulted to make a decision about inclusion.

2.3. Data extraction and analysis

Two of the authors (PCRS, FAB) extracted the papers, independently, and synthesized data in tables and together, both authors checked the tables. In case of an indecision, a third author (TH) was consulted. The data were coded for: number of participants, age, sex, protocol to induce performance fatigability (sit-to-stand, cognitive task, walking test), measurement of fatigue (decline in performance, increase in self-reported fatigue), gait protocol (treadmill, level walking, walking with obstacle crossing), and gait outcomes (kinematic and kinetic data, variability, muscle activity). It was not necessary to contact any authors to get information regarding the included papers. We used Cohen's *d* to calculate the effect sizes (ES) to quantify whether the magnitude of changes in gait outcomes induced by sustained muscle or mental activity is relevant. ES values of 0.21 - 0.49 indicate small, 0.50 - 0.79 indicate medium, and ≥ 0.80 indicate large practical effects [41]. Due to the heterogeneity of the outcomes, lack of consistent results, and the low number of studies that met eligibility criteria, we were unable to perform a meta-analysis.

3. RESULTS

3.1. Study Characteristics

The Pubmed and Web of Science searches yielded 1,274 studies and one study was included from the list of reference [42]. After screening for title, abstract and remove the duplicates, 61 studies were selected for analyses, and, after reading the full text, a final sample size of 11 studies was included in the review (Fig 1). The included studies stated the aims sufficiently, gave an appropriate description of the methods, detailed the outcomes clearly, and provided an interpretation of the key findings (S2 Table).

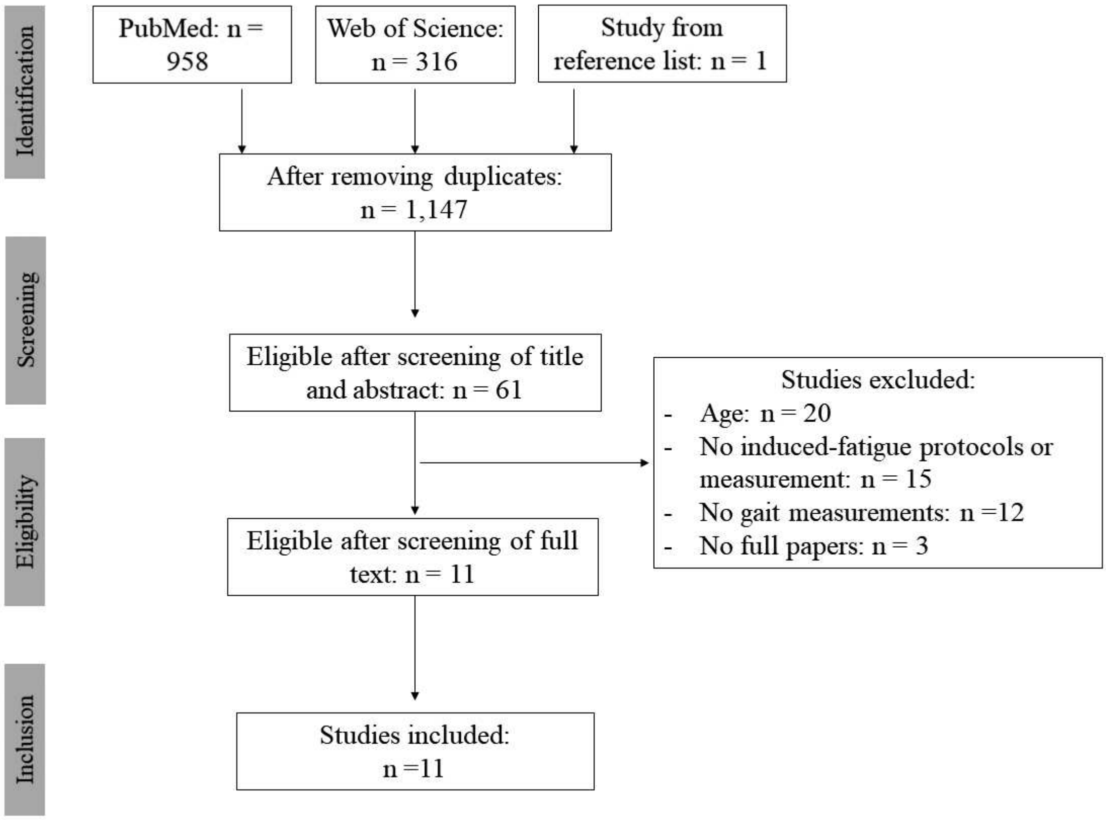


Figure 1. PRISMA flow diagram.

The current review was based on 249 healthy older adults with a mean age of 71.5 (±4.66) years (Table 1), 92 females (based on data of 9 studies that reported sex), with normal body composition (body mass index: 26.1±1.94 kg/m^2). Two studies did not report the subjects' sex [23,43] (Table 1).

3.2. Effects of fatigue protocols on fatigue outcomes

The studies used heterogeneous protocols to induce a decline in muscle performance, including repeated muscle contractions (n=7 studies), knee extension/flexions (n=5), sit-to-stands (n=4), endurance (n=3, treadmill and cycling), isokinetic (n=2, knee and ankle), hip abductions (n=1), and prolonged mental tasks (n=1, go/no go task for 90 min) (Tables 1, 2). Six, three, and two studies indicated the state of fatigue, respectively, as a decline in voluntary force, inability to perform the movement, and movement slowing (Table 1). The reduction in force ranged between ~10 to ~55% and varied between protocols. The sit-to-stand task, for example, reduced voluntary force by ~9 to 13% [25,26]. The isokinetic protocols considered fatigue as reductions to 50% of the initial maximum voluntary torque [27,44]. Unilateral squats performed until exhaustion reduced knee extension force by 17% [45]. Longer reaction time was also observed post vs. pre sustained endurance protocol [21]. Five studies reported an increase in self-reported fatigue (indicated by the rating of perceived exertion and by fatigue perception) (Table 1 and 2) [21,25,32,43,46]. Two studies [25,46] indicated that older adults reported near maximal perceived exertion ('very hard' to 'maximum exertion') after repeated muscle contractions. Two studies [21,43] indicated a high rating of self-reported fatigue in response to endurance protocol, scores ranged from 'hard' (15) to 'maximal exertion' (20) on the Borg scale. One study [32] determined fatigue as a decrease in motivation by 10%, as examined by wakefulness, mood, and arousal dimension of the Multidimensional Mood Questionnaire (ES range: 0.27 to 0.95) and up 2x of increase in fatigue state assessed by Profile of Mood States (ES: 0.92) following a prolonged period of mental activity. One study [23] also indicated an increase (range: 25 to 35 beats per minute) in heart rate (ES: 0.65) after endurance exercise.

Table 1. Description of the characteristics of the papers selected.

	Helbostad et al.[47]	**Granacher et al. [27]**	**Granacher et al.[44]**	**Hatton et al.[26]**	**Barbieri et al. [25]**	**Nagano et al. [23]**	**Toebes et al. [45]**	**Arvir et al. [46]**	**Hamacher et al. [43]**	**Morrison et al. [21]**	**Behrens et al. [32]**
Participants	44	14	16	30	40	11	10	17	18	30	16
male/female (N)	10/34	14/0	8/8	17/13	40/0	n/m	4/6	5/12	n/m	14/16	6/10
age (yrs)	79.3	67.2	71.3	78.3	69.3	74.2	63.4	73.2	69	69.4	72.2
body index (kg/m²)	24.4	25.1	25.2	27.2	26.6	26.2	n/m	24.7	25.5	31.1	25.5
Fatigue protocol											
muscle contraction	STS - Knee	IK – Ankle	IK - Knee	STS – Knee	STS – Knee		Squat - Knee UL	Abd - Hip UL			
endurance						6-min fast-Walking			Cycle – Ergometer	Treadmill - Walk	
mental task											Go/ no go test
Fatigue outcomes											
parameters	↓ Pace of Mov	↓Force	↓Force	↓Force	↓Force ↑ RPE	↑Heart Rate	↓Force	↑ RPE ↓Prop	↑ RPE	↓Force ↓RT ↑RPE	↓Motiv ↑ Fatigue state

N: sample, n/m: not mentioned, STS: Sit-to-Stand test, IK: Isokinetic, ABD: Abduction, UL: unilateral, Mov: Movement, RPE: Rating of Perceived Exertion, RT: Reaction Time, Prop: Proprioception, Motiv: Motivation.

2

Table 2. Study characteristics for included studies.

	Fatigability			Gait		
Study	**N – older adults**	**Protocol**	**Outcomes**	**Gait Conditions**	**Gait Outcomes**	**Fatigue-related changes (effect sizes)**
Helbostad et al. [47]	22 - Fatigue Group (FG) 22 - Control Group (CG)	Sit-to-stand	↓ time and vertical displacement of movement the sit-to-stand	Overground level walking (LW)	AP, ML and V. Trunk acc. and inter-stride trunk acc var;. SL, SW, and Sp; SL-var and SW-var.	FG vs. CG: ↑ SW (ES: 1.51), ML trunk acc (ES: 1.27), SL Var (ES: 2.61) and ↓ V. (ES: 2.06) and AP (ES: 0.80) inter-stride Trunk acc var
Granacher et al. [27]	14	Isokinetic ankle extension	↓ in ~50% of maximal torque	Perturbation (decelerating) on treadmill walking	Functional reflex activity (FRA) and latency of m. Tibialis Anterior (TA), Latency in TA, EMG activity of the m. Peroneus, Soleus and Vastus Medialis, Coactivity and maximal angular velocity.	↓ FRA in TA (ES: 0.56), ↑ coactivity (ES: 0.58) and maximal angular velocity (ES: 0.64).
Granacher et al. [44]	16	Isokinetic knee extension	↓ in ~50% of maximal torque	LW in single-(ST) and dual-task (DT)	SdL, Gait Sp, DT cost in SdL and gait Sp and the Standard deviation of the SdL in ST and DT conditions	DT: ↑ Gait Sp (ES: 0.55); SdL (ES: 0.45) and ↓ SD of SdL (ES: 095).
Hatton et al. [26]	30	Sit-to-stand	↓ in 9.5% of the peak of force on knee extension	Obstructed walking (OW) with a secondary visual task	Std, Sp of obstacle crossing, Trail and lead limb vertical and horizontal distance to the obstacle, and V. loading rate.	↑ V loading rate of the lead limb (ES: 0.27).
Barbieri et al. [25]	20 – (60-70 years - G60) 20 – (over 70 years - G70)	Sit-to-stand	↓ in ~13% of the peak of force ↑ RPE	LW and OW	SdL, SdD, Sp, and SW (LW and OW). SL, Sd, Sp, Trail (T) and Lead (L) vertical distance to the obstacle (VO).	LW and OW: ↑ SdL / SL (ES: 0.35 / 0.04), SW (ES: 0.36 / 0.19), Sp (ES: 0.65 and 0.31), ↓ SdD/Sd (ES: 0.43 and 0.45). OW: ↑ TVO (ES: 0.1)
Nagano et al. [23]	11	Endurance (treadmill walking)	↑ ~35% in heart rate	Treadmill walking	SL (normalized by limb length), DsT (%) and SW and Minimum Foot Clearance	↑ SL (ES: 0.63), DsT (ES: 0.12), Var SW (ES: n/p) ↓ Minimum Foot Clearance (ES: 0.7)

Table 2. Study characteristics for included studies. (continued)

		Fatigability		Gait		
Study	**N – older adults**	**Protocol**	**Outcomes**	**Gait Conditions**	**Gait Outcomes**	**Fatigue-related changes (effect sizes)**
Toebes et al. [45]	10	Unilateral squat exercise until task failure.	↓ 17.3% Knee extension strength	Unperturbed and perturbed (push the trunk) treadmill walking	3-D LyE of the trunk, trunk vel, and var of trunk vel, time to return to unperturbed gait pattern on stance and swing phase. Deviation of trunk kinematic after perturbation.	↓ Time to return to the unperturbed gait pattern on swing phase (ES: 0.67) and deviation after perturbation (ES: 1.8)
Arvir et al. [46]	17	Unilateral hip abductor	↓ Hip position sense and ↑ RPE	Treadmill walking	SdD means and standard deviations; ML trunk vel; Harmonic Ratio (HR) of ML and AP; Local Divergent Exponents of ML and AP, acceleration and position.	↑ SdD Var (n/p) and ↓ HR of ML (ES: 0.49).
Hamacher et al. [43]	18	Endurance (cycle ergometer)	↑ RPE	Treadmill walking	Local dynamic Stability (LDS) of the walking (LyE) of 3D trunk linear acc.	↓ LDS (ES: 0.73)
Morrison et al. [21]	15 – (60-70 years - G60) 15 – (over 70 years - G70)	Endurance (incremental incline treadmill walking)	↑ RPE; ↓ Strength G70: ↓ Reaction time.	LW	Gait SP, SdL, SdD, and CAD.	G70: ↑ Gait SP, SdL, SdD and CAD
Behrens et al. [32]	16	Mental demanding (90min) vs. and control task.	↓ 10 % Motivation; ↑ 100% Fatigue state	LW in ST and DT	Mean and Coeficicient of variation (CoV) of Gait Sp, SdL, StT, DsT and SwT in ST and DT condition	↑ CoV of Sp (ES: 0.66), SdL (ES: 0.67), StT (ES: 0.59), DsT (ES: 0.59) and SwT (ES: 0.41)

SL: Step Length; SdL: Stride Length; SW: Step Width; SdW: Stride Width; SD: Step Duration; SdD: Stride duration Sp: Speed; StT: Stance Time; SwT: Swing Time; DsT: Double support Time; CAD: Cadence; LW: Overground level walking; OW: Obstacle walking; acc: acceleration; vel: velocity, RPE: Rating of Perceived Exertion; var: Variability; CoV: Coefficient of variation; ML: Medial-lateral; AP: Anteroposterior; V.: Vertical, FRA: Functional Reflex Activity; DT: Dual-Task; ST: Single-Task; RW: Regular Walking; OW: Obstacle walking; LDS: Local Dynamic Stability.

3.3. Effects of fatigue protocols on gait

Table 2 shows changes and ESs in gait outcomes after sustained muscle and mental activities. Six studies evaluated outcomes during overground walking with [25,26] or without obstruction [21,25,26,32,44,47] while single- and dual-task walking [32,44]. Five studies assessed the effects of muscle performance fatigability on gait while walking on a motorized treadmill with [27,45] or without a perturbation [23,27,43,45,46].

Muscle performance fatigability affected stride outcomes [23,25,26,44–47], gait stability [43], gait variability [44,46,47], and muscle activation [27] during gait. Stride velocity increased by ~10 cm/s (ES= 0.6), stride length by 4.8cm (ES: 0.27) [21,25,44] or by 0.3 units of normalized stride length (ES: 0.63) [23], step width by ~2 cm (ES: 0.80) [25,47], percentage of double support (~2%, ES: 1.22) [23], and a decrease in stride duration by 2ms (ES: 0.42) [25] and standard deviation of stride length by 1 cm (large ES: 0.95) [44] after sustained muscle activity. After muscle performance fatigability, local dynamic stability of 3-D trunk acceleration and symmetry in medial-lateral direction of trunk acceleration decreased by 0.1 max LyE (ES: 0.73) [43] and by 22 in harmonic rate (ES: 0.49) [46], respectively and the anteroposterior and vertical inter-stride trunk acceleration variability increased by 8% and 11% (ES: 0.8 and 2.06), respectively [47]. However, other studies did not indicate effects of muscle performance fatigability on step length ($p > 0.05$) [26,45,47], and unilateral muscle fatigability protocols did not affect the local dynamic stability during treadmill walking [45,46].

A decline in force induced by sustained muscle activity increased the coactivity between m. soleus and m. tibialis anterior by ~12% (ES: 0.6) and delayed functional reflex activity in the m. tibialis anterior over a 120-ms interval following treadmill decelerations by ~41% (215.7 to 174.7; ES: 0.56) [27]. While walking on an obstacle course, muscle performance fatigability reduced step duration by 5ms (ES: 0.45) and increased step velocity by 6 cm/s (ES: 0.31), step width by 1 cm (ES: 0.20), toe clearance of trailing limb to obstacle by 1 cm (ES: 0.10) [25], and the vertical loading by 4.3 N kg^{-1} m^{-1} (ES: 0.27; all $p < 0.05$) [26]. These results suggest that muscle performance fatigability induced adaptations in the mean and variability of spatial-temporal stride parameters during overground level walking and obstacle negotiation and increased the coactivation and delayed functional muscle reflex during treadmill walking decelerations.

Reduced mental performance was associated with an increased coefficient of variation of gait velocity from ~6% to 11%, stride length from ~4% to 7%, stance time from ~7% to 13%, double support time from ~7% to 16% (ES: 0.50 to 0.68) and swing time from ~9% to 14% (ES: 0.41, all $p < 0.05$) during level walking in dual- but not in single-task condition [32].

4. DISCUSSION

We systematically reviewed studies that compared the effects of experimentally induced muscle and mental performance fatigability on gait kinematics, variability, kinetics, and muscle activity in healthy older adults. Muscle performance fatigability affects spatial and temporal features of gait and, mainly, inter-stride trunk acceleration variability. In contrast, sustained mental activity tends only to affect step variability during dual-tasking. The evidence supports the hypothesis that healthy older adults adapt spatial-temporal features of gait in a fatigue-type specific manner. We discuss these findings with a perspective on whether experimentally induced fatigue is a viable model for the study of gait adaptability in old age.

Muscle fatigue protocols were effective and induced sizable reductions in voluntary force (ES range: 0.30 to 1.32), an accepted marker of performance fatigability [8]. However, the protocols varied widely and included: 1) Repetitive muscle contractions of knee and ankle extensors with different instructions; 2) The STS task performed rapidly or at a fixed speed, and 3) Endurance tasks involving rapid walking for six minutes, incline walking on a treadmill, or incremental cycle-ergometer tests (Table 2). This large variation in methods inducing fatigue is one source of the inconsistent effects on gait because cyclical lower extremity tasks could, in fact, entrain rather than perturb gait, diminishing the interference effects and the need for participants to invoke adaptations in their walking pattern.

It is however curious that even when participants performed ~70 knee extensions or ankle plantarflexions at a maximal effort and the maximum voluntary force decreased by 50% (ES: ~1.3) [27,44], changes in spatiotemporal gait variables were moderate but in the unexpected direction (ES: 0.47 to 0.58, Table 2). Indeed, stride length (~4%), gait speed (~10%), and step width (~11%) tended to increase and stride duration (~4%) tended to decrease (ES: 0.4 to 0.8) [21,25,44]. It seems that gait has actually become more dynamic. The step and speed changes might reflect adaptations to the marked increase in trunk acceleration and variability in the vertical and anteroposterior directions (ES: 0.80 to 2.06, Table 2) [47].

Why did performance fatigability not elicit larger changes in gait and necessitate more substantive adaptive responses to the perturbations? One possibility is that torque and power demands during gait were still below the levels of joint torques and powers fatigued muscles could produce [48]. It was also reported that participants could compensate by more strongly activating muscles that were less or not affected by the task [28]. Whether gait is tested overground or on a treadmill affected the results, as studies that reported small fatigue effects on spatial-temporal parameters tested gait using an overground protocol [21,25,44,47] but those that found no effects used a treadmill [45,46]. Walking on a treadmill at a set speed makes gait kinematically uniform and minimizes the potential for adaptations to occur [49,50], especially in step variability [51,52]. This argument is borne out by a lack of fatigue effects on gait when participants were tested on treadmill [45,46] compared with the small but meaningful decreases in the autocorrelation and increases in variability of ML trunk acceleration during overground gait [47]. The use of unilateral fatigue protocols did induce some gait asymmetry but left all other gait outcomes virtually unaffected in older adults [46]. Finally, increases in gait velocity and step length after a fatigue protocol suggest that a warm-up instead of an interference effect might have occurred. However, we need to consider even these small changes in gait with caution because a number of studies reported no changes in gait metrics after a variety of muscle fatigue protocols, making all of the data combined inconsistent [26,45,46].

Muscle performance fatigability can modify muscle activation in single joint tasks and also during gait. For example, decreases in level of force delayed muscle activation onset in older adults while rising from a chair [31]. After ankle muscle fatigability, coactivation of agonist and antagonist ankle muscles increased by ~12% during gait and there was 41% delay in a functional reflex when older adults were prompted to respond to gait perturbations [27]. It is speculated that sustained muscle activity-related increase in coactivation during gait [53,54] reflects changes in the afferent feedback [29,55]. However, such an interpretation is complicated by a coupled increase in plantarflexion angular velocity and increase in coactivation of the soleus and tibialis anterior muscles during gait, a counterintuitive outcome because coactivation would tend to stiffen instead of accelerating joint motion. While suggested [28], we found no direct evidence for activation substitution, i.e., reduction in muscle activation of the fatigued muscle group being compensated by increases in activation of muscles at adjacent joints. Together, the evidence is scant that there is an age- and perturbation-specific adaptation in muscle activation in response to fatigue perturbations.

Performing a mental task for a prolonged period increased gait variability only during dual-task gait [32]. This limited effect is in line with the hypothesis emerging from imaging studies suggesting the involvement of complementary brain areas in gait, attention, and executive function while walking and performing a cognitive task at the same time [36,56]. Accordingly, sustained mental activity affects cognitive functions known to be involved in gait control, resulting in an interference with gait automaticity. This interference increases step variability. In single-task conditions, the interference created by the sustained mental activity may not be large enough, producing no measurable effects on any of the gait outcomes reviewed here.

While there has been a concerted effort to use fatigue as a perturbation model (Tables 1-2), its viability to study the effects of age on gait adaptability remains unclear. When combined with data from young individuals, the reviewed data revealed a lack of age effect, suggesting that the nature, magnitude, and focality of the perturbations lacks specificity to age and gait. Indeed, fatigue-induced changes in gait were quantitatively similar in healthy younger and older adults and also similar in healthy older adults and Parkinsonian patients [25,28,57]. The original intent of these studies was to make healthy, fatigue-free older adults fatigued to simulate the fatigued state. However, it is unclear if the experimentally induced fatigue state and the fatigue state de novo present in older people are qualitatively and quantitatively similar. It seems that when muscle fatigue is induced with repetitive single-joint muscle contractions such as knee extension-flexion, the ensuing fatigue is predominantly a localized force impairment while the fatigue state in older adults is the result of a combination of impaired physiology, reduced homeostasis, a bias in effort perception, and altered cognitive function. When however, a multi-joint protocol is used (i.e., six-minute walk test), any adaptation in gait after the task is the result of a combined physiological and cognitive (behavioral) effect.

Such limitations and the diversity in fatigue protocols shape the implementation of this perturbation model in the future. The viability of the model will increase if studies move from its descriptive application to hypothesis-driven designs. There is a need to determine the effects of muscle performance fatigability on motor outcomes that are specific and also not specific to the fatigue task, an approach that would improve experimental control and the validity of conclusions. Future studies should also evaluate cognitive outcomes because the adaptive processes may not be confined to motor (gait) function alone. Therefore, future studies should include motor-cognitive dual-task assessments when probing age-differences in adaptations to fatigue. There is a strong need for studies examining the effects of prolonged mental tasks on gait biomechanics and variability. Such studies should set fatigability and gait as the main outcomes in older adults [58]. Such an approach would strengthen our understanding of the role cognition plays in gait control. Perhaps the most critical gap in knowledge is related to a lack of studies comparing gait outcomes in older adults with and without self-reported fatigue. Only after such studies could we meaningfully interpret gait adaptations in healthy older adults after experimentally induced muscle or mental fatigue.

In conclusion, muscle performance fatigability affects spatial and temporal features of gait and, mainly, inter-stride trunk acceleration variability. In contrast, sustained mental activity tends only to affect step variability during dual-tasking. A critical and immediate step for future studies is to determine the effects of self-reported fatigue on gait biomechanics and variability in healthy older adults to verify the viability of experimentally induced fatigue as a model for the study of gait adaptability in old age.

REFERENCES

[1] Alexander NB, Taffet GE, Horne FM, Eldadah BA, Ferrucci L, Nayfield S, et al. Bedside-to-Bench conference: research agenda for idiopathic fatigue and aging. J Am Geriatr Soc 2010;58:967–75. doi:10.1111/j.1532-5415.2010.02811.x.

[2] Lewis G, Wessely S. The epidemiology of fatigue: more questions than answers. J Epidemiol Community Health 1992;46:92–7.

[3] Liao S, Ferrell BA. Fatigue in an older population. J Am Geriatr Soc 2000;48:426–30.

[4] Stackhouse SK, Stevens JE, Lee SC, Pearce KM, Snyder-Mackler L, Binder-Macleod SA. Maximum voluntary activation in nonfatigued and fatigued muscle of young and elderly individuals. Phys Ther 2001;81:1102–9.

[5] Rannou F, Nybo L, Andersen JE, Nordsborg NB. Monitoring Muscle Fatigue Progression during Dynamic Exercise. Med Sci Sport Exerc 2019:1. doi:10.1249/MSS.0000000000001921.

[6] Gandevia SC. Spinal and supraspinal factors in human muscle fatigue. Physiol Rev 2001;81:1725–89. doi:10.1152/physrev.2001.81.4.1725.

[7] Boksem MAS, Meijman TF, Lorist MM. Effects of mental fatigue on attention: An ERP study. Cogn Brain Res 2005;25:107–16. doi:10.1016/j.cogbrainres.2005.04.011.

[8] Enoka RM, Duchateau J. Translating Fatigue to Human Performance. Med Sci Sport Exerc 2016;48:2228–38. doi:10.1249/MSS.0000000000000929.

[9] Davis JM. Central and peripheral factors in fatigue. J Sports Sci 1995;13:S49–53. doi:10.1080/02640419508732277.

[10] Grenier JG, Millet GY, Peyrot N, Samozino P, Oullion R, Messonnier L, et al. Effects of extreme-duration heavy load carriage on neuromuscular function and locomotion: a military-based study. PLoS One 2012;7:e43586. doi:10.1371/journal.pone.0043586.

[11] Salavati M, Moghadam M, Ebrahimi I, Arab AM. Changes in postural stability with fatigue of lower extremity frontal and sagittal plane movers. Gait Posture 2007;26:214–8. doi:10.1016/j.gaitpost.2006.09.001.

[12] Paillard T. Effects of general and local fatigue on postural control: A review. Neurosci Biobehav Rev 2012;36:162–76. doi:10.1016/J.NEUBIOREV.2011.05.009.

[13] Boksem MAS, Tops M. Mental fatigue: Costs and benefits. Brain Res Rev 2008;59:125–39. doi:10.1016/j.brainresrev.2008.07.001.

[14] Lorist MM, Boksem MAS, Ridderinkhof KR. Impaired cognitive control and reduced cingulate activity during mental fatigue. Cogn Brain Res 2005;24:199–205. doi:10.1016/j.cogbrainres.2005.01.018.

[15] Wascher E, Rasch B, Sänger J, Hoffmann S, Schneider D, Rinkenauer G, et al. Frontal theta activity reflects distinct aspects of mental fatigue. Biol Psychol 2014;96:57–65. doi:10.1016/j.biopsycho.2013.11.010.

[16] de Jong M, Jolij J, Pimenta A, Lorist MM. Age Modulates the Effects of Mental Fatigue on Typewriting. Front Psychol 2018;9:1113. doi:10.3389/fpsyg.2018.01113.

[17] Van Cutsem J, Marcora S, De Pauw K, Bailey S, Meeusen R, Roelands B. The Effects of Mental Fatigue on Physical Performance: A Systematic Review. Sport Med 2017;47:1569–88. doi:10.1007/s40279-016-0672-0.

[18] Pires FO, Silva-Júnior FL, Brietzke C, Franco-Alvarenga PE, Pinheiro FA, de França NM, et al. Mental Fatigue Alters Cortical Activation and Psychological Responses, Impairing Performance in a Distance-Based Cycling Trial. Front Physiol 2018;9:227. doi:10.3389/fphys.2018.00227.

[19] Lorist MM. Impact of top-down control during mental fatigue. Brain Res 2008;1232:113–23. doi:10.1016/j.brainres.2008.07.053.

[20] Mizuno K, Tanaka M, Yamaguti K, Kajimoto O, Kuratsune H, Watanabe Y. Mental fatigue caused by prolonged cognitive load associated with sympathetic hyperactivity. Behav Brain Funct 2011;7:17. doi:10.1186/1744-9081-7-17.

[21] Morrison S, Colberg SR, Parson HK, Neumann S, Handel R, Vinik EJ, et al. Walking-Induced Fatigue Leads to Increased Falls Risk in Older Adults. J Am Med Dir Assoc 2016;17:402–9. doi:10.1016/j.jamda.2015.12.013.

[22] Lew FL, Qu X. Effects of mental fatigue on biomechanics of slips. Ergonomics 2014;57:1927–32. doi:10.1080/00140139.2014.937771.

[23] Nagano H, James L, Sparrow WA, Begg RK. Effects of walking-induced fatigue on gait function and tripping risks in older adults. J Neuroeng Rehabil 2014;11:155. doi:10.1186/1743-0003-11-155.

[24] Parijat P, Lockhart TE. Effects of quadriceps fatigue on the biomechanics of gait and slip propensity. Gait Posture 2008;28:568–73. doi:10.1016/j.gaitpost.2008.04.001.

[25] Barbieri FA, dos Santos PCR, Simieli L, Orcioli-Silva D, Van Dieën JH, Gobbi LTB. Interactions of age and leg muscle fatigue on unobstructed walking and obstacle crossing. Gait Posture 2014;39:985–90. doi:10.1016/J.GAITPOST.2013.12.021.

[26] Hatton AL, Menant JC, Lord SR, Lo JCM, Sturnieks DL. The effect of lower limb muscle fatigue on obstacle negotiation during walking in older adults. Gait Posture 2013;37:506–10. doi:10.1016/j.gaitpost.2012.09.004.

[27] Granacher U, Gruber M, Förderer D, Strass D, Gollhofer A. Effects of ankle fatigue on functional reflex activity during gait perturbations in young and elderly men. Gait Posture 2010;32:107–12. doi:10.1016/j.gaitpost.2010.03.016.

[28] Barbieri FA, Gobbi LTB, Lee YJ, Pijnappels M, van Dieën JH. Effect of triceps surae and quadriceps muscle fatigue on the mechanics of landing in stepping down in ongoing gait. Ergonomics 2014;57:934–42. doi:10.1080/00140139.2014.903302.

[29] Taylor JL, Amann M, Duchateau J, Meeusen R, Rice CL. Neural Contributions to Muscle Fatigue: From the Brain to the Muscle and Back Again. Med Sci Sports Exerc 2016;48:2294–306. doi:10.1249/MSS.0000000000000923.

[30] Barbieri FA, Beretta SS, Pereira VAI, Simieli L, Orcioli-Silva D, dos Santos PCR, et al. Recovery of gait after quadriceps muscle fatigue. Gait Posture 2016;43:270–4. doi:10.1016/j.gaitpost.2015.10.015.

[31] Bryanton MA, Bilodeau M. The influence of knee extensor fatigue on lower extremity muscle activity during chair rise in young and older adults. Eur J Appl Physiol 2019;119:61–71. doi:10.1007/s00421-018-3999-4.

[32] Behrens M, Mau-Moeller A, Lischke A, Katlun F, Gube M, Zschorlich V, et al. Mental Fatigue Increases Gait Variability During Dual-task Walking in Old Adults. J Gerontol A Biol Sci Med Sci 2018;73:792–7. doi:10.1093/gerona/glx210.

[33] Verlinden VJA, van der Geest JN, Hofman A, Ikram MA. Cognition and gait show a distinct pattern of association in the general population. Alzheimer's Dement 2014;10:328–35. doi:10.1016/j.jalz.2013.03.009.

[34] Iseki K, Hanakawa T, Shinozaki J, Nankaku M, Fukuyama H. Neural mechanisms involved in mental imagery and observation of gait. Neuroimage 2008;41:1021–31. doi:10.1016/j.neuroimage.2008.03.010.

[35] Zwergal A, Linn J, Xiong G, Brandt T, Strupp M, Jahn K. Aging of human supraspinal locomotor and postural control in fMRI. Neurobiol Aging 2012;33:1073–84. doi:10.1016/j.neurobiolaging.2010.09.022.

[36] Lo O-Y, Halko MA, Zhou J, Harrison R, Lipsitz LA, Manor B. Gait Speed and Gait Variability Are Associated with Different Functional Brain Networks. Front Aging Neurosci 2017;9:390. doi:10.3389/fnagi.2017.00390.

[37] Studenski S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, et al. Gait speed and survival in older adults. JAMA 2011;305:50–8. doi:10.1001/jama.2010.1923.

[38] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. J Clin Epidemiol 2009;62:1006–12. doi:10.1016/j.jclinepi.2009.06.005.

[39] Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions. 7th ed. West Sussex: John Wiley & Sons Ltd; 2017.

[40] Galna B, Peters A, Murphy AT, Morris ME. Obstacle crossing deficits in older adults: A systematic review. Gait Posture 2009;30:270–5. doi:10.1016/J.GAITPOST.2009.05.022.

[41] Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd. Hillsdale (NJ): Lawrence Erlbaum Associates; 1988.

[42] Da Rocha ES, Kunzler MR, Bobbert MF, Duysens J, Carpes FP. 30 min of treadmill walking at self-selected speed does not increase gait variability in independent elderly. J Sports Sci 2018;36:1305–11. doi:10.1080/02640414.2017.1375139.

[43] Hamacher D, Törpel A, Hamacher D, Schega L. The effect of physical exhaustion on gait stability in young and older individuals. Gait Posture 2016;48:137–9. doi:10.1016/j.gaitpost.2016.05.007.

[44] Granacher U, Wolf I, Wehrle A, Bridenbaugh S, Kressig RW. Effects of muscle fatigue on gait characteristics under single and dual-task conditions in young and older adults. J Neuroeng Rehabil 2010;7:56. doi:10.1186/1743-0003-7-56.

[45] Toebes MJP, Hoozemans MJM, Dekker J, van Dieën JH. Effects of unilateral leg muscle fatigue on balance control in perturbed and unperturbed gait in healthy elderly. Gait Posture 2014;40:215–9. doi:10.1016/j.gaitpost.2014.03.194.

[46] Arvin M, Hoozemans MJM, Burger BJ, Rispens SM, Verschueren SMP, van Dieën JH, et al. Effects of hip abductor muscle fatigue on gait control and hip position sense in healthy older adults. Gait Posture 2015;42:545–9. doi:10.1016/j.gaitpost.2015.08.011.

[47] Helbostad JL, Leirfall S, Moe-Nilssen R, Sletvold O. Physical fatigue affects gait characteristics in older persons. J Gerontol A Biol Sci Med Sci 2007;62:1010–5.

[48] Hunt MA, Hatfield GL. Ankle and knee biomechanics during normal walking following ankle plantarflexor fatigue. J Electromyogr Kinesiol 2017;35:24–9. doi:10.1016/j.jelekin.2017.05.007.

[49] Malatesta D, Canepa M, Menendez Fernandez A. The effect of treadmill and overground walking on preferred walking speed and gait kinematics in healthy, physically active older adults. Eur J Appl Physiol 2017;117:1833–43. doi:10.1007/s00421-017-3672-3.

[50] Lee SJ, Hidler J. Biomechanics of overground vs. treadmill walking in healthy individuals. J Appl Physiol 2008;104:747–55. doi:10.1152/japplphysiol.01380.2006.-The.

[51] Hollman JH, Watkins MK, Imhoff AC, Braun CE, Akervik KA, Ness DK. A comparison of variability in spatiotemporal gait parameters between treadmill and overground walking conditions. Gait Posture 2016;43:204–9. doi:10.1016/J.GAITPOST.2015.09.024.

[52] Hanley B, Tucker CB. Gait variability and symmetry remain consistent during high-intensity 10,000 m treadmill running. J Biomech 2018;79:129–34. doi:10.1016/j.jbiomech.2018.08.008.

[53] Kellis E, Kellis S. Effects of agonist and antagonist muscle fatigue on muscle coactivation around the knee in pubertal boys. J Electromyogr Kinesiol 2001;11:307–18. doi:10.1016/S1050-6411(01)00014-1.

[54] Arellano CJ, Caha D, Hennessey JE, Amiridis IG, Baudry S, Enoka RM. Fatigue-induced adjustment in antagonist coactivation by old adults during a steadiness task. J Appl Physiol 2016;120:1039–46. doi:10.1152/japplphysiol.00908.2015.

[55] Hortobagyi T, Tracy J, Hamilton G, Lambert J. Fatigue Effects on Muscle Excitability. Int J Sports Med 1996;17:409–14. doi:10.1055/s-2007-972870.

[56] Allali G, Montembeault M, Brambati SM, Bherer L, Blumen HM, Launay CP, et al. Brain Structure Covariance Associated with Gait Control in Aging. J Gerontol A Biol Sci Med Sci 2018. doi:10.1093/gerona/gly123.

[57] Santos PCR, Gobbi LTB, Orcioli-Silva D, Simieli L, van Dieën JH, Barbieri FA. Effects of leg muscle fatigue on gait in patients with Parkinson's disease and controls with high and low levels of daily physical activity. Gait Posture 2016;47:86–91. doi:10.1016/j.gaitpost.2016.04.002.

[58] Tieland M, Trouwborst I, Clark BC. Skeletal muscle performance and ageing. J Cachexia Sarcopenia Muscle 2018;9:3–19. doi:10.1002/jcsm.12238.

[59] Barbieri FA, Santos PCR, Simieli L, Orcioli-Silva D, van Dieën JH, Gobbi LTB. Interactions of age and leg muscle fatigue on unobstructed walking and obstacle crossing. Gait Posture 2014;39:985–90. doi:10.1016/j.gaitpost.2013.12.021.

[60] Hamacher D, Törpel A, Hamacher D, Schega L. The effect of physical exhaustion on gait stability in young and older individuals. Gait Posture 2016;48:137–9. doi:10.1016/J.GAITPOST.2016.05.007.

S1. Checklist. Prisma checklist

	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2 - 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6, S1 Table
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8

S1. Checklist. Prisma checklist (continued)

	#	Checklist item	Reported on page #
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8-9, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9, 14-15, Table 2 and 3.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9, 14-15, Table 2 and 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9, Table 1, 2 and 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A

S1. Checklist. Prisma checklist (continued)

	#	Checklist item	Reported on page #
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15 -19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19 - 20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15 -20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Others

S1 Table. Search Terms

The PubMed search terms (syntax) used in the present review to identify to determine the effects of muscle and mental performance fatigability on kinematics, variability, kinetics, and muscle activity of healthy older adults' gait. Syntax was adapted to Web of Science.

	Terms	Keywords
Inclusion	#1 - Population AND	(Old OR Elderly OR Adults)
	#2 - Intervention AND	(Fatigue OR Tiredness OR Fatigability)
	#3 - Outcomes NOT	(Gait OR Walking OR "kinematic parameters" OR "Gait biomechanics" OR "Muscle activation" OR "Joint Coordination" OR Kinetic OR "Inverse Dynamic" OR "Gait Variability" OR "Gait Stability")
Exclusion	#4 - Exclusion	(Patient NOT Disease NOT Stroke NOT Diabetes NOT Neuropathy NOT Amputation NOT "Multiple sclerosis" NOT "Cerebral palsy" NOT Parkinson NOT Cancer NOT Obese NOT Fracture NOT Dysfunction NOT "Cognitively impaired" NOT Frail NOT Demented NOT Alzheimer NOT "Pilot study")
Additional Filters	Language	English
	Data	1987 - 2019

S2 Table. Methodological quality appraisal results. Y – yes; L - Lacking detail or clarity; N – No; AV – average. A score of one indicated high quality research and zero indicated lower quality.

Question	Scoring criteria	Helbostad et al.[47]	Granacher et al.[27]	Granacher et al.[44]	Hatton et al.[26]	Barbieri et al.[59]	Nagano et al. [23]	Toebes et al. [45]	Arvir et al. [46]	Hamacher et al. [60]	Morrison et al. [21]	Behrens et al. [32]	AV
1. Research aims or questions stated clearly	Y: 1, L: 0.5, N: 0	1	1	1	1	1	1	1	1	1	1	1	1
	Number	1	1	1	1	1	1	1	1	1	1	1	1
	Age	1	1	1	1	1	1	1	1	1	1	1	1
2. Participants detailed	Sex	1	1	1	1	1	0	1	1	0	1	1	0.8
	Height	0	1	1	1	1	1	0	1	0	1	1	0.7
	Sub Total	0.8	1	1	1	1	0.8	0.8	1	0.6	1	1	0.9
3. Recruitment and sampling methods described	Y: 1, L: 0.5, N: 0	0.5	0	0.5	1	1	1	0	0	0.5	1	0	0.5
4. Inclusion and exclusion criteria detailed	Y: 1, L: 0.5, N: 0	1	0.5	1	1	1	1	0.5	0.5	0.5	1	1	0.8
	Height	0	0	0	0	0	0	0	0	0	0	1	0.1
	Gait Speed	1	0	1	0	0	1	1	0	0	0	0	0.4
	Age	1	1	1	1	1	1	1	1	1	1	1	1
5. Controlled covariates	Gender	0	1	1	0	1	0	0	0	0	1	0	0.4
	Asymmetry	0	1	1	1	0.5	1	1	1	0	0	0	0.6
	Strength	0	1	1	1	1	1	1	0	0	1	0	0.6
	Sub Total	0.3	0.7	0.8	0.5	0.6	0.7	0.7	0.3	0.2	0.5	0.3	0.5
6. Key outcome variables clearly described	Y: 1, L: 0.5, N: 0	1	1	1	1	1	1	1	1	1	1	1	1

2

S2 Table. Methodological quality appraisal results. Y – yes; L - Lacking detail or clarity; N – No; AV – average. A score of one indicated high quality research and zero indicated lower quality. (continued)

Question	Scoring criteria	Helbostad et al.[47]	Granacher et al.[27]	Granacher et al.[44]	Hatton et al.[26]	Barbieri et al.[59]	Nagano et al. [23]	Toebes et al. [45]	Arvir et al. [46]	Hamacher et al. [60]	Morrison et al. [21]	Behrens et al. [32]	AV
7. Adequate methodology able to repeat study	Participants	1	1	1	1	1	1	1	1	1	1	1	1
	Equipment	1	1	1	1	1	1	1	1	1	1	1	1
	Procedure	1	1	1	1	1	1	1	1	0	1	1	0.9
	Processing	1	1	1	1	1	1	1	1	1	1	1	1
	Statistics	1	1	1	1	1	1	1	1	1	1	1	1
	Sub total	1	1	1	1	1	1	1	1	0.8	1	1	1
8. Methodology able to answer research question	Participants	1	1	1	1	1	1	1	1	1	1	1	1
	Equipment	1	1	1	1	1	1	1	1	1	1	1	1
	Procedure	1	1	1	1	1	1	1	1	1	1	1	1
	Processing	1	1	1	1	1	1	1	1	1	1	1	1
	Statistics	1	1	1	1	1	1	1	1	1	1	1	1
	Sub total	1	1	1	1	1	1	1	1	1	1	1	1
9. Reliability of the methodology stated	Y: 1, N: 0	0	0	0	0	0	0	0	0	0	0	0	0
10. Internal validity of the methodology stated	Y: 1, N: 0	0	0	0	0	0	0	0	0	0	0	0	0
11 Research questions answered adequately in the discussion	Y: 1, N: 0	1	1	1	1	1	1	1	1	1	1	1	1
12. Key findings supported by the results	Y: 1, N: 0	1	1	1	1	1	1	1	1	1	1	1	1
13. Key findings interpreted in a logical manner which is supported by references	Y: 1, N: 0	1	1	1	1	1	1	1	1	1	1	1	1
14. Clinical implications stated	Y: 1, L: 0.5, N: 0	1	1	1	1	1	1	1	1	1	1	1	1

3

Minimal effects of age and prolonged physical and mental exercise on healthy adults′ gait

P. C. Rocha dos Santos[1,2]
T. Hortobágyi[1]
I. Zijdewind[3]
L.T.B. Gobbi[2]
F. A. Barbieri[4]
C. Lamoth[1]

[1] Department of Human Movement Sciences, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands,

[2]Posture and Gait Studies Laboratory (LEPLO), Graduate Program in Movement Sciences, Institute of Biosciences, São Paulo State University (UNESP), Rio Claro, Brazil,

[3]Department of Biomedical Sciences of Cells and Systems, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.

[4]Human Movement Research Laboratory (MOVI-LAB), Graduate Program in Movement Sciences, Department of Physical Education, São Paulo State University (UNESP), Bauru, Brazil.

Gait & Posture 74, 205-21, 2019.

ABSTRACT

Background: Gait adaptability in old age can be examined by responses to various perturbations. Fatigability due to mental or muscle exercises can perturb internal cognitive and muscle resources, necessitating adaptations in gait.

Research question: What are the effects of age and mental and muscle fatigability on stride outcomes and gait variability?

Methods: Twelve older (66 to 75yrs) and twelve young (20 to 25 yrs) adults walked at 1.2 m/s before and after two fatigue conditions in two separate sessions. Fatigue conditions were induced by repetitive sit-to-stand task (RSTS) and by 30-min of mental tasks and randomized between days (about a week apart). We calculated the average and coefficient of variation (CV) of stride length, width, single support, swing time and cadence, and the detrended fluctuations analysis (DFA) based on 120 strides time intervals. We also calculated multi-scale sample entropy (MSE) and the maximal Lyapunov exponent (λmax) of mediolateral (ML) and anteroposterior (AP) trajectories of the Center of Pressure (CoP).

Results: In both age groups, RSTS modestly affected stride length, single support time, cadence, and CV of stride length ($p \leq 0.05$), while the mental task did not affect gait. After fatigability, λmax - ML increased ($p \leq 0.05$), independent of fatigue condition. All observed effects were small (η^2: 0.001 to 0.02).

Significance: Muscle and mental fatigability had minimal effects on gait in young and healthy older adults possibly because treadmill walking makes gait uniform. It is still possible that age-dependent muscle activation underlies the uniform gait on the treadmill. Age- and fatigability effects might be more overt during real life compared with treadmill walking, creating a more effective model for examining gait and age adaptability to fatigability perturbations.

Key Words: Performance fatigability; Perceived fatigability; Gait dynamics; Stride outcomes; Treadmill walking; Aging

List of abbreviations: AP, anteroposterior;Cong, Congruent answer; CoP, Center of Pressure Position; CPT, continuous performance test; CV, coefficient of variation; DFA, detrended fluctuation analysis; Incong, Incongruent Answer; MFI, multidimensional fatigue inventory; ML, mediolateral; MMSE, mini-mental state examination; MSE, multi-scale sample entropy; MVIF, maximum voluntary isometric force; PVT, Psycho-motor vigilant test; RSTS, repetitive sit-to-stand task; RT, reaction time; SL, stride length; SPPB, short physical performance battery; SST, single support time; SW, step width; SwT, swing time; V, vertical; VA, Voluntary Activation; VAS, visual analogue scale; η^2, eta Squared; λmax, maximum Lyapunov exponent.

1. INTRODUCTION

Natural aging modifies gait [1]. Older compared to young adults walk slower, with shorter strides, longer single-support and swing time, and higher gait variability [1]. Age-typical changes on gait also involve gait dynamics outcomes which reflect complementary characteristics of gait performance. Whereas Detrended Fluctuations Analysis (DFA) indicates absence/presence of correlation between strides [2], Multi-scale Sample Entropy (MSE) and maximal Lyapunov exponent (λmax) measure the complexity/regularity of signal and the capacity to resist to small perturbation, respectively [3,4]. These outcomes are associated with a decline in cognitive function, mobility disability, and higher fall risk [3–5]. An important question is how older adults adapt their gait to external perturbations. Mechanical/external perturbations, as models [6], evoke age-specific adaptations in gait. Another model of gait perturbation is fatigue that interferes with internal resources [7]. There is still an inadequate understanding of how behavioral interventions, such as fatigue by enrollment in physical and cognitive exercise, may affect gait outcomes in older adults. Fatigue, as a state, emerges from a decline in an objective measure of performance over time (performance fatigability), and from a subjective increase in difficulty to continue a task (perceived fatigability) [7]. Protocols to induce fatigability involve sustained muscle/physical and/or demanding mental tasks. The responses to fatigability due to cognitive and/or physical exercises could be of interest in the assessment and development of interventions aiming to improve mobility in older adults.

Repetitive sit-to-stand (RSTS) is a model to induce fatigability and to examine age-adaptations in gait [8–10]. After RSTS, there is a decrease in maximal voluntary isometric force (MVIF) of the quadriceps muscle by 9% in older adults [8,9] and an increase in the level of activation of the fatigued quadriceps coupled with compensatory increases in plantarflexor activation [11]. After RSTS, older adults walk overground with 4% shorter stride duration, 2 cm wider steps [9,10], and increase step length and trunk variability [10]. Endurance activity [12,13] and leg press and calf raise exercise [14] produced inconsistent changes in local dynamic stability during treadmill walking.

Gait is not a fully automated motor act involving cortical and cognitive control [5]. Interference with executive function and attention, as in dual-tasking, slows gait and increases stride duration variability [5]. Specifically, performing a demanding mental task for a prolonged period can reduce intrinsic motivation, executive function, and attention and increase up to two times the coefficient of variation (CV) of stride outcomes in older adults [15]. Because older adults may have impaired cognition, it is conceivable that fatigability-induced by demanding mental tasks would amplify age-differences in gait.

Therefore, we determined the effects of age, RSTS, and a prolonged mental effort on the spatial and temporal stride outcomes and gait dynamics during treadmill walking. For gait dynamics, we quantified the center of pressure (CoP) variability and stability. We also examined the effects of age and sustained periods of mental task on stride outcomes and gait dynamics. We hypothesized that both forms of fatigability would decrease stride length and stability, increase cadence, and variability of step times and CoP trajectories. However, we expected larger effects in older compared with young adults and greater effects on gait as a result of the RSTS compared with a sustained period of demanding mental task.

2. METHOD

2.1. Participants

Twelve older and twelve young adults were recruited by word of mouth from the community to participate in the study (Table 1). Exclusion criteria were: neurological and cardiovascular disease; self-reported pain, musculoskeletal injury or surgery in the lower extremities that could affect the protocol; inability to walk without an assistive device; high-level of self-reported fatigue. All participants signed an informed consent form approved by the Ethical Committee of the Center for Human Movement Sciences at the UMCG.

Table 1. Participants Characteristics and score on questionnaires.

	Older		Young		p-value
Groups' characteristics					
N (male and female)	12 (7 and 5)		12 (7 and 5)		-
Age (yrs)	71	±3.76	22.45	±1.69	< 0.01
Height (cm)	173.13	±7.70	177.45	±9.17	0.17
Body mass (kg)	73.92	±10.15	69.81	±11.38	0.71
SPPB (scores)	12.00	±0.00	12.00	±0.00	1.00
MFI (scores)	34.58	±9.81	38.18	±9.36	0.52
STS					
Repetition (rep)	134.12	±114.71	583.3	±173.62	< 0.01
Duration (min)	4.47	±3.99	19.48	±5.92	< 0.01

Values are means and SDs. SPPB: Short Physical Performance Battery; MFI: Multidimensional fatigue inventory; STS: Sit-to-Stand.

2.2. Procedure

Participants visited the laboratory on two days about 6 to 8 days apart at the same time of the day for ~2h each. They were instructed to avoid exhaustive exercises the day before testing. During the first visit, participants completed Mini-Mental State Examination (MMSE) [16], Multidimensional Fatigue Inventory (MFI) [17], the Short Physical Performance Battery (SPPB) [18], and had the demographic characteristics recorded. The experimental conditions were randomized between sessions: Session A: RSTS; Session B: Mental Task. In both Sessions, participants walked on the treadmill and performed the MVIF before and after experimental conditions (Fig. 1).

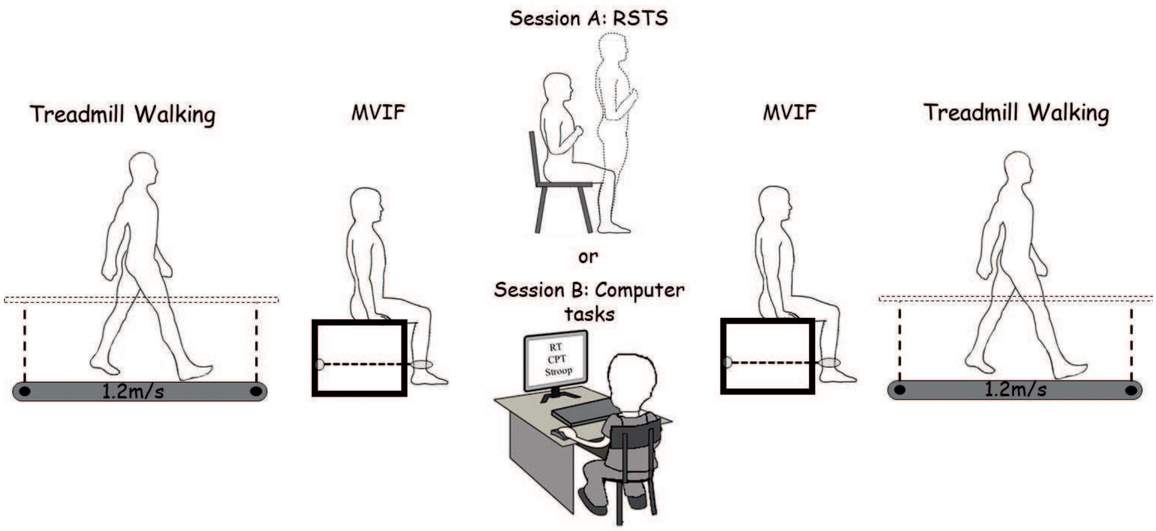


Fig. 1. Experimental design. MVIF, Maximum Voluntary Isometric Force; RSTS, repetitive Sit-to-stand.

2.3. Walking condition

Without holding the handrail but wearing a harness, participants walked on a treadmill with two embedded force plates (M-gait, Motekforce, Amsterdam, NL) that measured 3-D ground reaction forces (N) and moments of force (Nm) under each leg at 1 kHz. Participants walked for 3 min at a fixed speed of 1.2 m/s. This speed was chosen to be similar to the older adults' comfortable speed [19,20] and to test both age groups in the same condition, eliminating a speed-effect on gait [19,20].

2.4. MVIF and electrical stimulation

MVIF and twitch interpolation were done on a custom-built dynamometer [21]. Participant's non-dominant leg was strapped to the lever arm with the knee 90° flexed. Placement of electrodes, the procedure to determine the stimulation intensity, and the stimulator were described previously [21]. Participants then performed maximum voluntary contractions before and after each experimental condition. Participants were instructed to contract the quadriceps as rapidly and forcefully as possible and maintain it for 5 s. Double electrical pulses were discharged on the plateau of MVIF (superimposed twitch), followed by two twitches at rest. We calculated the MVIF before twitch and the voluntary activation (1-(superimposed twitch /potentiated twitch))*100 [21]

2.5. Experimental conditions

Participants performed RSTS, with the arms crossed at the chest, at 30 beats/min (chair: 0.43x0.41x0.42m). The protocol was stopped either when participants indicated an inability to continue or after 30 minutes. Duration and number of repetitions were recorded.

In session B, participants performed three mentally demanding tasks on a computer for 10 min each [22]: the Psychomotor Vigilance Task (PVT) [23], the Continuous Performance Test (CPT) and the Stroop test [22]. RT was assessed for all tasks and the accuracy (% of the correct answer) for Stroop (congruent and incongruent responses) test and CPT. Outcomes of the mental tasks were averaged over windows of 1 min, then an overall mean was calculated considering Time 1 (2 to 5min) and Time 2 (6 to 10min). Participants, after familiarized with the scales, reported perceived fatigue (Visual Analogue Scale - VAS, 0mm=no perceived fatigue 100mm=completely fatigued) for session B [22], and rate of perceived exertion (6 to 20 Borg scale) [24], for both sessions, before and immediately after experimental conditions.

2.6. Gait analysis and outcomes

We combined the data from the two force plates to identify heel contact and toe-off from ground forces and, combined with the moments data, we computed the Center of Pressure Position (CoP) in AP and ML directions [6].

Taking the middle 120 strides, mean and CV was calculated for Stride length (SL), Step width (SW), Single support time (SST), Swing time (SwT), Cadence and, DFA. DFA quantifies absence/presence of long-range correlations between stride time intervals using a window of length n (n=N/4), being N=120 strides that are considered as acceptable power in between- and within-subjects designs involving older adults [2]. Values of $\alpha>0.5$ indicate persistence in the stride time intervals and <0.5 indicate alternation of larger- and smaller-than the average values.

Based on CoP trajectories in ML and AP direction, we calculated: 1) MSE, as an indication of gait complexity. It implies predictability of fluctuation patterns over time by increasing the length τ (τ=7) in the average of data point non-overlapping window (*r*=0.02).MSE=Zero represents data predictability [25]; 2) The λmax was quantified by the log of the expansion between the CoP trajectories by using Wolf algorithm (embedding of *n*=7 dimensions, delay τ of 10 samples), which is the most appropriated to evaluate λmax from relatively small data sets [26]. Large λmax indicate lower local dynamic stability (smaller ability to resist perturbations) [26]. Both methods, MSE and λmax, were previously employed in relatively small lengths, i.e., 3 min walking [4,26].

2.7. Statistical analysis

Power calculation (G*Power software) required a minimum of 24 participants (probability of 82% to detect a difference in SL at 5% of significance). Using, SPSS (SPSS Inc., USA), when the Shapiro-Wilk test revealed non-normal distribution, data were log-transformed. A Student's t-test between groups was applied to compare the characteristics, questionnaires and SPPB, and RSTS outcomes. To compare mental task performance, an ANOVA was applied with between-Group factor group (young vs. older) and within-Time factor (time 1 vs. time 2). ANOVAs with between-Group factor and within-Experimental condition (RSTS vs. mental), and Time (pre- vs. post-experimental conditions) factors were applied for the Borg scale, MVIF and voluntary activation, and the gait outcomes. Tukey's post hoc contrast was used to identify significant differences. The level of significance adopted was $p \leq 0.05$. Effect sizes were estimated concerning eta square (η^2). $\eta^2 \geq 0.02$ indicate small, ≥0.13 intermediate, and ≥0.26 large effects [27].

3. RESULTS

3.1. Participants

Table 1 shows that the two age groups had similar characteristics (all $p>0.05$).

3.2. Experimental conditions

Young performed up 4x longer RSTS than older participants (Table 1, T_{22}=7.40, $p<0.01$, T_{22}=7.39, $p<0.01$ respectively). Fig. 2a and Table 2 show the group by experimental condition by time interaction for the Borg scale ($p<0.01$), indicating an increase after RSTS ($p < 0.01$) but not after the mental tasks ($p>0.05$). Older vs. young adults reported higher exertion levels pre-fatigue. Fig. 2b and Table 2 show time by experimental conditions interaction for MVIF indicated a decrease by 17% in both groups after RSTS ($p<0.05$) but only ~2% after the mental tasks ($p>0.05$). Group main effect revealed that older adults performed ~40% less MVIF than young ($p<0.01$).

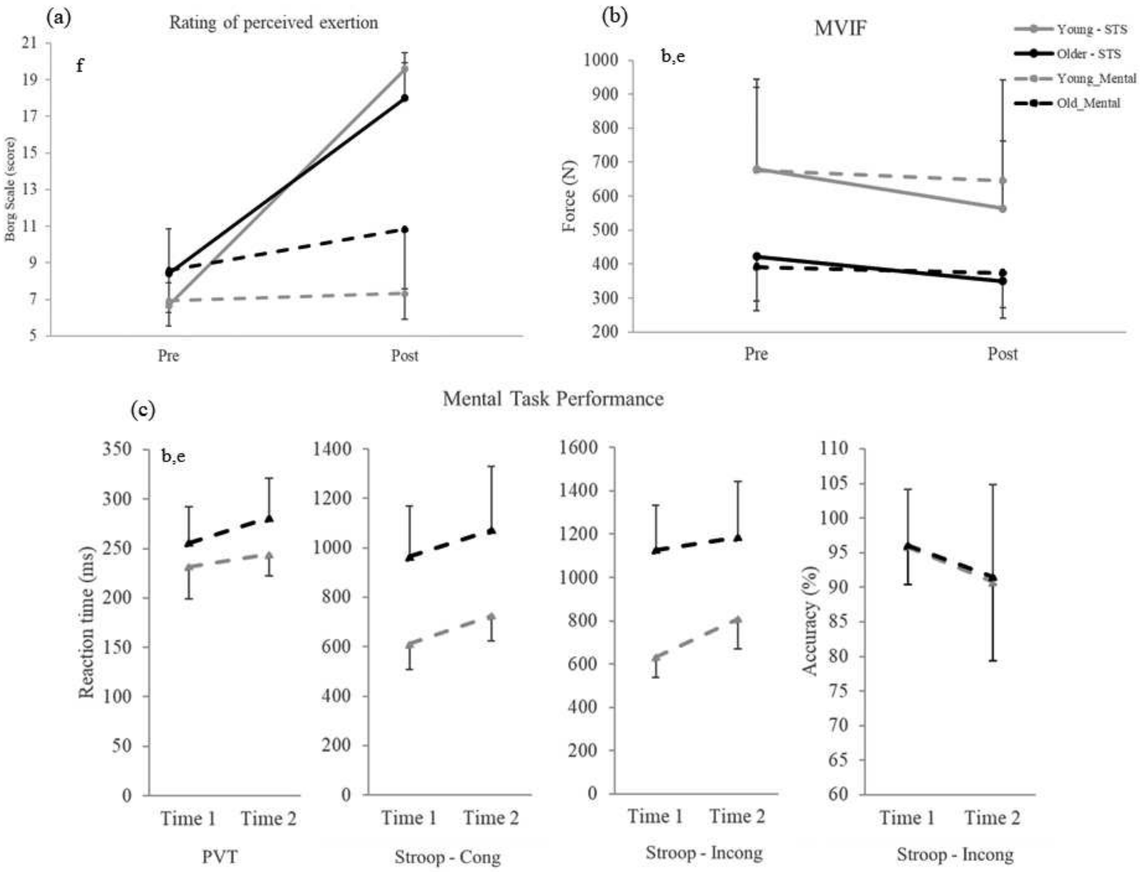


Fig. 2. Average and standard deviation of young (grey line) and older (black line) adults: (a) rating of perceived exertion and (b) MVIF pre- and post-fatigue, and (c) mental task performance for the RT of PVT and Stroop test (congruent and incongruent answers) and for accuracy on Stroop test, considering time 1 (first minutes) and time 2 (last minutes). Continuous and dashed lines represent RSTS and mental task, respectively. [a]Time main effect, [b]Group main effect, [e]Time by Experimental conditions interaction, [f]Group by Experimental conditions by Time interaction.

Table 2. Mean and standard deviation of experimental conditions outcomes in Older and Young groups.

Experimental conditions outcomes		RSTS		Mental tasks	
		Pre	Post	Pre	Post
Borg Scale [f]	Older	8.42 ±2.42	19.58 ±9.0	8.58 ±2.39	10.83 ±3.21
	Young	6.67 ±1.23	18.00 ±1.91	6.92 ±1.38	7.33 ±1.43
MVIF (N) [b, e, f]	Older	422.08 ±133.17	354.83 ±116.33	391.25 ±188.57	373.92 ±102.41
	Young	676.25 ±244.71	563.27 ±208.72	676.17 ±270.81	657.83 ±284.57
VA (%)	Older	86.50 ±11.22	87.56 ±13.21	85.50 ±14.78	89.33 ±13.47
	Young	88.65 ±17.65	87.93 ±14.35	90.67 ±11.22	90.58 ±8.64

MVIF, Maximum Voluntary Isometric Force; VA, Voluntary Activation.
[a]Time main effect, [b]Group main effect, [c]Experimental condition main effect, [d]Time by Group interaction, [e]Experimental conditions by Time interaction, [f] Time by Group by Experimental conditions interaction.

Fig. 2c shows time main effect ($p<0.05$) with a longer RT for PVT (~7%) and Stroop test (~15% for congruent and incongruent), and Accuracy for incongruent responses in Stroop decreased by 5% ($p<0.05$), and CPT RT was ~9% shorter at time 2 compared with time 1. ($p<0.05$). The VAS was significantly higher after (~30mm) than before the mental task. Group main effects ($p<0.05$) indicated that the older had longer RTs for the PVT (12%), and the Stroop test (congruent responses by 56%; incongruent responses by 65%) than young adults (Table 3). There was no Time by Group interaction ($p>0.05$).

Table 3. Mean and standard deviation of mental tasks outcomes in Older and Young groups, considering time 1 (minutes 2 to 5) and time 2 (minutes 6 to 10).

		Mental Tasks Outcomes			
		Time 1		Time 2	
RT (ms)					
PVT [a, b, d]	Older	256.02	±37.78	281.05	±41.85
	Young	231.68	±34.44	244.15	±23.11
Stroop – Cong [a, b, d]	Older	965.01	±214.13	1130.87	±420.33
	Young	611.43	±91.45	725.71	±108.09
Stroop – Incong [a, b, d]	Older	1127.92	±286.75	1261.8	±514.39
	Young	632.35	±97.79	807.43	±145.35
CPT [a, b]	Older	395.02	±125.22	370.35	±93.93
	Young	306.16	±71.35	302.22	±66.89
Accuracy (%)					
Stroop – Cong [a, b]	Older	99.08	±1.49	96.06	±4.81
	Young	94.93	±4.31	95.66	±4.98
Stroop – Incong [a, b, d]	Older	95.83	±8.40	91.47	±14.01
	Young	96.11	±5.74	90.77	±11.84
CPT [a, b, d]	Older	80.00	±19.05	80.47	±17.58
	Young	89.59	±9.35	92.39	±5.06
Visual Analogue Scale (mm) [a]		Pre - mental tasks		Post - mental tasks	
	Older	9.75	±8.35	47.83	±26.18
	Young	10.33	±8.66	49.25	±15.25

RT, Reaction Time; PVT, Psychomotor Vigilance Test; Cong, Congruent answer; Incong, Incongruent Answer; CPT, Continuous Performance Test; RT.
[a]Time main effect, [b]Group main effect, [c]Experimental condition main effect, [d]Time by Group interaction, [e]Experimental conditions by Time interaction, [f] Time by Group by Experimental conditions interaction.

3.3. Effects of the experimental condition and age on gait

As a secondary analysis, we separately compared the effects of experimental conditions on gait outcomes in a speed condition from 20-30% faster than the comfortable. For both gait speed, detailed ANOVA and outcomes are presented in Supplementary Material T1, T2, and T3.

Fig. 3a shows the experimental condition by time interaction in stride outcomes. Post hoc revealed significant effects of RSTS on SL, CV of SL, SST, and cadence ($p \leq 0.05$). No significant changes were observed after the mental task ($p > 0.05$) (η^2: 0.001 to 0.007).

Group main effects revealed that older adults walked with a higher CV of SL, CV of SST, CV of SwT, and lower SwT ($p<0.05$ for all) than young adults (η^2: 0.10 to 0.155).

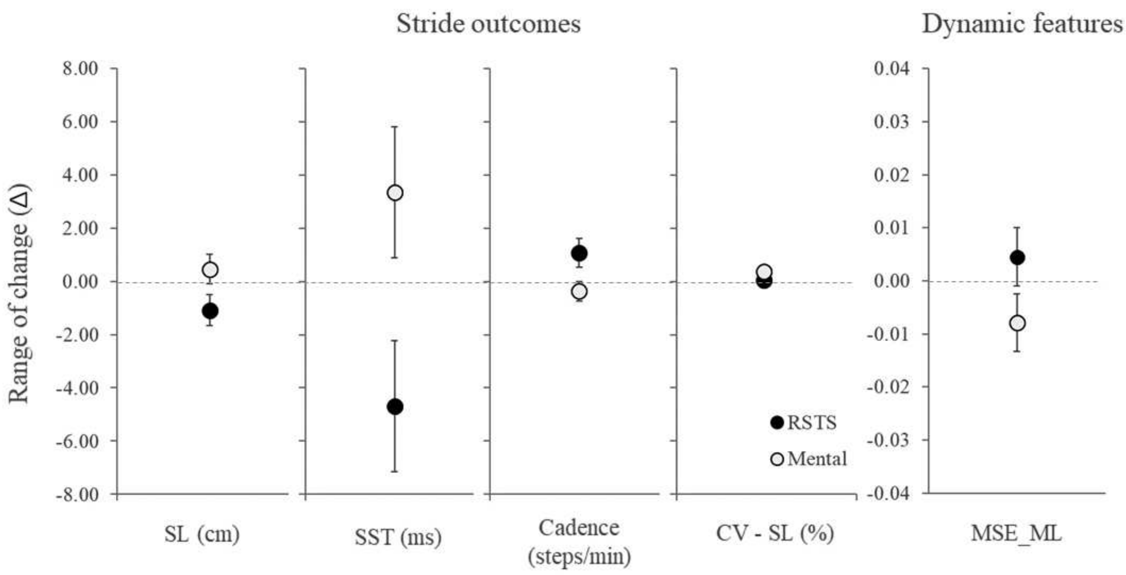


Fig. 3. Change in magnitude (Δ post – pre experimental conditions) and standard errors considering (a) STS (black dots) and mental task (grey dots) of the stride outcomes and (b) gait dynamics for fixed and fast speed condition independent of the groups, for the outcomes that presented significant differences.

3.4. Gait Dynamics

Time main effect ($p<0.05$) indicated an increase by 11% in ML λmax after the experimental condition ($p<0.05$, η^2: 0.020). Experimental conditions by time interaction for MSE of ML-CoP ($p<0.05$, Fig. 3b) showed a 5% decrease after the mental tasks (η^2: 0.015).

Group main effects revealed up to 50% higher in AP and ML λmax in older than young adults ($p<0.05$ for all, η^2: 0.20 and 0.215).

4. DISCUSSION

We determined the effects of age, RSTS, and prolonged mental effort on gait. RSTS reduced MVIF and increased perceived exertion in both age groups. After the mental task, perceived fatigue was higher, and RT of PVT and Stroop tests lower. While both manipulations effectively induced fatigability, these interventions produced minimal effects on healthy adults' treadmill walking.

While the mental tasks did not affect stride outcomes, after RSTS SL and single ST decreased by ~2cm and ~5ms, respectively and cadence increased by ~1.5 steps/min. Corresponding effect sizes suggested minimal functional effects (Fig. 3). These results agree with data collected after sustained endurance exercise, showing small (Cohen d: 0.10–0.4) or no effects on stride outcomes, gait variability [28], or on local dynamic stability of foot contact velocity and trunk accelerations [12–14] during treadmill walking. In contrast, when older adults walked overground, RSTS did affect stride outcomes and gait variability [9,10]. Repetitive leg-press plus calf and toe rises also increased the average and variability of the margin of stability during treadmill walking at a comfortable speed [14]. The inconsistent results between studies may be due to differences in the assessment of walking (treadmill vs. overground) and models to induce fatigability (muscles, tasks).

While treadmill vs. overground walking has the advantage of examining gait under a standardized condition, there are biomechanical differences in gait under in the two conditions [29]. Overground walking requires the participants to actively adjust features of gait, whereas the belt movement presets steps during treadmill walking. Treadmill walking is more reactive, which, compared with overground walking, necessitates lower muscle activation to generate force to advance the legs [29], making the cyclical movements of the legs uniform [28] and, compressing stride variability by 15% [30]. Thus, treadmill walking could minimize fatigue-effects on gait [28].

Muscle contributions to gait mechanics can also account for the small perturbation effects on gait. RSTS tends to reduce MVIF and median frequency of the EMG of the knee extensors but not of the ankle muscles [9]. During walking, the knee extensors decelerate the center of mass and stabilize the leg at heel strike [31]. However, the joint power generated by the knee extensors compared with the plantarflexors is ~4 times lower and plantarflexor power correlates (r^2 >0.5) with the age-related decrease in SL and gait speed [32]. These factors support prior data [14], showing the effects of combined knee and ankle fatiguing exercises on gait variability (~10% increase in variation of the AP and ML margin of stability and SW) and a ~ 8% increase in SL.

Notwithstanding the lower contribution of knee than ankle muscles to limb mechanical work during walking, previous studies revealed that quadriceps muscle fatigue induced by RSTS modified contributions of the non-fatigued ankle muscles to gait [33]: Ankle joint work increased ~2 times while stepping down from a curb after RSTS [33]. Additionally, prior EMG data indicated that older women increased quadriceps activity during the stance phase by ~10% after 20 min of treadmill walking, suggesting that compensation was needed to maintain gait [34].

The small effects induced by the RSTS task on treadmill walking in our study could be related to joint work during gait being submaximal. Ample reserve is left in the quadriceps to respond to the fatigue-induced reductions in force-generating capacity after hundreds of STS movements. Previous data indicated that EMG activation of the quadriceps muscle during habitual gait was less than 25% of the maximal activation [35,36]. It thus appears that, while RSTS substantially reduced the MVIF (Fig. 2) and its activation [11], these reductions were too small to necessitate changes in the mechanics of treadmill walking.

It is also conceivable that participants compensated for reduced quadriceps force by increasing the reliance on non-fatigued muscles [33] to keep up with belt speed on the treadmill. Increases in muscle activation by hip flexors and plantarflexors could increase stride length through an increased hip range of motion and more effective push-off, overriding any stride length shortening effects due to quadriceps fatigue. Future studies, thus, should determine if compensatory muscle activation appeared during walking after fatigue.

Our results indicate that sustained mental task did not affect gait outcomes, agreeing with previous data [15]. However, these authors reported an increase in the CV of speed, SL, stance phase, double support and swing time during dual-task walking, after the mental task [15]. These data seem to support the idea that prolonged mental activity is a reasonable model to study the effects of sustained mental task-induced fatigability on gait, resembling dual- but not single-task walking [15]. Moreover, after the mental tasks, perhaps participants rely on feedback from leg muscles and capitalize on the imposed pattern by the treadmill to compensate for the reduced availability of cognitive resources. Despite minimal fatigability effects on gait, this study proposed novel insights into the understanding how the mental fatigue-induced interference with cognitive functions would affect gait dynamics.

Although older vs. young adults walked with shorter SL (~6 cm), higher cadence (~6 steps /min), variability (~20% of CV in SL and SwT), and λmax in AP and ML (~30%), unexpectedly, there was no interaction between fatigue and task in our outcomes. Interaction involving age and sustained muscle activity reported previously [9,37], did result in more pronounced adjustments in stride length (~4%), duration (~4%) and speed (up to 8%) in older compared with young adults during overground walking [9] and dual-task walking [37]. It seems to complement the argument that overground compared with treadmill walking represents a more complex and challenging task, and dual-task walking requires greater sensory integration and executive function that could amplify the fatigability effects.

A limitation of this study is that older and young were similar in physical performance, global cognition, and trait of fatigue, minimizing the effects of age and experimental manipulations on gait. Duration of the RSTS varied between participants. However, the 16% average force loss we observed was greater than reductions reported previously [8,9]. Fatigability in the plantarflexors or combined knee and ankle exercises could be effective to probe the effects of age and fatiguability on gait [14]. Concerning mental tasks, this protocol appears to be effective to examine age-related changes in dual-task walking [15]. A comparison between treadmill vs. real world walking in the fatigue context would provide information if the treadmill does indeed minimize fatigability-effects on gait.

5. CONCLUSION

Muscle and mental fatigability had minimal effects on gait in young and healthy older adults possibly because treadmill walking makes gait uniform. It is still possible that age-dependent muscle activation underlies the uniform gait on the treadmill. Age- and fatigability effects might be more overt during real life compared with treadmill walking, creating a more effective model for examining gait and age adaptability to fatigability perturbations.

REFERENCES

[1] Aboutorabi A, Arazpour M, Bahramizadeh M, Hutchins SW, Fadayevatan R. The effect of aging on gait parameters in able-bodied older subjects: a literature review. Aging Clin Exp Res 2016;28:393–405. doi:10.1007/s40520-015-0420-6.

[2] Kuznetsov NA, Rhea CK. Power considerations for the application of detrended fluctuation analysis in gait variability studies. PLoS One 2017;12:e0174144. doi:10.1371/journal.pone.0174144.

[3] Hausdorff JM, Rios DA, Edelberg HK. Gait variability and fall risk in community-living older adults: a 1-year prospective study. Arch Phys Med Rehabil 2001;82:1050–6. doi:10.1053/apmr.2001.24893.

[4] Kikkert LHJ, Vuillerme N, van Campen JP, Appels BA, Hortobágyi T, Lamoth CJC. Gait characteristics and their discriminative power in geriatric patients with and without cognitive impairment. J Neuroeng Rehabil 2017;14:84. doi:10.1186/s12984-017-0297-z.

[5] Morris R, Lord S, Bunce J, Burn D, Rochester L. Gait and cognition: Mapping the global and discrete relationships in ageing and neurodegenerative disease. Neurosci Biobehav Rev 2016;64:326–45. doi:10.1016/j.neubiorev.2016.02.012.

[6] Buurke TJW, Lamoth CJC, Vervoort D, van der Woude LH V, den Otter R. Adaptive control of dynamic balance in human gait on a split-belt treadmill. J Exp Biol 2018;221:jeb.174896. doi:10.1242/jeb.174896.

[7] Enoka RM, Duchateau J. Translating Fatigue to Human Performance. Med Sci Sport Exerc 2016;48:2228–38. doi:10.1249/MSS.0000000000000929.

[8] Hatton AL, Menant JC, Lord SR, Lo JCM, Sturnieks DL. The effect of lower limb muscle fatigue on obstacle negotiation during walking in older adults. Gait Posture 2013;37:506–10. doi:10.1016/j.gaitpost.2012.09.004.

[9] Barbieri FA, dos Santos PCR, Simieli L, Orcioli-Silva D, Van Dieën JH, Gobbi LTB. Interactions of age and leg muscle fatigue on unobstructed walking and obstacle crossing. Gait Posture 2014;39:985–90. doi:10.1016/J.GAITPOST.2013.12.021.

[10] Helbostad JL, Leirfall S, Moe-Nilssen R, Sletvold O. Physical fatigue affects gait characteristics in older persons. J Gerontol A Biol Sci Med Sci 2007;62:1010–5.

[11] Roldán-Jiménez C, Bennett P, Cuesta-Vargas AI. Muscular Activity and Fatigue in Lower-Limb and Trunk Muscles during Different Sit-To-Stand Tests. PLoS One 2015;10:e0141675. doi:10.1371/journal.pone.0141675.

[12] Hamacher D, Törpel A, Hamacher D, Schega L. The effect of physical exhaustion on gait stability in young and older individuals. Gait Posture 2016;48:137–9. doi:10.1016/j.gaitpost.2016.05.007.

[13] Hamacher D, Hamacher D, Hohnbaum M, Gerth K, Schega L, Zech A. Effects of physical exhaustion on local dynamic stability and automaticity of walking. Gait Posture 2018;66:135–8. doi:10.1016/J.GAITPOST.2018.08.031.

[14] Kao P-C, Pierro MA, Booras K. Effects of motor fatigue on walking stability and variability during concurrent cognitive challenges. PLoS One 2018;13:e0201433. doi:10.1371/journal.pone.0201433.

[15] Behrens M, Mau-Moeller A, Lischke A, Katlun F, Gube M, Zschorlich V, et al. Mental Fatigue Increases Gait Variability During Dual-task Walking in Old Adults. J Gerontol A Biol Sci Med Sci 2018;73:792–7. doi:10.1093/gerona/glx210.

[16] Tombaugh TN, McIntyre NJ. The Mini-Mental State Examination: A Comprehensive Review. J Am Geriatr Soc 1992;40:922–35. doi:10.1111/j.1532-5415.1992.tb01992.x.

[17] Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995;39:315–25.

[18] Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-Extremity Function in Persons over the Age of 70 Years as a Predictor of Subsequent Disability. N Engl J Med 1995;332:556–62. doi:10.1056/NEJM199503023320902.

[19] Krasovsky T, Lamontagne A, Feldman AG, Levin MF. Effects of walking speed on gait stability and interlimb coordination in younger and older adults. Gait Posture 2014;39:378–85. doi:10.1016/j.gaitpost.2013.08.011.

[20] Kang HG, Dingwell JB. Effects of walking speed, strength and range of motion on gait stability in healthy older adults. J Biomech 2008;41:2899–905. doi:10.1016/J.JBIOMECH.2008.08.002.

[21] Zult T, Gokeler A, van Raay JJAM, Brouwer RW, Zijdewind I, Hortobágyi T. An anterior cruciate ligament injury does not affect the neuromuscular function of the non-injured leg except for dynamic balance and voluntary quadriceps activation. Knee Surgery, Sport Traumatol Arthrosc 2017;25:172–83. doi:10.1007/s00167-016-4335-3.

[22] Rifai Chai, Smith MR, Nguyen TN, Sai Ho Ling, Coutts AJ, Nguyen HT. Comparing features extractors in EEG-based cognitive fatigue detection of demanding computer tasks. 2015 37th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc., vol. 2015, IEEE; 2015, p. 7594–7. doi:10.1109/EMBC.2015.7320150.

[23] Khitrov MY, Laxminarayan S, Thorsley D, Ramakrishnan S, Rajaraman S, Wesensten NJ, et al. PC-PVT: a platform for psychomotor vigilance task testing, analysis, and prediction. Behav Res Methods 2014;46:140–7. doi:10.3758/s13428-013-0339-9.

[24] Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14:377–81.

[25] Costa M, Peng C-K, L. Goldberger A, Hausdorff JM. Multiscale entropy analysis of human gait dynamics. Phys A Stat Mech Its Appl 2003;330:53–60. doi:10.1016/J.PHYSA.2003.08.022.

[26] Cignetti F, Decker LM, Stergiou N. Sensitivity of the Wolf's and Rosenstein's Algorithms to Evaluate Local Dynamic Stability from Small Gait Data Sets. Ann Biomed Eng 2012;40:1122–30. doi:10.1007/s10439-011-0474-3.

[27] Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd. Hillsdale (NJ): Lawrence Erlbaum Associates; 1988.

[28] Hanley B, Tucker CB. Gait variability and symmetry remain consistent during high-intensity 10,000 m treadmill running. J Biomech 2018;79:129–34. doi:10.1016/j.jbiomech.2018.08.008.

[29] Lee SJ, Hidler J. Biomechanics of overground vs. treadmill walking in healthy individuals. J Appl Physiol 2008;104:747–55. doi:10.1152/japplphysiol.01380.2006.

[30] Hollman JH, Watkins MK, Imhoff AC, Braun CE, Akervik KA, Ness DK. A comparison of variability in spatiotemporal gait parameters between treadmill and overground walking conditions. Gait Posture 2016;43:204–9. doi:10.1016/j.gaitpost.2015.09.024.

[31] Teixeira-Salmela LF, Nadeau S, Milot M-H, Gravel D, Requião LF. Effects of cadence on energy generation and absorption at lower extremity joints during gait. Clin Biomech 2008;23:769–78. doi:10.1016/J.CLINBIOMECH.2008.02.007.

[32] Judge JO, Davis RB, Ounpuu S. Step length reductions in advanced age: the role of ankle and hip kinetics. J Gerontol A Biol Sci Med Sci 1996;51:M303-12.

[33] Barbieri FA, Gobbi LTB, Lee YJ, Pijnappels M, van Dieën JH. Effect of triceps surae and quadriceps muscle fatigue on the mechanics of landing in stepping down in ongoing gait. Ergonomics 2014;57:934–42. doi:10.1080/00140139.2014.903302.

[34] Pereira MP, Gonçalves M. Effects of Fatigue Induced by Prolonged Gait When Walking on the Elderly. Hum Mov 2011;12:242–7.

[35] Hortobágyi T, DeVita P. Muscle pre- and coactivity during downward stepping are associated with leg stiffness in aging. J Electromyogr Kinesiol 2000;10:117–26.
[36] Murdock GH, Hubley-Kozey CL. Effect of a high intensity quadriceps fatigue protocol on knee joint mechanics and muscle activation during gait in young adults. Eur J Appl Physiol 2012;112:439–49. doi:10.1007/s00421-011-1990-4.
[37] Granacher U, Wolf I, Wehrle A, Bridenbaugh S, Kressig RW. Effects of muscle fatigue on gait characteristics under single and dual-task conditions in young and older adults. J Neuroeng Rehabil 2010;7:56. doi:10.1186/1743-0003-7-56.

Supplementary Table 1. ANOVA outcomes for the significant main and interaction effects and effect sizes.

	Time			Group			Experimental conditions			Time × Group			Time × Experimental conditions			Experimental conditions × Group			Time × Experimental conditions × Group		
	F	*P*	η^2	F	*P*	η^2	F	*P*	η^2	F	*P*	η^2	F	*P*	η^2	F	*P*	η^2	F	*P*	η_p^2
Fatigue outcomes																					
Borg Scale	100.958	0.000	0.222	8.151	0.011	0.017	362.968	<0.01	0.389	6.992	0.015	0.015	224.131	0.000	0.241	ns	ns	ns	15.21	0.000	0.016
MVF (N)	32.683	0.000	0.034	10.614	0.000	0.693	ns	ns	ns	ns	ns	ns	5.809	0.025	0.011	ns	ns	ns	ns	ns	ns
VA (%)	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
VAS (mm)	46.405	0.000	0.44	ns	ns	ns	-	-	-	ns	ns	ns	-	-	-	-	-	-	-	-	-
PVT – RT (ms)	15.346	0.000	0.060	5.174	0.033	0.161	-	-	-	ns	ns	ns	-	-	-	-	-	-	-	-	-
Stroop Congruent – RT (ms)	8.627	0.000	0.051	18.174	0.000	0.372	-	-	-	ns	ns	ns	-	-	-	-	-	-	-	-	-
Stroop Incongruent – RT (ms)	7.906	0.011	0.040	17.750	0.000	0.050	-	-	-	ns	ns	ns	-	-	-	-	-	-	-	-	-
Stroop Congruent – AC (%)	ns	ns	ns	ns	ns	ns	-	-	-	ns	ns	ns	-	-	-	-	-	-	-	-	-
Stroop Incongruent – AC (%)	4.249	0.049	0.055	ns	ns	ns	-	-	-	4.900	0.037	0.048	-	-	-	-	-	-	-	-	-
CPT – RT (ms)	4.410	0.047	0.005	4.487	0.046	0.163	-	-	-	ns	ns	ns	-	-	-	-	-	-	-	-	-
CPT – Acc (%)	ns	ns	ns	ns	ns	ns	-	-	-	ns	ns	ns	-	-	-	-	-	-	-	-	-
Stride outcomes - Fixed Speed																					
Stride Length (cm)	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	6.748	0.016	0.002	ns	ns	ns	ns	ns	ns
Step Width (cm)	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Single Support time (s)	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	8.291	<0.01	0.005	ns	ns	ns	ns	ns	ns
Swing Time (ms)	ns	ns	ns	4.987	0.036	0.133	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Cadence (steps/min)	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	7.231	0.013	0.003	ns	ns	ns	ns	ns	ns
CV – Stride Length (%)	6.709	0.017	0.028	9.253	<0.01	0.157	ns	ns	ns	ns	ns	ns	4.068	0.050	0.007	ns	ns	ns	ns	ns	ns
CV – Step width (%)	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
CV – Single Support time (%)	ns	ns	ns	5.370	0.03	0.125	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
CV – Swing Time (%)	ns	ns	ns	6.411	0.019	0.122	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
DFA	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
MSE - AP	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	4.491	0.047	0.012	ns	ns	ns

Supplementary Table 1. ANOVA outcomes for the significant main and interaction effects and effect sizes. (continued)

	Time			Group			Experimental conditions			Time × Group			Time × Experimental conditions			Experimental conditions × Group			Time × Experimental conditions × Group		
	F	*P*	η^2	F	*P*	η^2	F	*P*	η^2	F	*P*	η^2	F	*P*	η^2	F	*P*	η^2	F	*P*	η_p^2
MSE - ML	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	5.061	0.036	0.015	ns	ns	ns	ns	ns	ns
λ_{max} - AP	**ns**	ns	ns	11.351	<0.01	0.20	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
λ_{max} - ML	7.218	0.015	0.020	8.23	<0.01	0.215	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Stride outcomes – Fast speed[ϑ]																					
Stride Length (cm)	ns	ns	ns	6.993	0.023	0.223	ns	ns	ns	ns	ns	ns	11.866	<0.01	0.002	ns	ns	ns	ns	ns	ns
Step Width (cm)	ns	ns	ns	ns	ns	ns	11.487	<0.01	0.003	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Single Support time (s)	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	20.608	<0.01	0.015	ns	ns	ns	ns	ns	ns
Swing Time (ms)	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	4.276	0.049	0.004	ns	ns	ns	ns	ns	ns
Cadence (steps/min)	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	9.524	<0.01	0.009	ns	ns	ns	ns	ns	ns
CV – Stride Length (%)	5.020	0.035	0.034	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
CV – Step width (%)	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
CV – Single Support time (%)	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
CV – Swing Time (%)	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
DFA	5.850	0.025	0.051	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
MSE - AP	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
MSE - ML	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	9.290	<0.01	0.021	ns	ns	ns	ns	ns	ns
λ_{max} - AP	ns	ns	ns	7.824	0.011	0.110	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
λ_{max} - ML	ns	ns	ns	11.22	<0.01	0.241	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns

Legend: MVIF, Maximum Voluntary Isometric Force; VA, Voluntary Activation; VAS, Visual Analog Scale; PVT, Psychomotor Vigilance Task; RT, Reaction Time; Acc, Accuracy; CV, Coefficient of Variation; DFA, Detrend Fluctuation Analysis; MSE, Multi-scale Sample Entropy; λmax, Max Lyapunov exponent; AP, Antero-posterior; ML, Mediolateral; ns, Non-significant; - non-considered factor in the analysis.

[ϑ]Fast speed for young (YA: 1.73 ±0.09m/s) and Older adults (OA: 1.66 ±0.11m/s) was determined by 20 to 30% higher than the comfortable speed (YA: 1.38 ±0.12m/s, OA: 1.32 ±0.15m/s, both groups ranged from 1.10 to 1.60m/s). The range of 20 to 30% was necessary to guarantee a substantially faster than 1.2 m/s (fixed speed condition) and to avoid jogging instead of walking.

Supplementary Table 2. Mean and standard deviation of the stride outcomes, variability, and gait dynamic for the fixed speed gait condition in older and young adults pre and post STS task and mental tasks.

			Gait outcomes - Fixed Speed Condition			
			Pre - RSTS	Post - RSTS	Pre Mental	Post Mental
Mean	Stride length (cm) [e]	Older	125.10 ±7.02	125.20 ±8.37	125.10 ±8.25	126.20 ±8.66
		Young	132.04 ±8.51	129.91 ±8.54	132.65 ±8.50	132.46 ±8,99
	Step Width (cm) [a]	Older	9.78 ±3.22	9.82 ±3.09	10.28 ±4.57	9.93 ±3.33
		Young	11.23 ±4.57	10.78 ±4.04	10.01 ±3.60	9.71 ±4.14
	Single support (ms) [e]	Older	371.6 ±25.28	372.6 ±31.60	369.6 ±28.13	375.2 ±32.79
		Young	391.2 ±25.88	380.8 ±25.87	385.8 ±27.13	386.9 ±28.40
	Swing time (ms) [b]	Older	672.0 ±38.32	670.7 ±42.05	672.9 ±43.95	676.5 ±44.31
		Young	709.1 ±49.25	701.8 ±47.72	719.7 ±47.15	717.0 ±49.08
	Cadence (steps/min) [e]	Older	114 ±6	114 ±7	114 ±7	113 ±7
		Young	108 ±7	110 ±6	108 ±7	108 ±7
Coefficient of variation	Stride length (%) [a, b, e]	Older	2.30 ±0.68	2.37 ±0.62	2.06 ±0.04	2.48 ±0.68
		Young	1.88 ±0.39	1.87 ±0.43	1.68 ±0.36	1.96 ±0.58
	Step Width (%)	Older	11.73 ±7.69	11.94 ±4.33	11.73 ±7.69	11.05 ±4.77
		Young	9.41 ±2.03	10.22 ±2.58	12.67 ±7.35	13.84 ±7.46
	Single support (%) [b, f]	Older	4.53 ±1.19	4.82 ±1.74	4.95 ±1.57	4.78 ±1.24
		Young	3.61 ±0.79	3.67 ±0.85	3.50 ±087	4.35 ±1.14
	Swing time (%) [b, f]	Older	3.85 ±0.91	4.24 ±1.46	4.04 ±0.96	4.33 ±1.2
		Young	3.29 ±0.56	3.18 ±0.52	3.07 ±0.81	3.88 ±1.29
Gait Dynamics	DFA	Older	0.83 ±0.25	0.74 ±0.17	0.71 ±0.20	0.75 ±0.21
		Young	0.74 ±0.19	0.79 ±0.11	0.72 ±0.17	0.77 ±0.19
	λmax - AP b	Older	0.66 ±0.24	0.61 ±0.24	0.48 ±0.16	0.59 ±0.24
		Young	0.38 ±0.15	0.37 ±0.15	0.36 ±0.15	0.47 ±012
	λmax - ML [b, e]	Older	1.06 ±0.50	1.04 ±0.29	0.99 ±0.27	1.10 ±0.43
		Young	0.66 ±0.10	0.81 ±0.27	0.64 ±0.23	0.80 ±021
	MSE - AP [b]	Older	0.10 ±0.02	0.11 ±0.02	0.10 ±0.02	0.10 ±0.02
		Young	0.11 ±0.02	0.12 ±0.01	0.11 ±0.02	0.12 ±0.02
	MSE - ML [e]	Older	0.25 ±0.03	0.25 ±0.03	0.25 ±0.03	0.24 ±0.03
		Young	0.24 ±0.02	0.26 ±0.02	0.25 ±0.02	0.24 ±0.02

Legend: MSE, Multi-scale Sample Entropy; λmax, Max Lyapunov exponent; AP, Antero-posterior; ML Mediolateral. [a]Time main effect, [b]Group main effect, [c]Experimental conditions main effect, [d]Time by Group interaction, [e]Time by Experimental conditions interaction, [f]Group by Experimental condition by Time interaction.

Supplementary Table 3. Mean and standard deviation of the stride outcomes, variability, and gait dynamic for the fast speed gait condition in older and young groups pre and post STS task and mental tasks.

			Gait outcomes – Fast Speed Condition			
			Pre - RSTS	Post - RSTS	Pre - Mental	Post - Mental
Mean	Stride length (cm) [a, b]	Older	152.70 ±15.6	151.51 ±15.87	153.38 ±15.01	154.25 ±16.20
		Young	167.56 ±8.75	164.06 ±9.81	168.85 ±9.16	166.87 ±10.19
	Step Width (cm)	Older	8.28 ±2.98	8.18 ±2.73	8.21 ±3.62	7.48 ±3.37
		Young	9.28 ±3.78	9.80 ±3.96	8.73 ±3.70	8.87 ±3.71
	Single support (ms) [e]	Older	356.6 ±15.51	353.1 ±21.04	384.5 ±16.97	352.8 ±21.34
		Young	360.3 ±16.68	352.0 ±15.52	360.1 ±15.51	361.5 ±17.45
	Swing time (ms) [a]	Older	594.2 ±36.79	590.2 ±37.24	584.2 ±33.62	584.9 ±36.78
		Young	590.8 ±20.91	578.7 ±0.03	595.1±22.28	593.6 ±22.33
	Cadence (steps/min) [e]	Older	125 ±6	126 ±6	127 ±6	126 ±7
		Young	124 ±4	127 ±5	124 ±4	124 ±5
Coefficient of variation	Stride length (%) [a, e]	Older	1.81 ±0.42	1.73 ±0.38	1.92 ±0.69	2.13 ±0.98
		Young	1.51 ±0.71	1.44 ±0.38	1.47 ±0.41	1.47 ±0.41
	Step Width (%)	Older	18.41 ±7.18	17.82 ±5.21	17.1 ±4.94	21.44 ±8.48
		Young	15.08 ±6.41	15.92 ±7.53	18.8 ±7.67	17.10 ±7.84
	Single support (%)	Older	3.66 ±1.08	10 ±1.2	4.84 ±3.87	4.23 ±1.48
		Young	3.27 ±1.58	3.33 ±1.66	3.36 ±1.32	3.21 ±1.09
	Swing time (%)	Older	3.30 ±0.96	3.29 ±0.61	3.99 ±2.63	3.92 ±1.47
		Young	3.11 ±1.94	3.00 ±1.66	3.25 ±1.05	3.04 ±0.87
Gait Dynamics	DFA	Older	0.66 ±0.16	0.75 ±0.14	0.66 ±0.16	0.79 ±0.16
		Young	0.74 ±0.15	0.75 ±0.18	0.61 ±0.19	0.68 ±0.15
	λmax - AP [b]	Older	0.53 ±0.20	0.59 ±0.17	0.57 ±0.23	0.58 ±0.23
		Young	0.39 ±0.17	0.49 ±0.28	0.40 ±0.14	0.43 ±0.17
	λmax - ML [b]	Older	0.81 ±0.25	0.82 ±0.32	0.84 ±0.32	0.77 ±0.39
		Young	0.59 ±0.18	0.51 ±0.16	0.45 ±0.14	0.54 ±0.19
	MSE - AP [b]	Older	0.25 ±0.07	0.28 ±0.07	0.31 ±0.12	0.31 ±0.09
		Young	0.34 ±0.09	0.36 ±0.08	0.36 ±0.12	0.33 ±0.08
	MSE - ML [e]	Older	0.45 ±0.10	0.47 ±0.08	0.52 ±0.13	0.49 ±0.14
		Young	0.49 ±0.10	0.53 ±0.14	0.51 ±0.14	0.47 ±0.09

Legend: MSE, Multi-scale Sample Entropy; λmax, Max Lyapunov exponent; AP, Antero-posterior; ML Mediolateral. [a]Time main effect, [b]Group main effect, [c]Experimental conditions main effect, [d]Time by Group interaction, [e]Time by Experimental conditions interaction, [f]Group by Experimental condition by Time interaction.

[ϑ]Fast speed for Young (YA: 1.73 ±0.09m/s) and Older adults (OA: 1.66 ±0.11m/s) was determined by 20 to 30% higher than the comfortable speed (YA: 1.38 ±0.12m/s, OA: 1.32 ±0.15m/s, both groups ranged from 1.10 to 1.60m/s). The range of 20 to 30% was necessary to guarantee a substantially faster than 1.2 m/s (fixed speed condition) and to avoid jogging instead of walking.

4

Older compared with young adults perform 467 fewer sit-to-stand trials resulting in minimized changes in muscle activation and voluntary force

P. C. Rocha dos Santos[1,2]
C. Lamoth[1]
L.T.B. Gobbi[2]
I. Zijdewind[3]
F. A. Barbieri[4]
T. Hortobágyi[1]

[1]*Department of Human Movement Sciences, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands,*
[2]*Posture and Gait Studies Laboratory (LEPLO), Graduate Program in Movement Sciences, Institute of Biosciences, São Paulo State University (UNESP), Rio Claro, Brazil,*
[3]*Department of Biomedical Sciences of Cells and Systems, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.*
[4]*Human Movement Research Laboratory (MOVI-LAB), Graduate Program in Movement Sciences, Department of Physical Education, São Paulo State University (UNESP), Bauru, Brazil.*

Submitted for publication

ABSTRACT

Background: Repetitive sit-to-stand (rSTS) is a perturbation model to examine the age-effects on adaptability in posture and gait, yet the age-effects on muscle activation during rSTS per se are unclear.

Research question: Whether and how do the age and exhaustive rSTS affect muscle activation during ascent and descent phases of the STS task?

Methods: Healthy older (n=12) and younger (n=11) adults performed rSTS to failure or for 30min. We assessed muscle activation magnitude, onset, and duration of plantar flexors, dorsiflexors, knee flexors, knee extensors, and hip stabilizers during the initial and late-stages of rSTS. Before and after rSTS, we measured maximal voluntary isometric force (MVIF), and rate of perceived exertion (RPE), which was also measured during rSTS.

Results: Older vs. younger adults had 35% lower MVIF. During the initial-stage of rSTS, older vs. younger adults activated the dorsiflexor 60% higher, all 5 muscle groups 37% longer, and the hip stabilizers 80% earlier. Older vs. younger adults completed 467 fewer STS trials and, at failure, their RPE was ~18.7 of 20 on the Borg scale. At the end of the rSTS, MVIC, activation of the dorsiflexor and knee extensor muscles decreased in both age groups (16-28%, $p<0.05$).

Significance: By performing remarkably fewer STS trials, older adults consequently had limited impact of rSTS in inducing failure in muscle activation, voluntary force, and motor function. Such a sparing effect may explain the minimal changes in gait after rSTS reported in previous studies, suggesting a limited scope of this perturbation model to probe the age-effects on muscle adaptation in gait and posture.

Keywords: Old; Fatigue; Electromyography; Functionality; Muscle strength.

List of abbreviations: ANOVA, Analysis of variance; BF, Biceps femoris long head; CI, Co-contraction index; CoM, Center of mass; CoP, Center of pressure; d, Cohen d effect size; DF, Dorsiflexors; EMG, Electromyography; GAS, Gastrocnemius; Glu, Gluteus medius; KE, Knee extensors; KF, Knee flexors; MFI, Multidimensional fatigue inventory; MVIF, Maximum voluntary isometric force; PF, Plantar Flexors; PL, Peroneus Longus; RF, Rectus Femoris; RMS, Root Mean Square; RPE, Rate of perceived exertion; rSTS, Repetitive sit-to-stand; SENIAM, Surface Electromyography for the Non-Invasive Assessment of Muscle; SL, Soleus; SPPB, Short Physical Performance Battery; ST, Semitendinosus; STS, Sit-to-stand; TA, Tibialis Anterior; TFL, Tensor Fasciae Latae; TKEO, Teager–Kaiser energy operator; VL, Vastus Lateralis; Δ, Delta; η_p^2, Partial Eta-Square.

1. INTRODUCTION

Rising from and sitting down in a chair is a demanding functional task, particularly for older adults, as it requires leg muscle strength, large joint excursions, inter-joint coordination, and balance [1–4]. Rising from a chair strongly activates the knee, ankle, and hip muscles in older adults [5–7], i.e., up to 90% of maximal knee extensor activation [8]. Not only the agonists but especially the antagonists become over-activated in older adults, resulting in agonist-antagonist coactivation [5,9]. Higher coactivation is associated with imbalances in the excitatory-inhibitory corticospinal circuits [10], which can also delay muscle relaxation in older adults [11]. Conceivably, the age-differences in muscle activation amplitude, combined with a delay in muscle relaxation during sit-to-stand (STS), would increase energy expenditure [10], underlying higher muscle fatigability in older adults [12].

Uncontrolled cadence and unnaturally slow execution rate [5] could mask age-differences in muscle activation during STS [3,6]. Additionally, previous studies examined the age-effects on muscle activity during the ascent phase [6] or the entire STS cycle [5] without considering potential age-effects on muscle activation during the descent phase or on the temporal signature of muscle activation of the STS task. Characterization of muscle activation during the descent phase could increase our understanding of neural control of STS because force variability during eccentric force generation increases with age [13], suggesting that muscle activation during the ascent and descent phases of STS after an exhaustive of STS series might vary by age. Therefore, we firstly determined the effects of age on muscle activation magnitude, onset, and duration during the ascent and descent phases of the STS, performed at a controlled, fast cadence. We hypothesized that older vs. younger adults would execute the STS task with a higher, earlier, and longer-lasting muscle activation duration and phase-dependent change in muscle activation varying by age [8,14].

Healthy aging affects motor adaptability to sensory and mechanical perturbations [15]. Several perturbation paradigms have been used to determine age-effects on motor adaptability [16–19], including fatigue [18,19]. Although studies have attributed changes in rSTS (fatigue perturbation) to explain the age-related adaptability in gait [18–20], the characterization of muscle activation during rSTS is lacking [5]. A typical compensatory strategy to submaximal fatiguing tasks involves an increase in muscle amplitude in the primary and recruitment of additional less involved muscles [5,6]. An examination of hip, knee, and ankle muscle activation profiles during rSTS could provide new insights into age-related motor adaptability. Therefore, the second aim was to determine the effects of age and fatigue induced by rSTS on muscle activation during initial and late-stages of STS. Given existing literature [6], we expected an increase in muscle amplitude in the primary agonist knee extensors and in muscles that show low activation at the start of the STS series. Because of the age-typical neuromuscular decline [3,5,8,21], we expected age-specific increases in muscle activation amplitude and duration after the execution of rSTS.

2. METHODS

2.1. Participants

Healthy older (n=12) and younger adults (n=11) participated in the study (Table 1). Exclusion criteria were self-reported pain, injury or surgery in the lower extremity muscles, and neurological and cardiologic disease. The local Ethics Committee approved the procedures and the informed consent document (#ECB2017.06.12_1).

2.2. General experimental procedures

Participants visited the laboratory once and completed the Multidimensional Fatigue Inventory [22]; performed the Short Physical Performance Battery [23], the maximal voluntary isometric force (MVIF) before and after rSTS (muscle fatigability), during which EMG activity and vertical acceleration were recorded.

2.3. MVIF

Participants, seated on a custom-built dynamometer (knee, hip in 90° of flexion), with the non-dominant lower leg strapped (~10cm superior to lateral malleolus), were instructed to contract the quadriceps as forcefully as possible and maintain it for 5s [18]. After familiarization, MVIF was determined as the peak of force before and after rSTS.

2.4. rSTS

Seated in a chair (0.43m height X 0.41m width X 0.42m depth), with the arms crossed at the chest, and feet placed comfortably, participants were instructed to stand up to full knee and hip extension and sat back until touching the seat, to the beat of a metronome (30 beats/min, cycle=2s). After task and cadence familiarization, participants performed rSTS until failure or for 30min with task duration and STS trials recorded. Before, during each minute, and after rSTS, participants rated their perceived exertion (RPE, 6–20 Borg scale) [24].

2.5. EMG and accelerometry data recording

Following SENIAM [25], wireless EMG sensors (Trigno System, Delsys Inc.) were placed on Gastrocnemius Lateralis (GAS), Soleus (SL), Tibialis Anterior (TA), Peroneus Longus (PL), Rectus Femoris (RF), Vastus Lateralis (VL), Biceps Femoris long head (BF), Semitendinosus (ST), Tensor Fasciae Latae (TFL) and the Gluteus medius (Glu) on the dominant leg (ball kicking) [3]. Sampling frequency was 2.0kHz. Vertical acceleration was recorded at 148.1Hz from the mid-thigh (RF) Trigno acceleration channel (16-bits resolution, 50-Hz Bandwidth).

2.6. Data analysis

Data were analyzed in MatLab (The MathWorks, Inc.). The vertical acceleration signal was low-pass filtered (5Hz 4th order Butterworth). Each STS cycle (seat-off to seat-off) comprised the ascent, stand, descent, and sitting phases based on the vertical acceleration signal [26]. After excluding the first five STSs (adaptation period), the next five (initial-stage) and the last five STSs (late-stage) were considered for the analyses, in which for each phase, we calculated the jerk, derivative of the acceleration per time (m/s^3), and phase duration (time intervals, s).

EMG data were visually inspected and bandpass filtered (20-450Hz). Then, two procedures were used: (1) For the RMS-amplitude, data were rectified and smoothed using a 50ms moving window. In ascent and descent phases, non-normalized RMS-amplitude was averaged for the initial and late-stage. (2) For muscle onset and offset detection, Teager–Kaiser energy operator was used [27]. The data were then rectified and low-pass filtered with a 50Hz cutoff frequency [27]. Relative to seat-off, activation onsets and offsets, and muscle activation duration (time between muscle onset and offset) were determined. We reduced the 10 muscles into five functional groups [6] and determined RMS-amplitude, muscle onset, and activation duration for: plantar flexors (GAS and SL), dorsiflexors (TA and PL), knee extensors (RF and VL), knee flexors (BF and ST), and hip stabilizers (TFL and Glu). Co-contraction index (CI) was computed for dorsiflexor vs. plantar flexors and knee extensors vs. knee flexors ((CI=2*Antagonist/(Agonist (primary action)+Antagonist))*100)[28].

2.7. Statistical analysis

In SPSS (IBM Corp.), we conducted Shapiro-Wilk tests to verify the normality of the outcomes. Outcomes that were not distributed normally were log-transformed. Group characteristics, and STS trials were compared using by T-test. We compared MVIF and RPE by a between-Age (younger, older adults) and within-Time (before, after rSTS) factors ANOVA. At initial-stage, jerk and phase duration were compared between-Age by T-test. To compare RMS-amplitude, we conducted ANOVA between-Age and within-Muscle (plantar flexors vs. dorsiflexors vs. knee flexors vs. knee extensors vs. hip stabilizers) and Phase (ascent vs. descent) factors. Muscle onset and activation duration were compared by ANOVA between-Age and within-Muscle factors. Regarding rSTS, accelerometer data were compared by ANOVA between-Age and within-Time (initial-stage=time 1 vs. late-stage=time 2) factors. CI was compared by ANOVAs between-Age and within-Phase and Time factors. We applied ANOVA (Age*Muscle*Phase) to compare the magnitude of change (Δ=time 2–time 1) of RMS-amplitude. ANOVA between-Age and within-Muscle was conducted to compare Δ of muscle onset and muscle activation. We set post-hoc and the level of significance ($p \leq 0.05$) was adjusted for multiple comparisons by Bonferroni correction. Cohen's d (d) was calculated and interpreted 0.21-0.50, 0.51-0.79, and >0.79 as small, medium and large effect sizes, respectively [29]. When main effects and/or interactions were observed, we reported the relative changes expressed as percentage, where younger, time 1 and ascent values were used as reference values for Age, Time, and Phase differences.

3. RESULTS

3.1. Participants and STS performance

The two age groups had similar characteristics (Table 1), but older vs. younger adults performed 467 fewer STS trials ($p<0.01$).

Table 1. Participants' characteristics and scores on questionnaires.

	Older	Younger	p-value
N (Male)	12 (7)	11 (6)	-
Age, range (yrs)	71 (66-77)	22 (20-25)	< 0.01
Height (cm)	173.1 ±2.2	177.5 ±2.8	0.17
Body mass (kg)	73.9 ±2.92	69.8 ±3.4	0.07
Body mass Index (kg/m^2)	24.7 ±1.07	22.1 ±0.6	0.04
SPPB (scores)	12.0 ±0.0	12 ±0	1
MFI (scores)	35.5 ±2.94	38.2 ±2.8	0.52
N. STS (rep)	134 ±29	601 ±53	< 0.01
STS duration (min)	4.5 ±1.13	20 ±1.7	< 0.01

Values are means and SEs. SPPB: Short Physical Performance Battery; MFI: Multidimensional fatigue inventory.

3.2. Force outcomes and RPE

ANOVA outcomes are detailed in Table 2.

Table 2. ANOVA main effects and interaction and partial eta-squared (η_p^2) for the outcomes.

Outcomes	ANOVA effects	F (1.21)	p	η_p^2
Force outcomes and RPE				
MVIF	Age main effect	8.58	< 0.01	0.29
	Time main effect	31.66	< 0.01	0.60
RPE (Borg)	Time main effect	424.27	< 0.01	0.95
Initial-stage				
RMS-amplitude	Muscle main effect	72.30	< 0.01	0.78
	Age*Phase*Muscle	4.34	< 0.01	0.17
Activation Onset	Muscle main effect	5.01	< 0.01	0.22
	Age*Muscle	2.41	0.05	0.11
Activation duration	Age main effect	16.07	0.01	0.43
	Muscle main effect	8.10	< 0.01	0.28
rSTS effects				
RMS-amplitude	Muscle main effect	6.57	< 0.01	0.24
Ascent Phase duration	Time main effect	9.95	< 0.01	0.36
CI – KF/KE Descent	Age main effect	10.08	< 0.01	0.34
CI – DF/PF Descent	Time main effect	12.69	< 0.01	0.28
CI – KF/KE Ascent	Time main effect	6.39	0.02	0.23

RPE: Rate of perceived exertion; MVIF: Maximum voluntary isometric force; CI: Co-contraction Index; KF: Knee flexors; KE: Knee extensors; DF: Dorsiflexors; PF: Plantar Flexors.

Older vs. younger adults had 35% lower MVIF (Age main effect, mean±SE: Older=388.47±48.45, Younger=595.61±50.6, d=1.19, Fig 1a). After rSTS, MVIF decreased (~16%) in both age groups (Time main effect, mean±SE: Time 1=533.7±38.15, Time 2=450.32±33.25, respectively, d=0.51, Fig 1a). RPE increased in both age groups combined (Time main effect; before rSTS=7.6±2.1 to after rSTS=18.7±1.7 score on Borg, d=5.8, Fig 1b).

4

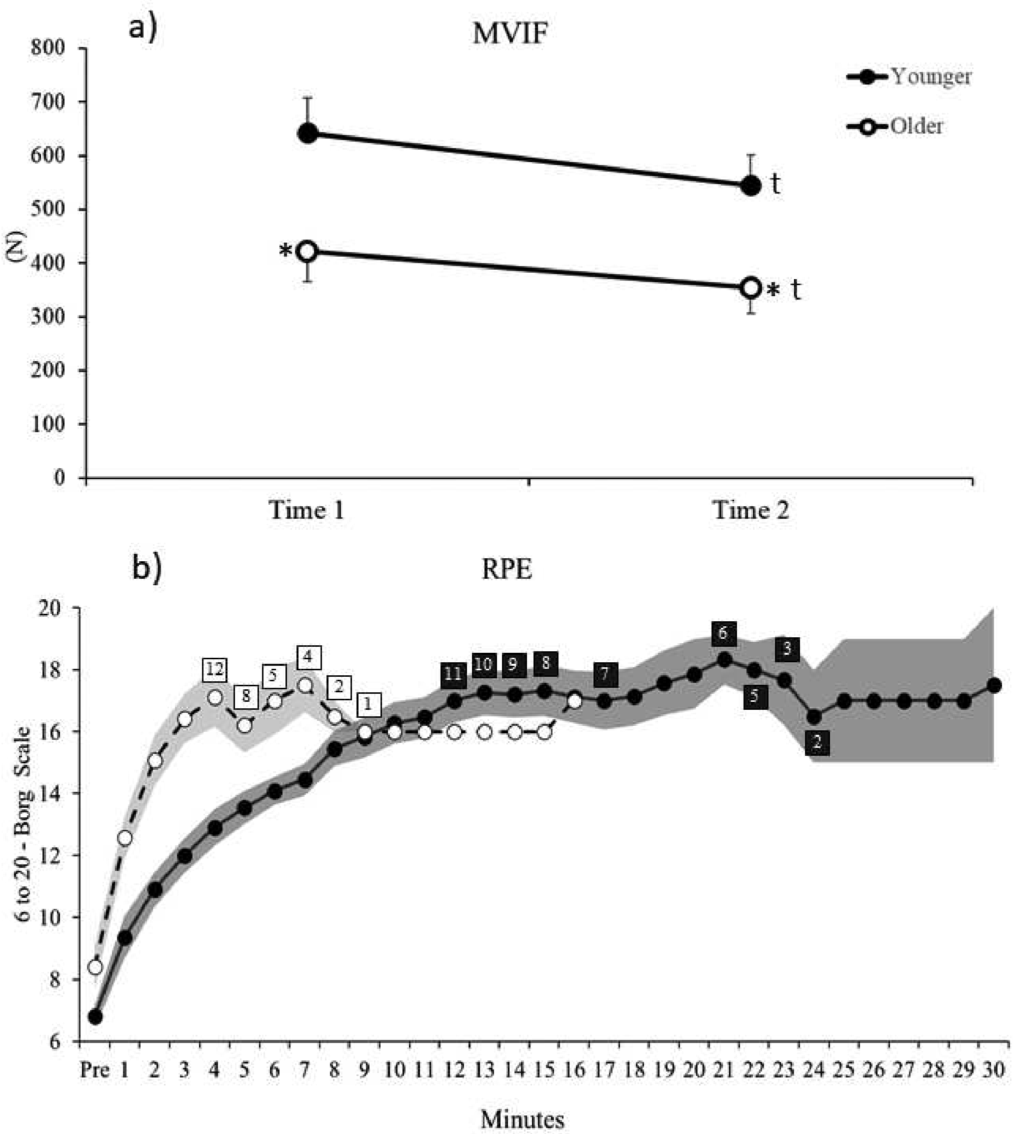


Figure 1. Mean and standard error of (a) Maximum voluntary isometric force (MVIF) at the beginning (Time 1) and end (Time 2) of rSTS. (b) Rate of perceived exertion (RPE) measured by 6 – 20 Borg scale during each minute of rSTS in younger (filled circles) and older adults (open circles). Numbers on open and filled rectangles indicate the amount of older and younger participants who continued performing rSTS at that time. *Age differences, ^{t}Time main effect.

3.3. Age-effects on muscle activation during STS in the initial-stage

Age did not affect jerk and phase duration during ascent and descent (p>0.05).

The Age*Muscle*Phase interaction for RMS-amplitude revealed that older vs. younger adults rose from the chair with ~60% greater dorsiflexor RMS-amplitude (d=1.16, p<0.01, Fig. 2). In ascent vs. descent, dorsiflexor RMS-amplitude was ~39% lower (d=0.53, Fig. 2), but knee extensor amplitude was ~41% higher (d=0.95, all p<0.01, Fig. 2) in older vs. younger adults. Younger vs. older adults had ~143% lower dorsiflexor RMS-amplitude in ascent (d=2.34, p<0.001, Fig. 2).

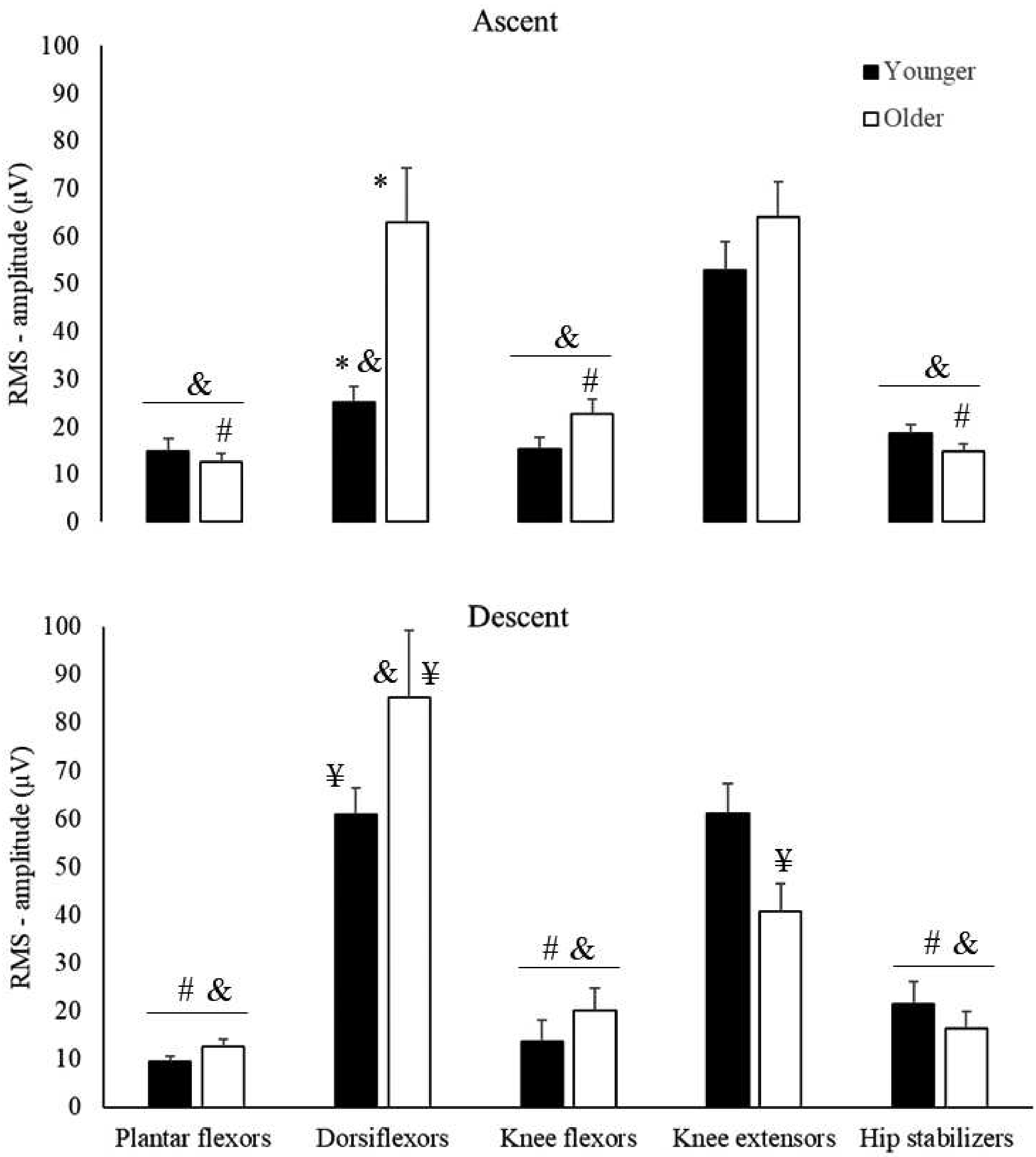


Figure 2. Means and Standard Errors for RMS-amplitude (Y-axis) for younger (filled columns) and older (open columns) adults by muscle groups (horizontal axis) and phases of the sit-to-stand task (Ascent, Descent). * Age differences; # muscles that are different from dorsiflexors; & muscles that are different from knee extensors; ¥ descent differs from ascent.

For muscle comparison, in ascent, older adults had 65-80% higher RMS-amplitude in the dorsiflexors, and knee extensors vs. plantar flexors, knee flexors, and hip stabilizers (d=1.22-2.64, all p<0.001). Younger adults' RMS-amplitude of knee extensors was 52-72% higher than dorsiflexors, plantar flexors, knee flexors and hip stabilizers (d=1.62-2.32, all p<0.01). In descent, both older and younger had 60-90% higher RMS-amplitude in the dorsiflexors and knee extensors than plantar flexors, knee flexors and hip stabilizers (d=1.38-3.11, all p<0.001).

Age*Muscle interaction for muscle activation onset (Fig. 3a) revealed that older vs. younger activated the hip stabilizers ~80% earlier (d=1.03; p<0.03). For muscle comparison, participants' muscle onsets of dorsiflexors, hip stabilizers, and knee extensors occurred earlier than plantar flexors (42-66%) and knee flexors (73-84%) (d=1.25-2.09, all p<0.01, Fig. 3a).

For muscle activation duration (Fig. 3b), older vs. younger adults had ~37% (d=1.02) longer muscle activation duration. Muscle main effect revealed ~32% longer activation in the dorsiflexors than the plantar flexors and hip stabilizers in both groups combined (d=1.12-1.16, all p>0.01, Fig. 3b).

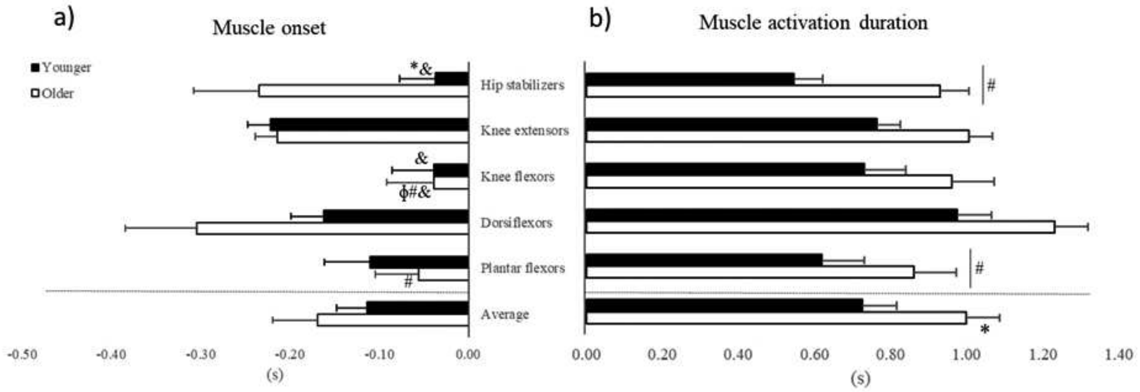


Figure 3. Mean and Standard Error for (a) muscle activation onset and (b) muscle activation duration in seconds (X-axis) relative to seat-off (Zero) for younger (filled bars) and older adults (open bars) in the initial-stage. * Age differences; # muscles that are different from dorsiflexors; & muscles that are different from knee extensors; Φ muscles that are different from hip stabilizers.

3.4. Effects rSTS on muscle activation

Ascent phase duration became ~20% longer at late-stage for both groups combined (Time main effect, d=0.72, supplementary table 1). Participants reduced dorsiflexor and knee extensor RMS-amplitude by 25% after rSTS (d=0.85-1.32, all p<0.02, Fig. 4a).

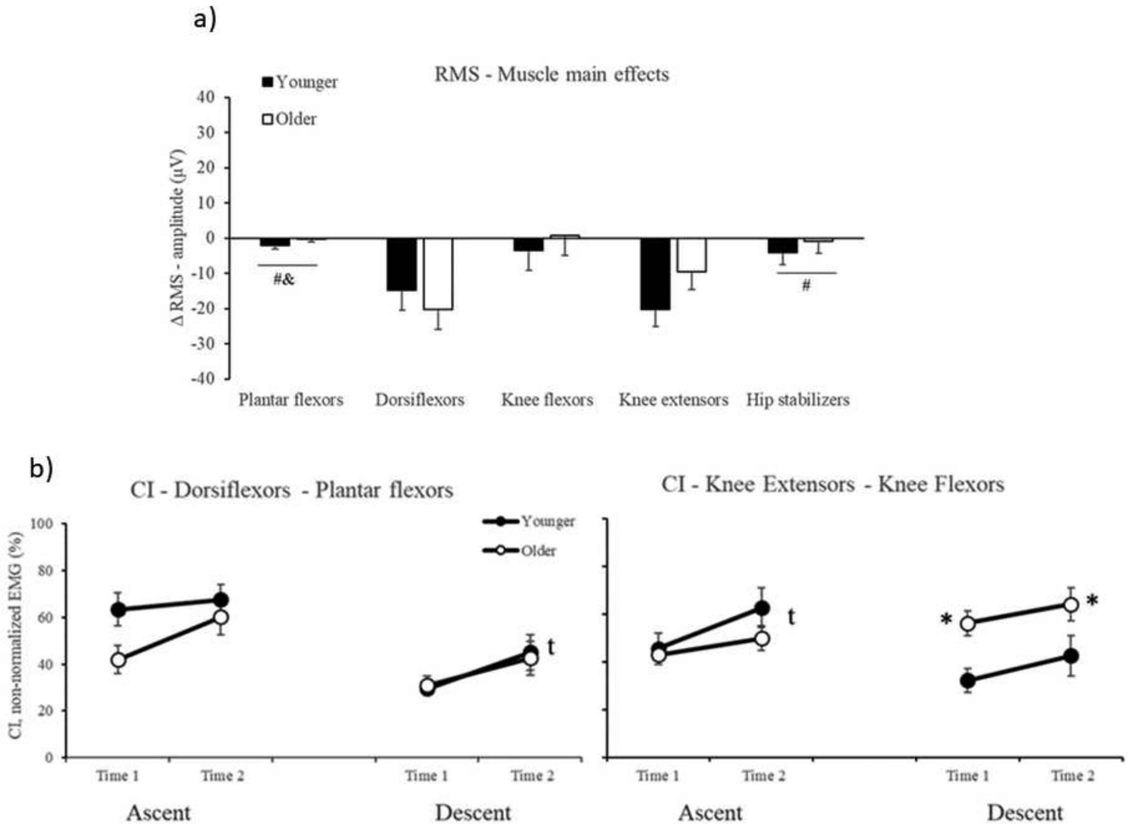


Figure 4. Mean and Standard Error for (a) muscle main effects for the delta score in RMS-amplitude (b) co-contraction index (CI) between dorsiflexors and plantar flexors, and between knee extensors and knee flexors in younger (filled symbols) and older (open symbols) adults. * Age differences, ^{t} Time main effect. # muscles that are different from dorsiflexors; & muscles that are different from knee extensors.

Knee extensor and flexor CI was ~40% higher in older vs. younger in descent (d=1.04, p>0.01). In ascent, knee extensor and flexor CI increased by 31% in both age groups (d=0.60, p=0.02). In descent, dorsiflexor and plantar flexor CI increased by ~45% after rSTS in the two groups combined (d=0.70, p>0.01, Fig. 4b).

No effects occurred for muscle activation onset and duration (all p>0.05).

4. DISCUSSION

In partial agreement with the hypothesis, older vs. younger had lower MVIF and activated dorsiflexors higher, all muscles longer, and hip stabilizer earlier before rSTS. Older vs. younger completed 467 fewer STSs, accompanied by a quicker increase in RPE. At the end of the rSTS, MVIF and dorsiflexor and knee extensor activation amplitude decreased similarly in both age groups. We interpret the data to mean that older adults, to perform remarkably fewer STS trials, had limited impact of rSTS in inducing failure in muscle activation, voluntary force, and motor function. Such a sparing effect may explain the minimal changes in gait after rSTS [18,19], suggesting a limited scope of this perturbation model to probe the age-effects on muscle adaptation in gait and posture.

4.1. Effects of age on muscle activation during STS before rSTS

During the first 5 STSs trials, activation of knee extensors and dorsiflexors was 70 to 80% higher than other muscle groups (Fig. 2), confirming that rising from a chair requires forceful contractions of lower extremity muscles [1]. As expected, older vs. younger adults rose from the chair with a higher, earlier, and longer muscle activation pattern. The age-specific 65-90% greater knee extensor activation preferentially helps older adults to accelerate the center of mass (CoM) upward [1,5,6]. Such strong activation of the knee extensors may be needed because MVIF was 35% lower in older than younger adults (Fig. 1) and the activation demand can be as high as 90% of the maximum during ascent [8]. These data are compatible with the idea that knee extensor function is a strong predictor of STS performance [4,5].

A new observation was that dorsiflexor activation amplitude was over two times higher in older vs. younger adults to rise from a chair, which may indicate a strategy to increase stability. The dorsiflexors control the center of pressure (CoP) under the limits of stability by keeping its position close to the CoM and stabilizing the ankle joint [1]. Age-specific strategy is also reflected by the 80% earlier onset of the hip stabilizers compared to plantar and knee flexors in older adults only (Fig. 3a). Because the phase duration of ascent was similar between groups, this early activation of hip stabilizers is indicative of a trunk strategy to let older adults keep up with the metronome. We interpret the age-specific 37% longer activation of the five muscle groups (Fig. 3) as an inability to relax muscles after force generation [11]. We conjecture that the increases in RMS-amplitude and duration are related to the dramatically fewer number of STS trials (Table 1) but correlation failed to confirm this (r range=0.01-0.4, p range=0.99-0.06).

While maximal eccentric compared with concentric voluntary force tends to decrease less with age [30], variability during eccentric force generation increases [13]. Indeed, we observed that older vs. younger had 40% lower EMG amplitude of the knee extensors and 30% greater activation of the dorsiflexors during descent vs. ascent (Fig. 2). This lower activation signifies altered inter-muscle coordination, as there was an age-specific 60% increase in CI (Fig. 4b). There is evidence suggesting an age-specific reduction in the ability to generate high levels of mechanical power for prolonged periods [12], agreeing with prolonged muscle activation results (Fig. 3b). Such changes in muscle activation are known to increase energy costs [10] and can partially explain the age-related higher fatigability (quicker increase in RPE and 4.5 less STS trials, Fig 1b) [31].

4.2. Effects of rSTS on muscle activation

A remarkable finding was that older vs. younger adults performed ~4.5 times fewer STS trials. Independent of age, the temporal structure of the STS changed so that ascent duration became 20% longer and the duration of the sitting portion decreased (Supplementary Table 1). In this manner, subjects were able to keep up with the tempo dictated by the beat of the metronome.

Contrary to the increase in EMG amplitude of the primer movers or compensatory shifts in activation reported previously [5,6], we observed a ~25% decrease in the dorsiflexor and knee extensor activation after rSTS (Fig. 4a). Reductions in EMG activity in submaximal fatiguing tasks might be the result of a decrease in number, and to a lesser extent, change in the shape of muscle fiber action potentials [32–34]. Because the MVIF also decreased by 16%, rSTS performance was probably limited by muscle fatigue and neural drive reductions. Such reductions possibly restricted older adults to perform 4.5 times fewer STS trials. The decrease in knee extensor and dorsiflexor RMS-amplitude explains the ~38% "apparent" increase in knee and ankle muscle coactivation. The inability to sustain the rSTS longer by older adults is likely due to the rapid increase in RPE (Fig. 1b), which represents a threshold for stopping, so then older adults' short performance resulted in minimized further loss in neuromuscular function.

Unlike the reductions after rapid rSTS in the present study, when rSTS was performed 2 times slower in a higher seat (80% of the lower leg lengths), EMG amplitude increased [5]. Therefore, the effects of rSTS on EMG amplitude may be velocity- and task-dependent. Faster repetitive contractions increase the mechanical demand on muscle [12], reducing muscle fiber action potential amplitude and increasing rate of muscle fatigability [33]. Faster contractions are particularly difficult for older adults due to a selective loss in type 2 muscle fibers, and prolonged relaxation time [12,30]. In contrast to our protocol, slower rSTS protocols [5] progressively increased RMS-amplitude first, followed by a decrease due to fatigability later [33]. A high seat decreases the mechanical load and muscle effort (i.e., ~25% less muscle knee extensors activation) and peak joint moments and angles (30% less at ankle and knee) [3].

The data point to the potential limitation of rSTS as a perturbation model to explore age-effects on gait adaptability. While participants were unable to continue the rSTS series, MVIF of the knee extensors declined only by 10% after 63 STS trials [19] and did not much further (16%) after 135 trials [18]. The small increase in force loss after twice as many STS trials implies that the knee extensors are spared from becoming dysfunctional. Such sparing effects may be one mechanism underlying the inexplicably trivial changes in gait biomechanics in obstacle crossing tasks after rSTS [19] and the nil changes in older adults' treadmill walking performance [18]. The substantially fewer STS trials by older vs. younger supports this interpretation because, with the pace fixed, reduction in trials was a key strategy for older adults that resulted in minimized demand of the rSTS in general and the load on the knee extensors in particular. Consequently, carry-over of fatigue induced by the rSTS to gait is minimized, so that walking performance remains unaffected notwithstanding the failure in the perturbation rSTS task just a few minutes earlier.

4.3. Limitations and conclusions

While the old group was unusually healthy (Table 1), the similarity between the two age groups also eliminated functional differences as confounders, allowing us to examine a "pure" age-effect. Second, it would have been necessary to concurrently measure metabolic cost with EMG recordings to see if age-differences in muscle activation in the initial and fatigued stage are functionally relevant. Although the lack of normalization would limit the comparison of our findings with the literature [5,6], which normalized the EMG signal for the sake of between-group comparisons, there is no consensus on this process [35]. Normalization process differed between protocols resulting in varied results [3,5,6,35], and this process does not necessarily affect the capability to resolve group differences [35]. Further studies should consider EMG activity of additional muscles combined with kinetic analyses, which would provide mechanistic insights into the nature of the perturbation created by rSTS. In conclusion, by performing remarkably fewer STS trials, older adults consequently had limited impact of rSTS in inducing failure in muscle activation, voluntary force, and motor function. Such a sparing effect may explain the minimal changes in gait after rSTS reported in previous studies, suggesting a limited scope of this perturbation model to probe the age-effects on muscle adaptation in gait and posture.

REFERENCES

[1] Jeon W, Jensen JL, Griffin L. Muscle activity and balance control during sit-to-stand across symmetric and asymmetric initial foot positions in healthy adults. Gait Posture 2019;71:138–44. doi:10.1016/j.gaitpost.2019.04.030.

[2] Netz Y, Ayalon M, Dunsky A, Alexander N. "The multiple-sit-to-stand" field test for older adults: What does it measure? Gerontology 2004;50:121–6. doi:10.1159/000076769.

[3] Hurley ST, Rutherford DJ, Hubley-Kozey C. The Effect of Age and Seat Height on Sit-to-Stand Transfer Biomechanics and Muscle Activation. Phys Occup Ther Geriatr 2016;34:169–85. doi:10.1080/02703181.2016.1267293.

[4] Mentiplay BF, Clark RA, Bower KJ, Williams G, Pua YH. Five times sit-to-stand following stroke: Relationship with strength and balance. Gait Posture 2020;78:35–9. doi:10.1016/j.gaitpost.2020.03.005.

[5] Bryanton M, Bilodeau M. The role of thigh muscular efforts in limiting sit-to-stand capacity in healthy young and older adults. Aging Clin Exp Res 2017;29:1211–9. doi:10.1007/s40520-016-0702-7.

[6] Bryanton MA, Bilodeau M. The influence of knee extensor fatigue on lower extremity muscle activity during chair rise in young and older adults. Eur J Appl Physiol 2019;119:61–71. doi:10.1007/s00421-018-3999-4.

[7] Roldán-Jiménez C, Bennett P, Cuesta-Vargas AI. Muscular Activity and Fatigue in Lower-Limb and Trunk Muscles during Different Sit-To-Stand Tests. PLoS One 2015;10:e0141675. doi:10.1371/journal.pone.0141675.

[8] Hortobágyi T, Mizelle C, Beam S, DeVita P. Old adults perform activities of daily living near their maximal capabilities. J Gerontol A Biol Sci Med Sci 2003;58:M453-60.

[9] Chandran VD, Calalo JA, Dixon PC, Dennerlein JT, Schiffman JM, Pal S. Knee muscle co-contractions are greater in old compared to young adults during walking and stair use. Gait Posture 2019;73:315–22. doi:10.1016/J.GAITPOST.2019.07.501.

[10] Hortobagyi T, Finch A, Solnik S, Rider P, DeVita P. Association Between Muscle Activation and Metabolic Cost of Walking in Young and Old Adults. Journals Gerontol Ser A Biol Sci Med Sci 2011;66A:541–7. doi:10.1093/gerona/glr008.

[11] Motawar B, Stinear JW, Lauer AW, Ramakrishnan V, Seo NJ. Delayed grip relaxation and altered modulation of intracortical inhibition with aging. Exp Brain Res 2016;234:985–95. doi:10.1007/s00221-015-4527-y.

[12] Petrella JK, Kim J, Tuggle SC, Hall SR, Bamman MM. Age differences in knee extension power, contractile velocity, and fatigability. J Appl Physiol 2005;98:211–20. doi:10.1152/japplphysiol.00294.2004.

[13] Hortobagyi T, Tunnel D, Moody J, Beam S, DeVita P. Low- or High-Intensity Strength Training Partially Restores Impaired Quadriceps Force Accuracy and Steadiness in Aged Adults. Journals Gerontol Ser A Biol Sci Med Sci 2001;56:B38–47. doi:10.1093/gerona/56.1.B38.

[14] Tracy BL, Enoka RM. Steadiness Training with Light Loads in the Knee Extensors of Elderly Adults. Med Sci Sport Exerc 2006;38:735–45. doi:10.1249/01.mss.0000194082.85358.c4.

[15] Sosnoff JJ, Newell KM. Age-Related Loss of Adaptability to Fast Time Scales in Motor Variability. Journals Gerontol Ser B Psychol Sci Soc Sci 2008;63:P344–52. doi:10.1093/geronb/63.6.P344.

[16] Liu J, Lockhart TE. Age-related joint moment characteristics during normal gait and successful reactive-recovery from unexpected slip perturbations. Gait Posture 2009;30:276–81. doi:10.1016/J.GAITPOST.2009.04.005.

[17] Vervoort D, den Otter AR, Buurke TJW, Vuillerme N, Hortobágyi T, Lamoth CJC. Effects of Aging and Task Prioritization on Split-Belt Gait Adaptation. Front Aging Neurosci 2019;11:10. doi:10.3389/fnagi.2019.00010.

[18] Santos PCR, Hortobágyi T, Zijdewind I, Bucken Gobbi LT, Barbieri FA, Lamoth C. Minimal effects of age and prolonged physical and mental exercise on healthy adults' gait. Gait Posture 2019;74:205–11. doi:10.1016/j.gaitpost.2019.09.017.

[19] Hatton AL, Menant JC, Lord SR, Lo JCM, Sturnieks DL. The effect of lower limb muscle fatigue on obstacle negotiation during walking in older adults. Gait Posture 2013;37:506–10. doi:10.1016/j.gaitpost.2012.09.004.

[20] Helbostad JL, Leirfall S, Moe-Nilssen R, Sletvold O. Physical Fatigue Affects Gait Characteristics in Older Persons. Journals Gerontol Ser A Biol Sci Med Sci 2007;62:1010–5. doi:10.1093/gerona/62.9.1010.

[21] Gross, Stevenson, Charette, Pyka, Marcus. Effect of muscle strength and movement speed on the biomechanics of rising from a chair in healthy elderly and young women. Gait Posture 1998;8:175–85.

[22] Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995;39:315–25.

[23] Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-Extremity Function in Persons over the Age of 70 Years as a Predictor of Subsequent Disability. N Engl J Med 1995;332:556–62. doi:10.1056/NEJM199503023320902.

[24] Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14:377–81.

[25] Hermens HJ, Freriks B, Disselhorst-Klug C, Rau G. Development of recommendations for SEMG sensors and sensor placement procedures. J Electromyogr Kinesiol 2000;10:361–74.

[26] Doheny EP, Walsh C, Foran T, Greene BR, Fan CW, Cunningham C, et al. Falls classification using tri-axial accelerometers during the five-times-sit-to-stand test. Gait Posture 2013;38:1021–5. doi:10.1016/J.GAITPOST.2013.05.013.

[27] Solnik S, Rider P, Steinweg K, DeVita P, Hortobágyi T. Teager-Kaiser energy operator signal conditioning improves EMG onset detection. Eur J Appl Physiol 2010;110:489–98. doi:10.1007/s00421-010-1521-8.

[28] Falconer K, Winter DA. Quantitative assessment of co-contraction at the ankle joint in walking. Electromyogr Clin Neurophysiol n.d.;25:135–49.

[29] Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd. Hillsdale (NJ): Lawrence Erlbaum Associates; 1988.

[30] Vandervoort AA. Aging of the human neuromuscular system. Muscle Nerve 2002;25:17–25. doi:10.1002/mus.1215.

[31] Stackhouse SK, Stevens JE, Lee SC, Pearce KM, Snyder-Mackler L, Binder-Macleod SA. Maximum voluntary activation in nonfatigued and fatigued muscle of young and elderly individuals. Phys Ther 2001;81:1102–9.

[32] Dideriksen JL, Enoka RM, Farina D. Neuromuscular adjustments that constrain submaximal EMG amplitude at task failure of sustained isometric contractions. J Appl Physiol 2011;111:485–94. doi:10.1152/japplphysiol.00186.2011.

[33] Dideriksen JL, Farina D, Enoka RM. Influence of fatigue on the simulated relation between the amplitude of the surface electromyogram and muscle force. Philos Trans R Soc A Math Phys Eng Sci 2010;368:2765–81. doi:10.1098/rsta.2010.0094.

[34] Wu R, Delahunt E, Ditroilo M, Ferri Marini C, De Vito G. Torque steadiness and neuromuscular responses following fatiguing concentric exercise of the knee extensor and flexor muscles in young and older individuals. Exp Gerontol 2019;124:110636. doi:10.1016/j.exger.2019.110636.

[35] Banks CL, Huang HJ, Little VL, Patten C. Electromyography Exposes Heterogeneity in Muscle Co-Contraction following Stroke. Front Neurol 2017;8:699. doi:10.3389/fneur.2017.00699.

Supplementary Table 1. Jerk and duration of sit-to-stand (STS) phases (ascent, stand, descent, sitting for younger and older adults considering time 1 (initial-stage) and time 2 (late-stage) of repetitive STS.

		Younger		Older	
		Time 1	Time 2	Time 1	Time 2
Jerk					
	Ascent	1.75 ±0.11	1.45 ±0.10	1.94 ±0.22	1.87 ±0.44
	Stand	0.05 ±0.06	0.03 ±0.05	-0.05 ±0.04	-0.03 ±0.04
	Descent	-1.44 ±0.10	-1.28 ±0.07	-1.43 ±0.15	-1.45 ±0.18
	Sitting	-0.18 ±0.09	-0.12 ±0.06	0.01 ±0.06	-0.05 ±0.04
Duration					
	Ascent	0.41 ±0.02	0.47 ±0.02[t]	0.37 ±0.04	0.49 ±0.06[t]
	Stand	0.48 ±0.06	0.49 ±0.05	0.58 ±0.05	0.66 ±0.06
	Descent	0.47 ±0.02	0.50 ±0.02	0.46 ±0.05	0.53 ±0.05
	Sitting	0.70 ±0.07	0.60 ±0.08	0.73 ±0.07	0.61 ±0.07

Values are means and SEs. [t] Time main effect.

4

5

Age-specific modulation of intermuscular beta coherence during gait before and after experimentally induced fatigue

P. C. Rocha dos Santos[1,2]
C. Lamoth[1]; F. A. Barbieri[3]
I. Zijdewind[4]
L.T.B. Gobbi[2]
T. Hortobágyi[1]

[1]Department of Human Movement Sciences, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands,
[2]Posture and Gait Studies Laboratory (LEPLO), Graduate Program in Movement Sciences, Institute of Biosciences, São Paulo State University (UNESP), Rio Claro, Brazil,
[3]Human Movement Research Laboratory (MOVI-LAB), Graduate Program in Movement Sciences, Department of Physical Education, São Paulo State University (UNESP), Bauru, Brazil.
[4]Department of Biomedical Sciences of Cells and Systems, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.

Submitted for publication

ABSTRACT

We examined the effects of age on intermuscular beta-band (15-35Hz) coherence during treadmill walking before and after muscle fatigability. Older (n=12) and younger (n=12) adults walked on a treadmill at 1.2m/s for 3min before and after fatigability (repetitive sit-to-stand, rSTS). We measured stride outcomes and coherence from 100 steps in the dominant leg for the synergistic (biceps femoris (BF) – semitendinosus, rectus femoris (RF) – vastus lateralis (VL), gastrocnemius lateralis (GL) – Soleus (SL), tibialis anterior (TA) – peroneus longus (PL)) and for the antagonistic (RF-BF and TA-GL) muscle pairs at late swing and early stance. Older vs. younger adults had 43-62% lower GL-SL, RF-VL coherence in swing and TA-PL and RF-VL coherence in stance. After rSTS, RF-BF coherence in late swing decreased by ~20% and TA-PL increased by 16% independent of age (p=0.02). Also, GL-SL coherence decreased by ~23% and increased by ~23% in younger and older, respectively. Age affects the common neural drive via corticospinal tracts to synergistic muscle pairs during treadmill walking and muscle fatigability elicits age-specific changes in the neural drive, which could be interpreted as compensation for fatigue to maintain gait performance.

Keywords: muscle fatigability; electromyography; treadmill walking; oscillatory synchronization

List of abbreviations: ANOVA, Analysis of variance; BF, Biceps femoris long head; CNS, central nervous system; d, Cohen's d; EMG, Electromyography; GL, Gastrocnemius Lateralis; MFI, Multidimensional fatigue inventory; MVIF, Maximum voluntary isometric force; PL, Peroneus Longus; RF, Rectus Femoris; RPE, Rate of perceived exertion; rSTS, Repetitive sit-to-stand; SENIAM, Surface Electromyography for the Non-Invasive Assessment of Muscle; SL, Soleus; SPPB, Short Physical Performance Battery; ST, Semitendinosus; STS, sit-to-stand; TA, Tibialis Anterior; VL, Vastus Lateralis; η_p^2, Partial Eta-Square.

1. INTRODUCTION

Healthy aging modifies the integrated and coordinated neural control of gait [1,2]. The age-related modifications in neuromuscular control are evidenced, among others, by the 40 to 50% increases in rectus (RF) - biceps femoris (BF) coactivation at heel strike during gait [3–5]. These alterations in neuromuscular control during gait are usually associated with age-related reductions in mechanical output at the ankle and increases in mechanical work generation at the hip joint [6]. Age-specific decreases in inhibitory cortical control are accompanied by decreases in Ia afferent input [7] that may lead to a depression of the inputs from muscle afferents compensated by an augmentation of coactivation antagonistic muscles during gait [3,4]. Such reductions in inhibitory/excitatory cortical control impair cortico-muscular communication by reducing the strengths of inputs via the corticospinal tract during muscle contraction [8], reflecting in muscular coherence during walking [1,9,10].

Intermuscular coherence is a correlational measure signifying the strength in the frequency domain between two signals recorded from two muscles, suggesting the oscillatory synchronization of action potentials discharged by motor units [1,11]. Motor unit synchronization implies common presynaptic inputs to the motor neuron pool of two or more muscles [12–14], as an attempt by the central nervous system (CNS) to reduce the dimensionality and complexity of control [15]. Data from neurological patients suggest that beta-band coherence in the range of 15-35 Hz emanates from cortical structures, including the sensorimotor cortex to control presynaptic inputs [12,16]. In older adults, there is diminished beta-band intramuscular coherence during swing phase, indicating a reduced common drive within the proximal and distal part of the tibialis anterior (TA) muscle [1], results consistent with data in hand muscles [17]. However, how healthy aging affects coherence among muscles crossing the ankle, knee and hip joints during such a functional task as gait has not yet been examined. Intermuscular coherence could provide information on age-related neuromuscular adaptation by inferring the oscillatory coupling of muscles spanning lower extremity joints.

Age-typical reductions in neuromuscular function are associated with an increase in effort to execute activities of daily living (41). The high effort-demand can increase susceptibility to muscle fatigability during gait [18]. Muscle fatigability, i.e., a decline in the capacity to generate voluntary force, affects motor control [19–22]. A consequence of exercise-induced fatigability is a decrease in the dimensionality of the control [23] by increasing common input to several muscles

[24–26], which would imply impaired motor coordination during complex tasks [27]. Indeed, exercise-induced fatigability is likely to be related to changes in the excitability along the neural axis, which might increase the coupling of oscillatory neural inputs [24,25]. Indeed, experimental data suggest 50 to 90% increase in beta-band cortico-muscular and muscular-muscular coherence during voluntary contraction [27–29] that may evolve as a neural compensatory strategy for the fatigue-induced decline in performance in healthy younger adults [22,25,27,28,30]. Because fatigue perturbs neuromuscular control, fatigability protocols have often been used to probe older adults' gait adaptability in response to this form of internal perturbations [31–35].

Repetitive Sit-to-Stand (rSTS) is a model to induce muscle fatigability in lower extremity muscles and probe gait adaptability [36]. Following bouts of rSTS, maximal voluntary force, the associated surface electromyography (EMG) activity, and median frequency of muscles involved in gait can decrease up to 18% [34,37]. However, previous studies found only weak evidence for age-related adaptations in stride metrics after fatigue [34]. The possibility exists that age-specific neural compensations to fatigue would minimize deterioration in stride metrics and preserve gait performance. In the present paper, we explore this hypothesis by further probing possible adaptive neural mechanisms through intermuscular coherence in the beta-band. Therefore, we determined the effects of age on beta-band coherence during treadmill walking before and after experimentally induced fatigability. Based on age-typical distal to proximal reductions in mechanical work generation during treadmill walking [6], we hypothesized that older compared with young adults would exhibit lower coherences in ankle muscles and higher coherences in muscles involved in hip flexion and extension. Concerning rSTS effects, we expected to find that muscle fatigability would strengthen coherence more in healthy younger compared with older adults in synergistic and antagonistic muscles around the ankle and knee joints during gait.

2. METHODS

2.1. Participants

Healthy younger (n=12, age range: 20-25y, 5F) and older (n=12, age range: 66-77y, 5F) participants completed the study. Inclusion criteria were: Age < 25 or >65y and either gender. Exclusion criteria were: Lower limb musculoskeletal injury or surgery that could affect walking ability; inability to walk unassisted on a treadmill; self-reported pain in the lower extremities, and neurological or cardiac diseases.

The procedures of this study were performed in accordance with the Declaration of Helsinki [38] and were approved by the Ethical Committee of the Center for Human Movement Sciences, University Medical Center Groningen (#ECB2017.06.12_1). All participants signed the informed consent document before testing.

2.2. Procedures

The cognitive status, physical fitness, and trait level of perceived fatigability were assessed by the Mini-Mental State Examination [39], Short Physical Performance Battery (SPPB) [40], and Multidimensional Fatigue Inventory (MFI) [41], respectively. Participants then walked on a treadmill for 3min, performed a knee extension to measure maximal voluntary isometric force (MVIF), executed the rSTS to induce muscle performance fatigability, performed an MVIF, and walked on the treadmill (Figure 1), described in detail previously [34].

2.2.1. Data acquisition

Participants, wearing a harness, walked on a treadmill instrumented with two force plates (Motek, Amsterdam, The Netherlands) for 3min before and after rSTS. They were asked not to hold onto the handrails and to look at a target (letter X) displayed on the wall in front of them 5m away. Walking speed was 1.2 m/s. We collected 3-D ground reaction forces and moments of force under each leg at 1 kHz using a D-Flow acquisition software (Motek, Amsterdam, The Netherlands).

To record EMG activity during walking, 8 wireless sensors (dimensions—37*26*15 mm, electrode material—silver; Trigno™ Wireless System, Delsys, Natick, MA, USA) were placed unilaterally on the following muscles: soleus (SL), gastrocnemius lateralis (GL), TA, peroneus longus (PL), vastus lateralis (VL), rectus femoris (RF), biceps femoris (BF), and semitendinosus (ST) according to SENIAM conventions [42]. EMG signals were sampled at 2 kHz. The areas where the sensors were placed, body hair was removed, and the skin was cleaned with alcohol. Treadmill and EMG data acquisition were electronically synchronized with a custom-built timer and event generator.

MVIF was assessed on a custom-built dynamometer. Participants, seated in a chair with the knee and hip in 90° of flexion, had the non-dominant lower leg strapped to the chairs' lever arm (~10cm up to lateral malleolus). We instructed participants to contract the quadriceps as rapidly and forcefully as possible and to maintain force generation for 5s. MVIF was determined as the peak of force.

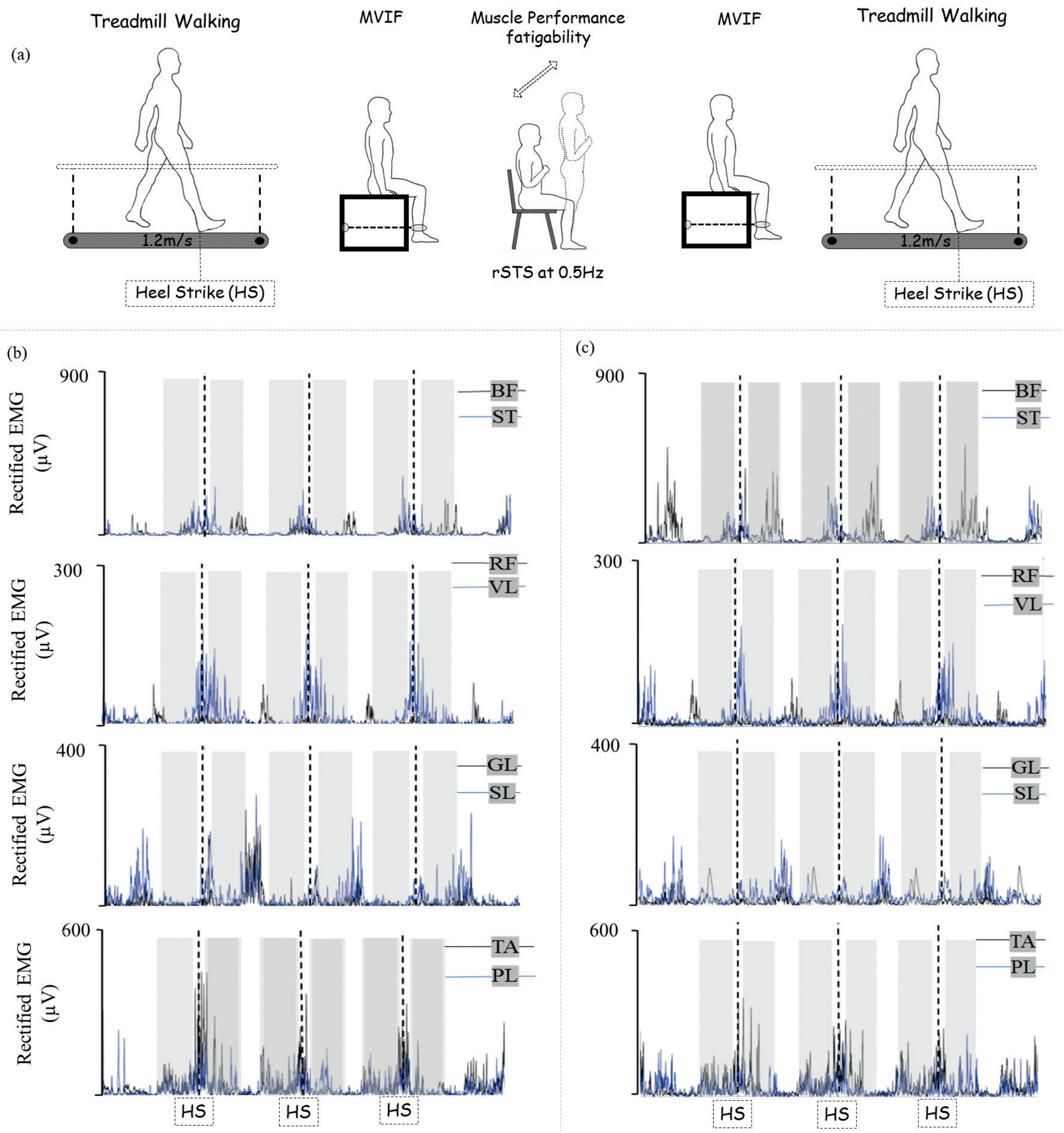


Figure 1. (a) Experimental setup and EMG data (data filtered 5 Hz using a high-pass second-order Butterworth filter, full-wave rectified using Hilbert transform data) of one younger subject before (b) and after (c) rSTS, considering 3 out of 100 heel strike (HS) events (dashed lines). Each plot on panel b and c consists of two muscles (represented in black and blue lines). Shaded areas illustrate the 350ms of analyses for late swing (-400 to -50ms before heel strikes) and early stance (50 to 400ms after heel strikes) phases. MVIF: Maximum voluntary isometric force; rSTS: repetitive sit-to-stand task; HS: Heel strike; BF: biceps femoris; ST: semitendinosus; RF: rectus femoris (RF); VL: vastus lateralis; GL: gastrocnemius lateralis; SL: soleus; TA: tibialis anterior, PL: peroneus longus (PL).

To induce muscle fatigability, participants performed the rSTS at 0.5 Hz in a standard dimension chair (0.43x0.41x0.42m). The protocol was stopped either when participants were unable to continue or after 30 minutes. Task duration and the number of repetitions were recorded. Before and after rSTS, we asked participants to rate their perceived exertion (RPE) on a 6 to 20 Borg Scale [43].

2.2.2. Data analysis

Data were analyzed using custom MATLAB routines (version r2018; The MathWorks Inc., Natick, MA). Ground reaction forces and moments of force were filtered with a 15-Hz low-pass second-order zero-phase Butterworth filter. Heel contact and toe-off were determined using a threshold of 50N vertical ground reaction force. Using heel strike and toe-off, we calculated stride length, step width, stance time, and swing time using the average of the middle 100 strides performed with the dominant leg during 3min of treadmill walking before and after rSTS.

EMG data were visually inspected to verify noise and artifacts. Then, the data were high-pass filtered at 5 Hz using a second-order Butterworth filter, full-wave rectified using Hilbert transform. Then, EMG data were downsampled to 1 kHz to obtain the same frequency of the force data plate.

2.2.2.1 Coherence calculation

We calculated the frequency-domain coupling between two EMG signals acquired during the treadmill walking before and after rSTS. For EMG coherence, we set two windows of 350ms for analysis [1]: late swing phase (from -400 to -50ms before the heel strike) and early stance phase (from 50 to 350ms after the heel strike) (Figure 1b and 1c). In both phases, we calculated coherence considering 4 synergistic muscle pairs: BF-ST, RF-VL, GL-SL, TA-PL, and 2 antagonistic muscle pairs: RF-BF; TA-GL.

To calculate intermuscular coherence, we first determine the auto-spectra of each muscle (f_{xx} and f_{yy}) and cross-spectrum (f_{xy}) of the muscle pairs (TA-PL, GL-SL, RF-VL, BF-ST, TA-GL, and RF-BF) using Welch's periodogram method [24,44]. Estimates were obtained using 350ms windows, nonoverlapping data segments, resulting in a frequency of resolution of 2.86Hz. Spectral estimates of individual strides were then averaged across the 100 strides (same used to calculate the stride outcomes) and used to calculate coherence. Intermuscular coherence was calculated by the squared modulus of cross-spectrum divided by the product of the two auto-spectra for each frequency (λ) [11]:

$$c(\lambda) = \frac{\left|f_{xy}(\lambda)\right|^2}{f_{xx}(\lambda) \cdot f_{yy}(\lambda)}$$

Where f_{xx} and f_{yy} are the auto-spectra of each muscle, and f_{xy} is the cross-spectrum of the muscle pairs (TA-PL, GL-SL, RF-VL, BF-ST, TA-GL, and RF-BF). Values of coherence range from 0 (absent) to 1 (completely correlated) [11] and in a frequency range of 0–55 Hz, normally choose to ensure that relevant frequency ranges for coherence are included, since coherences during walking are evident between 10-50 Hz [45,46]. However, in this study we focused only on beta-band frequency (15-35 Hz) that indicates a common drive originates from cortical structures [12,16]. For each subject, intermuscular coherence was significant when it exceeded the confidence limit for the number of segments (L) used to estimate the spectrum [11,47], as given:

$$1-(\alpha)^{\frac{1}{L-1}}$$

Where α=0.05 and L is the number of strides (N=100) used in the analysis.

For each subject and muscle pair, we ascertained from the cumulant density plots that high coherences were accompanied by near zero-lag synchronization suggesting that cross-talk did not affect coherences [16,48]. To compare coherence between age groups and time (before and after rSTS), intermuscular coherence of each subject was combined into pooled estimates for age groups for each walking phase before and after rSTS. Coherence estimates were Fisher transformed before pooling to stabilize variance [47,48]. The amount of coherence was calculated by the cumulative sum (area) on the range of the beta-band frequency domain (15–35 Hz), for those bins where the coherence were significant, for each age group, phase, and before and after rSTS.

2.2.3. Statistical analysis

Statistical analyses were performed in SPSS for Windows (Version 25, IBM Corp, Armonk, NY). We conducted Shapiro-Wilk tests to examine the normality of outcomes. Outcomes that were not distributed normally were log-transformed. T-tests were used to compare the effects of age on Groups' characteristics (age, height, body mass, SPPB, MFI), rSTS duration, and the number of STS repetitions, stride outcomes, and beta-band coherence before rSTS. To compare the effects of experimentally induced fatigability, we conducted a repeated-measures ANOVA with as between-Age (younger vs. older adults) and within-Time (time 1: before rSTS vs. time 2: after rSTS) factors for MVIF, strides outcomes and beta-band coherence. ANOVA effect size was estimated using partial eta squared (η_p^2) with η_p^2 <0.25, 0.26 to 0.63 and >0.64 as small, medium and large effects size [49]. If interactions were significant, post-hoc comparisons for each factor were made, and the level of significance was adjusted for multiple comparisons by using Bonferroni correction. For post-hoc and t-test comparisons, Cohen's d was calculated, and we interpreted 0.21 to 0.50, 0.51 to 0.79 and >0.79 as small, medium and large effect sizes (d), respectively [49]. To verify any possible association to age- and fatigue-effects on coherence, MVIF and its relationship with gait, as additional analysis, we computed correlations between the outcomes (beta-band coherence, MVIF, stride metrics). Before rSTS, a Spearman's correlation was computed between absolute values of the outcomes that indicated significant age differences ($p<0.05$). We also computed Spearman's correlations between absolute changes (delta, after - before rSTS) in the outcomes that revealed a significant Time effect. The level of significance was corrected by multiple correlations (p adjusted ≤0.006).

3. RESULTS

3.1. Participants characteristics and fatigability outcomes

Older and younger adults were not different in height, body mass, muscle mass, cognitive status, physical fitness, and trait level of perceived fatigability (Table 1).

Concerning muscle fatigability, older vs. younger performed ~4.3x fewer STS repetitions (T_{22}: 7.40, $p<0.01$) (Table 1), accompanied by an increase in RPE from ~8 to ~18 in the two groups ($F_{1.22}$: 346.24, $p<0.01$, η_p^2: 0.94, d: 1.90) (Table 2). There were Age and Time main effects for MVIF ($F_{1.22}$: 10.38 and 32.07, $p<0.01$ for all, η_p^2: 0.32 and 0.59) (Table 2). The Age main effect indicated that older compared to younger adults were weaker (~37% lower MVIF, d: 0.82). After rSTS, MVIF decreased in the two age groups by ~16% (d: 0.37).

Table 1. Participants' characteristics and scores on questionnaires.

	Younger	Older	p-value
Groups' characteristics			
n (Male)	12 (7)	12 (7)	
Age (range), y	22 (20 to 25)	71 (66 to 77)	<0.01
Height, cm	177.45 ±2.65	173.13 ±2.22	0.17
Body mass, kg	69.81 ±3.29	73.92 ±2.93	0.71
SPPB, scores	12 ±0.00	12 ±0.00	1.00
MFI, scores	38.18 ±2.71	34.58 ±2.83	0.52
STS			
Repetition	583.3 ±50.12	134.12 ±33.11	<0.01
Duration, min	19.48 ±1.71	4.47 ±1.15	<0.01

Values are mean ±SE. SPPB: Short Physical Performance Battery; MFI: Multidimensional fatigue inventory; STS: Sit-to-Stand.

3.2. Stride outcomes

Before rSTS, older vs. younger adults walked with 5% shorter strides ($T_{1.22=}$2.11, p=0.05, d: 0.86) (Table 2).

After rSTS, swing time decreased by 3% ($p<0.05$, d: 0.40) but rSTS did not affect any other stride metrics.

Table 2. Effects of age and rSTS on stride outcome.

	Time	Young Adults Mean ±SE	Older Adults Mean ±SE
Fatigability outcomes			
MVIF, N	Before rSTS	676.25 ±244.62	422.12 ±133.13*
	After rSTS	563.78 ±197.91 ^{t}	354.83 ±116.34*^{,t}
Borg, score	Before rSTS	6.75 ±1.22	8.42 ±2.43
	After rSTS	19.25 ±2.30^{t}	18 ±1.91^{t}
Stride outcomes			
Stride length, cm	Before rSTS	132.67 ±2.46	123.97 ±2.23*
	After rSTS	130.25 ±2.17	123.63 ±2.61
Width, cm	Before rSTS	10.19 ±1.30	10.3 ±0.89
	After rSTS	10.17 ±1.28	10.21 ±0.76
Swing time, s	Before rSTS	0.39 ±0.01	0.37 ±0.01
	After rSTS	0.38 ±0.01^{t}	0.37 ±0.01
Stance time, s	Before rSTS	0.72 ±0.04	0.67 ±0.04
	After rSTS	0.71 ±0.04	0.67 ±0.05

Values are mean ±SE. *Older ≠ Younger adults; ^{t}After ≠ Before rSTS.

3.1. Coherence

Supplementary Figures 1 and 2 detail the coherence data for all muscles and the two age groups before and after rSTS.

Before rSTS, older vs. younger adults had ~ 55% lower GL-SL beta-band coherence (t_{22}: 3.59, $p<0.01$, d: 2.08) in late swing and 62% and 48% lower TA-PL (t_{22}: 2.53, p=0.02, d: 4.44) and RF-VL coherence (t_{22}: 3.42, $p<0.01$, d: 0.36) in early stance (Figure 2).

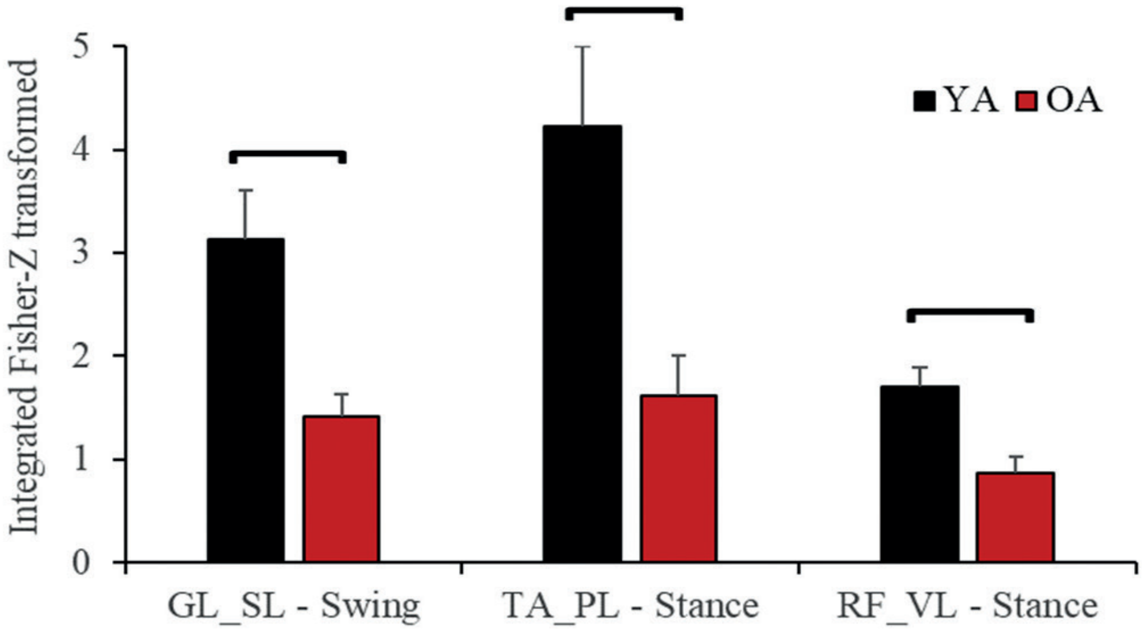


Figure 2. Mean and SE for the significant intermuscular coherence during walking before rSTS between Gastrocnemius lateralis (GL) - Soleus (SL) in swing phase and between Tibialis Anterior (TA) - Peroneus longus (PL) and Rectus Femoris (RF) and Vastus Lateralis in stance phase. YA: Younger adults. OA: Older adults.

After rSTS, in the two groups combined (Time main effect), RF-BF coherence decreased ($F_{1.22}$: 6.68, p=0.02, η_p^2: 0.23) in late swing and TA-PL coherence increased in early stance phases ($F_{1.22}$: 6.45, p=0.02; η_p^2: 0.23). RF-BF coherence decreased by 20% in swing phase (d: 0.35) (Figure 3a) and TA-PL coherence increased by 16% in stance phase (d: 0.21) (Figure 3a and 3b). After rSTS, older vs. younger had ~43 less RF-VL in stance ($F_{1.22}$: 7.63, p=0.01; η_p^2: 0.26; d: 0.86) (Figure 3c) and 44% less TA-PL coherences ($F_{1.22}$: 4.75, p=0.04; η_p^2: 0.18; d: 0.76) in stance phase.

There was a Group by Time effect for GL-SL coherence in swing phase ($F_{1.22}$: 5.03, p=0.04; η_p^2: 0.19) so that older vs. younger adults had 55% lower coherence at the baseline (p<0.01; d: 1.32), without group-difference after rSTS (p>0.05). This is because in younger adults, GL-SL coherence after rSTS decreased (23%) (p=0.03, d: 0.43), while older adults GL-SL coherence after rSTS increased (23%, n.s.) (Figure 3d).

Before rSTS, there were no correlations between beta-band coherence in GL-SL in late swing, TA-PL and RF-VL early stance with MVIF, and stride length (r=0.20 to 0.38; p>0.05) (Supplementary Figure 3). rSTS-induced decreases in GL-SL coherence during swing phase correlated with decreases in swing time (r=0.59, p=0.004) (Figure 4). Variables did not correlate with each other after rSTS (r=0.02 to 0.19, p>0.05) (Supplementary Figure 4).

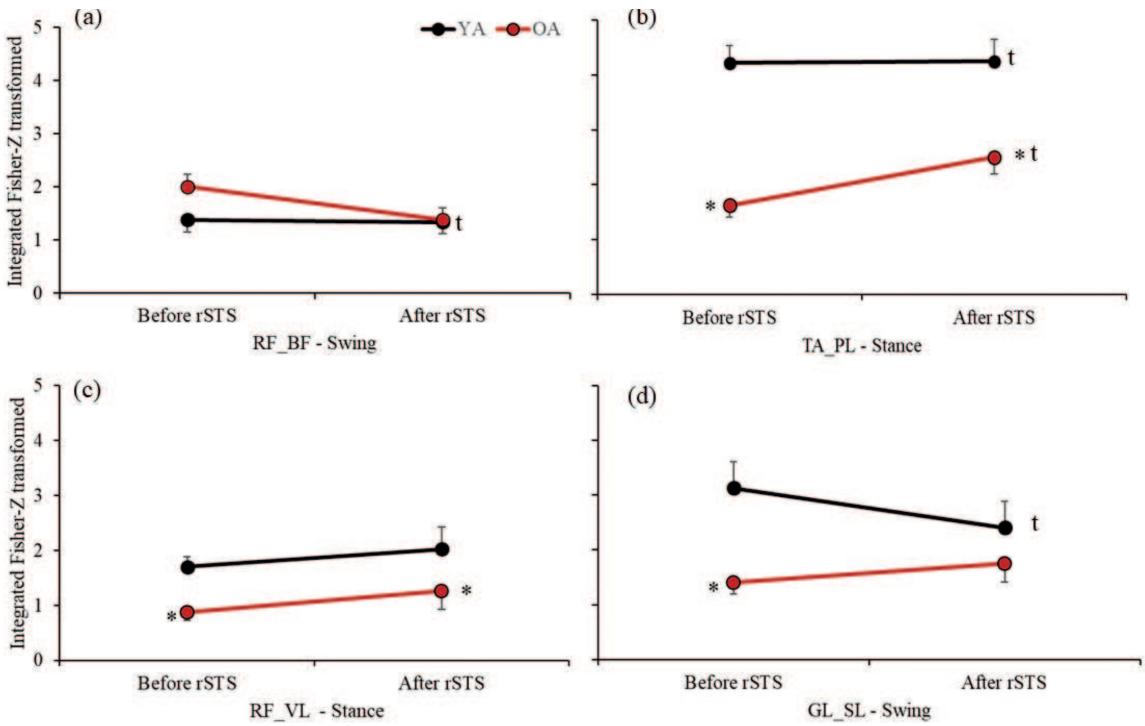


Figure 3. Mean ±SE for the significant intermuscular coherence between RF-BF in swing (a), TA-PL (b) and RF-VL (c) in stance phase, and GL-SL (d) in swing phase during treadmill walking and. *Older (OA) ≠ Younger adults (YA); [t] After repetitive sit-to-stand (rSTS) ≠ Before rSTS.

Figure 4. Significant correlations between absolute changes in GL-SL coherence in swing phase and swing time due to muscle fatigability.

4. DISCUSSION

We examined the effects of age on beta-band coherence during treadmill walking before and after experimentally induced fatigability. Our data confirmed the hypothesis of a lower beta-band coherence between specific ankle muscles during gait in older compared to younger adults. Against the hypothesis, we did not find the expected age-related increases in coherence among hip muscles. Also against the hypothesis, experimentally induced fatigability did not strengthen the beta-band coherence across synergistic and antagonistic muscle pairs around the ankle and knee joints during gait in an age-specific manner. We, however, observed that older adults developed a compensatory neural strategy by increasing the TA-PL and GL-SL beta-band coherence in response to experimentally induced fatigability. Together, age affects the common neural drive via corticospinal tracts to synergistic muscle pairs during treadmill walking and muscle fatigability elicits age-specific changes in the neural drive, which could be interpreted as compensation for fatigue to maintain gait performance.

Concerning the age-effects on beta-band coherence during treadmill walking, we found that beta-band coherence was 44 to 62% lower in TA-PL, GL-SL, and RF-VL in older vs. younger adults during gait before rSTS (Figure 2). The age-effects on intermuscular coherence agree with previous intramuscular coherence data indicating an age-typical reduction in coherence between proximal and distal TA [1,9]. However, our data extend those previous findings [1,9] by showing age-related reductions in coherence between synergistic ankle and knee muscle pairs. The age-related reductions in coherence between GL-SL, TA-PL, and RF-VL may be related to the age-typical decline/weakness of common presynaptic inputs to the motor neuron pool [17] that potentially result in a reduced oscillatory behavior between muscles activated during walking [1,10,50,51]. Indeed, brain data suggest enhanced inhibitory cortical control in old age that is associated with reduced oscillatory activation of motoneurons [52]. The inhibitory control may reflect the number and strength of neural commands from the cortex to the muscles, as confirmed by the reduced cortico-muscular coherence [1,50]. Because it is widely believed that intermuscular beta-band coherence may arise from shared inputs via branched corticospinal pathways [16,17,45,50], reduced beta-band coherence in older adults might be indicative of inefficiency in the CNS to reduce the dimensionality by sending common drives to muscles that exert similar functions [17]. The reductions in beta-band coherence, therefore, may reflect a decline in motor performance [53]. Indeed, the reduced beta-band coherence in the ankle and knee synergistic extensor muscles in older adults were accompanied by altered stride pattern, i.e., ~10cm shorter stride length (Table 2), although the correlation failed in showing any association.

Curiously, our results indicated age-differences only for synergistic (RF-VL, TA-PL, and GL-SL, Figure 2) but not for antagonistic muscle pairs coherence (RF-BF and TA-PL). Such findings only in synergistic and not in antagonistic muscle pairs are reasonable, considering synergistic/antagonistic muscle cooperation during the gait cycle. For example, the gastrocnemius and soleus act together to stabilize the ankle and to absorb the energy generated by the braking impulse at heel strike [54]. Reduced beta-band coherence in these muscles can imply event-related desynchronization during gait, indicating less muscle coordination to stabilize the ankle joint during the braking impulse [55].

The data also suggest a reduced common neural drive for TA and PL (62%) during early stance phase (Figure 2) and for RF and VL (48 and 43%) in both late swing and early stance phases in older compared with younger adults (Figure 2, 3b and 3c). These two muscle pairs work to decelerate the center of mass and stabilize the joints, keep the toe-clearance, and maintain the natural stance movement mechanics [54]. A lack of coherence for the antagonistic RF-BF and TA-GL muscle pairs before rSTS might suggest that independent neural commands are being delivered to each muscle. This idea is further supported by previous data showing lower intermuscular coherence in antagonistic vs. synergistic muscle pairs [46], and by studies that indicate that such antagonistic muscles activate in different moments of the gait cycle [54]. Although we observed age-related changes in beta-band coherence in synergistic muscles, there was an absence of accentuated antagonistic intermuscular beta-band coherence in healthy older adults, such as those observed in spinal cord injury population [16]. Possibly, the lack of antagonist beta-band coherence may be due to the relatively preserved condition of the corticospinal tract in healthy old vs. spinal cord injury population [16,56].

Our findings extend the current literature [1,9] to infer an age-related decline in the oscillatory coupling between muscles spanning lower extremity joints (ankle, knee and hip). The age-related decrease in common neural input occurred in synergistic lower extremity muscles. Curiously, such decreases seem not to be related to the age-typical reductions in mechanical output at the ankle and the increases in mechanical work generation at the hip joint [6]. Reduced RF-VL, TA-PL, and GL-SL beta-band coherence in older vs. younger adults indicated a general age reduction in the common neural drive via corticospinal tracks to synergistic muscle pairs during treadmill walking. Such age-specific reductions in beta-band coherence between synergistic muscle pairs before rSTS were further modulated in order to compensate for the muscle fatigability in older adults, thus keeping the stride metrics of gait performance unchanged (Table 2).

With regards to the fatigability effects on beta-band coherence, we expected that muscle fatigability would strengthen coherence around the ankle and knee joints during gait more so in healthy younger than in older adults. We, however, observed an age-specific modulation intermuscular coherence in ankle muscle pairs after muscle fatigability. Such a modulation suggests that older adults developed a compensatory strategy in response to the decline in motor performance induced by rSTS to maintain neural control of lower extremity muscles during gait, resulting in unchanged stride metrics of gait performance.

A common fatigue-related effect is an increase in intermuscular beta-band coherence due to a compensatory mechanism of CNS to increase the strength of the common neural drive to muscles to maintain the target force or performance [24,25,27]. Therefore, our result of a subtle increase in TA-PL beta-band coherence in stance phase is in line with the expected changes in coherence after rSTS. In contrast and unexpectedly, both age groups revealed a slight decrease in RF-BF (although it is only visible to older adults) intermuscular coherence in the stance phase. Additionally, the particular age adaptation in synergistic GL-SL intermuscular coherence in stance phase was also unforeseen.

Perhaps, the most intriguing result was the age-specific adaptation in intermuscular coherence in ankle muscle pairs after muscle fatigability. While there was 23% decrease in GL-SL common drive in younger adults, older adults showed 23% increase in this coherence after muscle fatigability (Figure 3d). In addition, the main effect indicated a 16% increase in TA-PL coherence in the two age groups after rSTS, driven by the 55 vs. 1% increase in older and younger adults (Figure 3b). Thus, there was a trend for age by time interaction in this important outcome (p=0.075; η_p^2: 0.14). One possible interpretation for age-differences in these intermuscular coherences is compensation for the decline in motor performance induced by rSTS. Age-specific increase in these coherences may reflect higher susceptibility to fatigability [18] and/or an age-related increase in demand of walking after muscle fatigability [5]. Indeed, while both age groups showed similar decreases in MVIF, older compared with younger adults performed remarkably fewer STS repetitions (Table 2).

Maximal voluntary contraction-induced fatiguability was associated with physiological tremor, which was interpreted as an increase in afferent feedback from muscle spindles to the motor units [29]. The increase in feedback presumably strengthens the correlated inputs to motor units as fatiguability progresses [29]. Our results partially support this finding because while we observed increases in beta-band coherence, the increase in alpha-band coherence was minimal, as were the correlations between these two coherences in older adults (data not shown). Concerning the higher walking demand, previous data showed that the metabolic cost of gait was ~20% higher, which was related to 67% higher agonist muscle activation and 153% greater antagonist coactivation during walking [5]. Together, the higher muscle fatigability effects and higher walking demand in older compared with younger adults seem to have elicited compensatory neural adaptations to muscle fatigability, making it possible for older adults to continue to walk.

The small decreases in intermuscular coherence between antagonist muscle pairs (RF-BF) were somewhat unexpected. Normally such coherences tend to increase rather than decrease after muscle fatigability. The increases are attributed to enhanced cortical excitability to compensate for muscle fatigability [24,30], normally associated with higher coactivation. Although high cortical excitability due to muscle fatigability is a physiological explanation for both increases in muscle amplitude and coherence [24,30], we recognize that increases in intermuscular coherence do not necessarily mean an increase in coactivation. In addition, both increased coactivation and antagonistic intermuscular coherence could impair muscle coordination and motor performance [4,25].

The changes in beta-band coherence after experimentally induced fatigability were not accompanied by any meaningful changes in stride outcomes during treadmill walking (Table 2). Our results indicating only small changes in swing time (0.01s) for young adults reiterate the minimal effects of age and fatigability on strides outcomes observed previously [34]. Possibly, those changes in beta-band coherence may represent a compensatory neural strategy in response to experimentally induced fatigability to maintain the strides metrics unchanged.

As limitations, albeit intermuscular coherence during gait has recently received attention, the interpretation of such data is not straightforward. It is because relating individual variation in intermuscular coherence to variation in gait behavior due to age or perturbations, as done here, has been moderately successful at best [1,9]. Furthermore, the influence of EMG rectification on coherence has been discussed [55,57,58]. We adopted an use EMG rectification procedure because it amplifies temporal information about motor unit action potentials during submaximal tasks, as gait [55,57–59], and helps with the interpretation of the results with the literature [1,10,45,46,50,55,60]. The Fourier transformation (a standard protocol used in coherence analyses [1,10,45,55]) is valid for stationary signals, a condition unlikely to be met in gait. To address this limitation, we analyzed coherence in short time windows during swing and stance phases of gait. Similarity of temporal features of gait before and after fatigability in younger and older adults further decreased the likelihood of non-stationarity in the signal (Table 2).

The current study contributes to the understanding of how healthy aging brings about adaptations to muscle activation during gait and how such adaptations might turn into compensations to help maintain gait performance on the treadmill. In conclusion, age affects the common neural drive via corticospinal tracts to synergistic muscle pairs during treadmill walking and muscle fatigability elicits age-specific changes in the neural drive, which could be interpreted as compensation for fatigue to maintain gait performance.

REFERENCES

[1] Spedden ME, Choi JT, Nielsen JB, Geertsen SS. Corticospinal control of normal and visually guided gait in healthy older and younger adults. Neurobiol Aging 2019;78:29–41. doi:10.1016/j.neurobiolaging.2019.02.005.

[2] Stuart S, Alcock L, Rochester L, Vitorio R, Pantall A. Monitoring multiple cortical regions during walking in young and older adults: Dual-task response and comparison challenges. Int J Psychophysiol 2019;135:63–72. doi:10.1016/j.ijpsycho.2018.11.006.

[3] Lee H-J, Chang WH, Choi B-O, Ryu G-H, Kim Y-H. Age-related differences in muscle co-activation during locomotion and their relationship with gait speed: a pilot study. BMC Geriatr 2017;17:44. doi:10.1186/s12877-017-0417-4.

[4] Hortobágyi T, Devita P. Mechanisms responsible for the age-associated increase in coactivation of antagonist muscles. Exerc Sport Sci Rev 2006;34:29–35.

[5] Hortobagyi T, Finch A, Solnik S, Rider P, DeVita P. Association Between Muscle Activation and Metabolic Cost of Walking in Young and Old Adults. Journals Gerontol Ser A Biol Sci Med Sci 2011;66A:541–7. doi:10.1093/gerona/glr008.

[6] Waanders JB, Hortobágyi T, Murgia A, DeVita P, Franz JR. Advanced Age Redistributes Positive but Not Negative Leg Joint Work during Walking. Med Sci Sport Exerc 2019;51:615–23. doi:10.1249/MSS.0000000000001828.

[7] Papegaaij S, Taube W, Baudry S, Otten E, Hortobágyi T. Aging causes a reorganization of cortical and spinal control of posture. Front Aging Neurosci 2014;6:28. doi:10.3389/fnagi.2014.00028.

[8] Matsuya R, Ushiyama J, Ushiba J. Inhibitory interneuron circuits at cortical and spinal levels are associated with individual differences in corticomuscular coherence during isometric voluntary contraction. Sci Rep 2017;7:1–11. doi:10.1038/srep44417.

[9] Gennaro F, Bruin ED. A pilot study assessing reliability and age-related differences in corticomuscular and intramuscular coherence in ankle dorsiflexors during walking. Physiol Rep 2020;8. doi:10.14814/phy2.14378.

[10] Roeder L, Boonstra TW, Kerr GK. Corticomuscular control of walking in older people and people with Parkinson's disease. Sci Rep 2020;10:2980. doi:10.1038/s41598-020-59810-w.

[11] Halliday DM, Rosenberg JR, Amjad AM, Breeze P, Conway BA, Farmer SF. A framework for the analysis of mixed time series/point process data-Theory and application to the study of physiological tremor, single motor unit discharges and electromyograms. Prog Biophys Mol Biol 1995. doi:10.1016/S0079-6107(96)00009-0.

[12] Grosse P, Cassidy MJ, Brown P. EEG-EMG, MEG-EMG and EMG-EMG frequency analysis: physiological principles and clinical applications. Clin Neurophysiol 2002;113:1523–31. doi:10.1016/s1388-2457(02)00223-7.

[13] De Luca CJ, Erim Z. Common Drive in Motor Units of a Synergistic Muscle Pair. J Neurophysiol 2002;87:2200–4. doi:10.1152/jn.00793.2001.

[14] Semmler JG, Kornatz KW, Enoka RM. Motor-unit coherence during isometric contractions is greater in a hand muscle of older adults. J Neurophysiol 2003;90:1346–9. doi:10.1152/jn.00941.2002.

[15] Del Vecchio A, Germer CM, Elias LA, Fu Q, Fine J, Santello M, et al. The human central nervous system transmits common synaptic inputs to distinct motor neuron pools during non-synergistic digit actions. J Physiol 2019;597:5935–48. doi:10.1113/JP278623.

[16] Norton JA, Gorassini MA. Changes in Cortically Related Intermuscular Coherence Accompanying Improvements in Locomotor Skills in Incomplete Spinal Cord Injury. J Neurophysiol 2006;95:2580–9. doi:10.1152/jn.01289.2005.

[17] Semmler JG, Kornatz KW, Meyer FG, Enoka RM. Diminished task-related adjustments of common inputs to hand muscle motor neurons in older adults. Exp Brain Res 2006;172:507–18. doi:10.1007/s00221-006-0367-0.

[18] Petrella JK, Kim J, Tuggle SC, Hall SR, Bamman MM. Age differences in knee extension power, contractile velocity, and fatigability. J Appl Physiol 2005;98:211–20. doi:10.1152/japplphysiol.00294.2004.

[19] Enoka RM, Duchateau J. Translating Fatigue to Human Performance. Med Sci Sport Exerc 2016;48:2228–38. doi:10.1249/MSS.0000000000000929.

[20] Gandevia SC. Spinal and supraspinal factors in human muscle fatigue. Physiol Rev 2001;81:1725–89. doi:10.1152/physrev.2001.81.4.1725.

[21] Taylor JL, Butler JE, Gandevia SC. Changes in muscle afferents, motoneurons and motor drive during muscle fatigue. Eur J Appl Physiol 2000;83:106–15. doi:10.1007/s004210000269.

[22] Fry A, Mullinger KJ, O'Neill GC, Brookes MJ, Folland JP. The effect of physical fatigue on oscillatory dynamics of the sensorimotor cortex. Acta Physiol (Oxf) 2017;220:370–81. doi:10.1111/apha.12843.

[23] Monjo F, Terrier R, Forestier N. Muscle fatigue as an investigative tool in motor control: A review with new insights on internal models and posture-movement coordination. Hum Mov Sci 2015;44:225–33. doi:10.1016/j.humov.2015.09.006.

[24] Boonstra TW, Daffertshofer A, van Ditshuizen JC, van den Heuvel MRC, Hofman C, Willigenburg NW, et al. Fatigue-related changes in motor-unit synchronization of quadriceps muscles within and across legs. J Electromyogr Kinesiol 2008;18:717–31. doi:10.1016/j.jelekin.2007.03.005.

[25] Semmler JG, Ebert SA, Amarasena J. Eccentric muscle damage increases intermuscular coherence during a fatiguing isometric contraction. Acta Physiol 2013;208:362–75. doi:10.1111/apha.12111.

[26] Wang L, Lu A, Zhang S, Niu W, Zheng F, Gong M. Fatigue-related electromyographic coherence and phase synchronization analysis between antagonistic elbow muscles. Exp Brain Res 2014;233:971–82. doi:10.1007/s00221-014-4172-x.

[27] Danna-Dos Santos A, Poston B, Jesunathadas M, Bobich LR, Hamm TM, Santello M. Influence of fatigue on hand muscle coordination and EMG-EMG coherence during three-digit grasping. J Neurophysiol 2010;104:3576–87. doi:10.1152/jn.00583.2010.

[28] Ushiyama J, Katsu M, Masakado Y, Kimura A, Liu M, Ushiba J. Muscle fatigue-induced enhancement of corticomuscular coherence following sustained submaximal isometric contraction of the tibialis anterior muscle. J Appl Physiol 2011;110:1233–40. doi:10.1152/japplphysiol.01194.2010.

[29] McManus L, Hu X, Rymer WZ, Suresh NL, Lowery MM. Muscle fatigue increases beta-band coherence between the firing times of simultaneously active motor units in the first dorsal interosseous muscle. J Neurophysiol 2016;115:2830–9. doi:10.1152/jn.00097.2016.

[30] Boonstra TW. Cortical adaptations during muscle fatigue: the role of sensorimotor oscillations. Acta Physiol 2017;220:307–9. doi:10.1111/apha.12879.

[31] Hatton AL, Menant JC, Lord SR, Lo JCM, Sturnieks DL. The effect of lower limb muscle fatigue on obstacle negotiation during walking in older adults. Gait Posture 2013;37:506–10. doi:10.1016/j.gaitpost.2012.09.004.

[32] Helbostad JL, Leirfall S, Moe-Nilssen R, Sletvold O. Physical Fatigue Affects Gait Characteristics in Older Persons. Journals Gerontol Ser A Biol Sci Med Sci 2007;62:1010–5. doi:10.1093/gerona/62.9.1010.

[33] Barbieri FA, dos Santos PCR, Simieli L, Orcioli-Silva D, Van Dieën JH, Gobbi LTB. Interactions of age and leg muscle fatigue on unobstructed walking and obstacle crossing. Gait Posture 2014;39:985–90. doi:10.1016/J.GAITPOST.2013.12.021.

[34] Santos PCR, Hortobágyi T, Zijdewind I, Bucken Gobbi LT, Barbieri FA, Lamoth C. Minimal effects of age and prolonged physical and mental exercise on healthy adults' gait. Gait Posture 2019;74:205–11. doi:10.1016/j.gaitpost.2019.09.017.

[35] Morrison S, Colberg SR, Parson HK, Neumann S, Handel R, Vinik EJ, et al. Walking-Induced Fatigue Leads to Increased Falls Risk in Older Adults. J Am Med Dir Assoc 2016;17:402–9. doi:10.1016/j.jamda.2015.12.013.

[36] Santos PCR, Barbieri FA, Zijdewind I, Gobbi LTB, Lamoth C, Hortobágyi T. Effects of experimentally induced fatigue on healthy older adults' gait: A systematic review. PLoS One 2019;14:e0226939. doi:10.1371/journal.pone.0226939.

[37] Roldán-Jiménez C, Bennett P, Cuesta-Vargas AI. Muscular Activity and Fatigue in Lower-Limb and Trunk Muscles during Different Sit-To-Stand Tests. PLoS One 2015;10:e0141675. doi:10.1371/journal.pone.0141675.

[38] World Medical Association Declaration of Helsinki. JAMA 2013;310:2191. doi:10.1001/jama.2013.281053.

[39] Tombaugh TN, McIntyre NJ. The Mini-Mental State Examination: A Comprehensive Review. J Am Geriatr Soc 1992;40:922–35. doi:10.1111/j.1532-5415.1992.tb01992.x.

[40] Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-Extremity Function in Persons over the Age of 70 Years as a Predictor of Subsequent Disability. N Engl J Med 1995;332:556–62. doi:10.1056/NEJM199503023320902.

[41] Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995;39:315–25.

[42] Hermens HJ, Freriks B, Disselhorst-Klug C, Rau G. Development of recommendations for SEMG sensors and sensor placement procedures. J Electromyogr Kinesiol 2000;10:361–74.

[43] Borg DN, Costello JT, Bach AJ, Stewart IB. Perceived exertion is as effective as the perceptual strain index in predicting physiological strain when wearing personal protective clothing. Physiol Behav 2017;169:216–23. doi:10.1016/j.physbeh.2016.12.009.

[44] Nandi T, Hortobágyi T, van Keeken HG, Salem GJ, Lamoth CJC. Standing task difficulty related increase in agonist-agonist and agonist-antagonist common inputs are driven by corticospinal and subcortical inputs respectively. Sci Rep 2019;9:1–12. doi:10.1038/s41598-019-39197-z.

[45] Jensen P, Frisk R, Spedden ME, Geertsen SS, Bouyer LJ, Halliday DM, et al. Using Corticomuscular and Intermuscular Coherence to Assess Cortical Contribution to Ankle Plantar Flexor Activity During Gait. J Mot Behav 2019;51:668–80. doi:10.1080/00222895.2018.1563762.

[46] Halliday DM, Conway BA, Christensen LOD, Hansen NL, Petersen NP, Nielsen JB. Functional Coupling of Motor Units Is Modulated During Walking in Human Subjects. J Neurophysiol 2003;89:960–8. doi:10.1152/jn.00844.2002.

[47] Amjad AM, Halliday DM, Rosenberg JR, Conway BA. An extended difference of coherence test for comparing and combining several independent coherence estimates: Theory and application to the study of motor units and physiological tremor. J Neurosci Methods 1997;73:69–79. doi:10.1016/S0165-0270(96)02214-5.

[48] Halliday DM, Rosenberg JR. On the application, estimation and interpretation of coherence and pooled coherence. J Neurosci Methods 2000;100:173–4. doi:10.1016/S0165-0270(00)00267-3.

[49] Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd. Hillsdale (NJ): Lawrence Erlbaum Associates; 1988.

[50] Spedden ME, Nielsen JB, Geertsen SS. Oscillatory Corticospinal Activity during Static Contraction of Ankle Muscles Is Reduced in Healthy Old versus Young Adults. Neural Plast 2018;2018. doi:10.1155/2018/3432649.

[51] Yoshida T, Masani K, Zabjek K, Chen R, Popovic MR. Dynamic cortical participation during bilateral, cyclical ankle movements: Effects of aging. Sci Rep 2017;7:1–11. doi:10.1038/srep44658.

[52] Nielsen JB, Tijssen MAJ, Hansen NL, Crone C, Petersen NT, Brown P, et al. Corticospinal transmission to leg motoneurones in human subjects with deficient glycinergic inhibition. J Physiol 2002;544:631–40. doi:10.1113/jphysiol.22.024091.

[53] Bayram MB, Siemionow V, Yue GH. Weakening of Corticomuscular Signal Coupling During Voluntary Motor Action in Aging. J Gerontol A Biol Sci Med Sci 2015;70:1037–43. doi:10.1093/gerona/glv014.

[54] Ivanenko YP, Poppele RE, Lacquaniti F. Five basic muscle activation patterns account for muscle activity during human locomotion. J Physiol 2004;556:267–82. doi:10.1113/jphysiol.2003.057174.

[55] Roeder L, Boonstra TW, Smith SS, Kerr GK. Dynamics of corticospinal motor control during overground and treadmill walking in humans. J Neurophysiol 2018;120:1017–31. doi:10.1152/jn.00613.2017.

[56] Nielsen JB, Brittain JS, Halliday DM, Marchand-Pauvert V, Mazevet D, Conway BA. Reduction of common motoneuronal drive on the affected side during walking in hemiplegic stroke patients. Clin Neurophysiol 2008. doi:10.1016/j.clinph.2008.07.283.

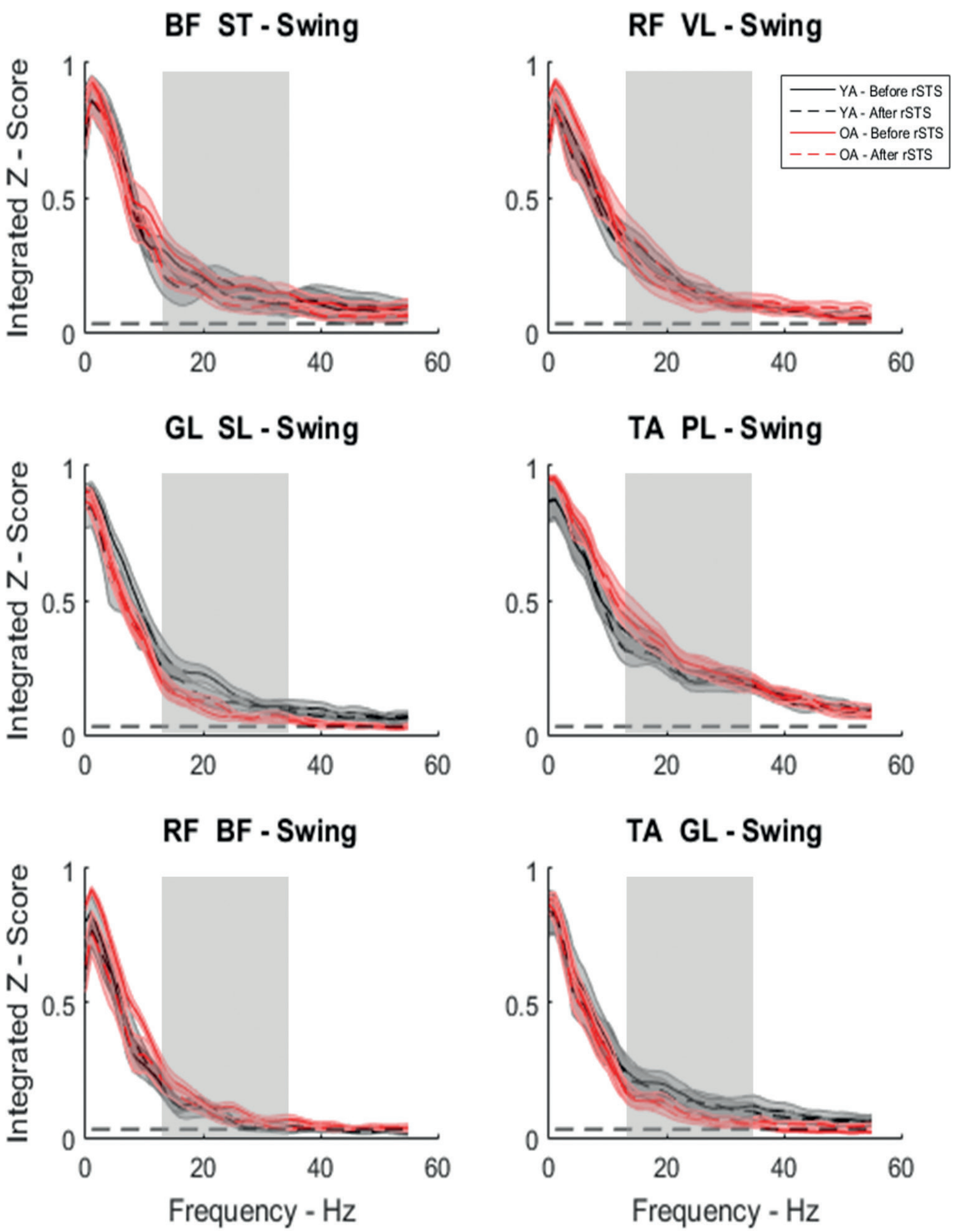
[57] Ward NJ, Farmer SF, Berthouze L, Halliday DM. Rectification of EMG in low force contractions improves detection of motor unit coherence in the beta-frequency band. J Neurophysiol 2013;110:1744–50. doi:10.1152/jn.00296.2013.

[58] Halliday DM, Farmer SF. On the Need for Rectification of Surface EMG. J Neurophysiol 2010;103:3547–3547. doi:10.1152/jn.00222.2010.

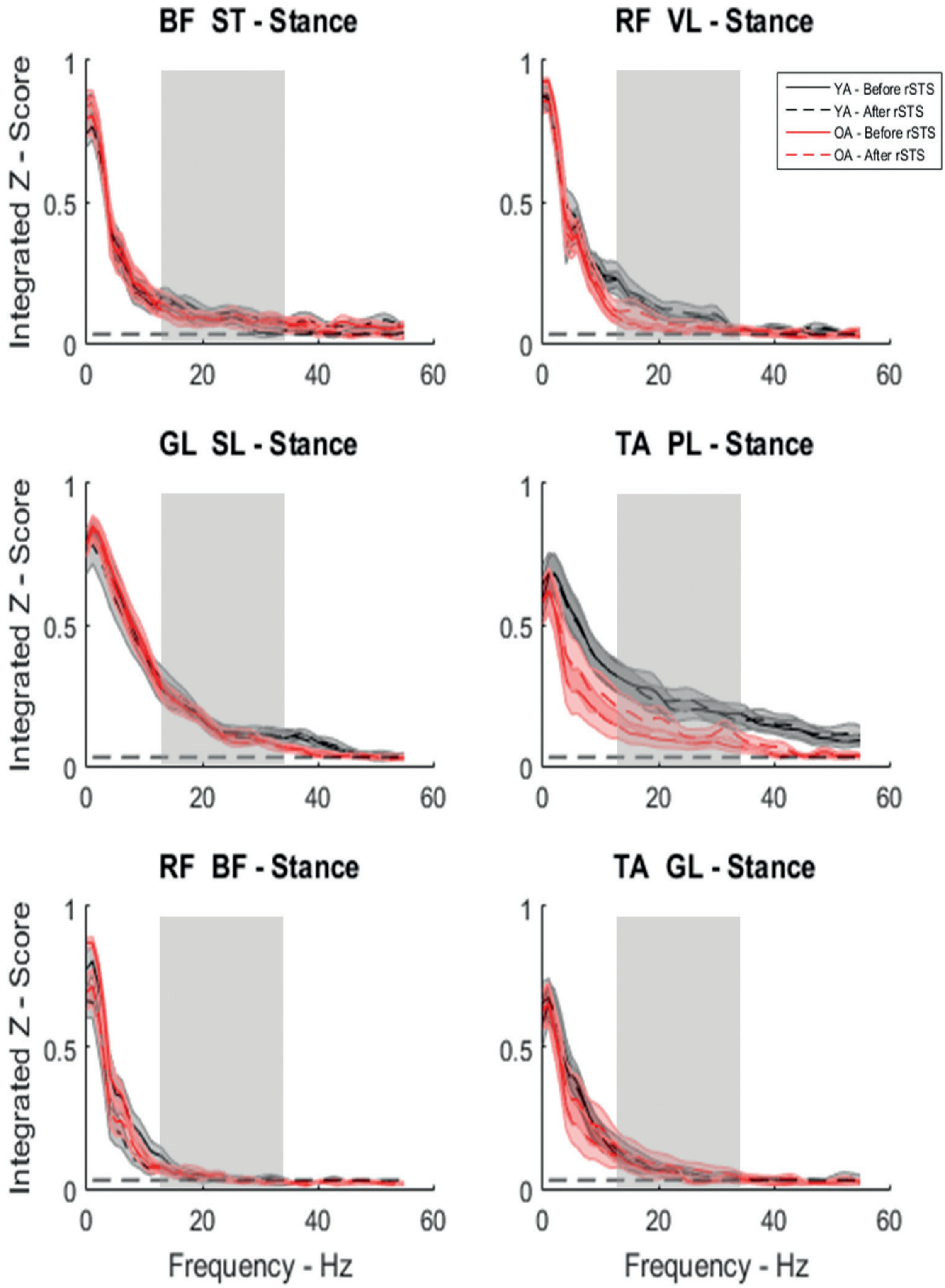
[59] Boonstra TW, Breakspear M. Neural mechanisms of intermuscular coherence: implications for the rectification of surface electromyography. J Neurophysiol 2012;107:796–807. doi:10.1152/jn.00066.2011.

[60] Jensen P, Jensen NJ, Terkildsen CU, Choi JT, Nielsen JB, Geertsen SS. Increased central common drive to ankle plantar flexor and dorsiflexor muscles during visually guided gait. Physiol Rep 2018;6:e13598. doi:10.14814/phy2.13598.

SUPPLEMENTARY MATERIALS

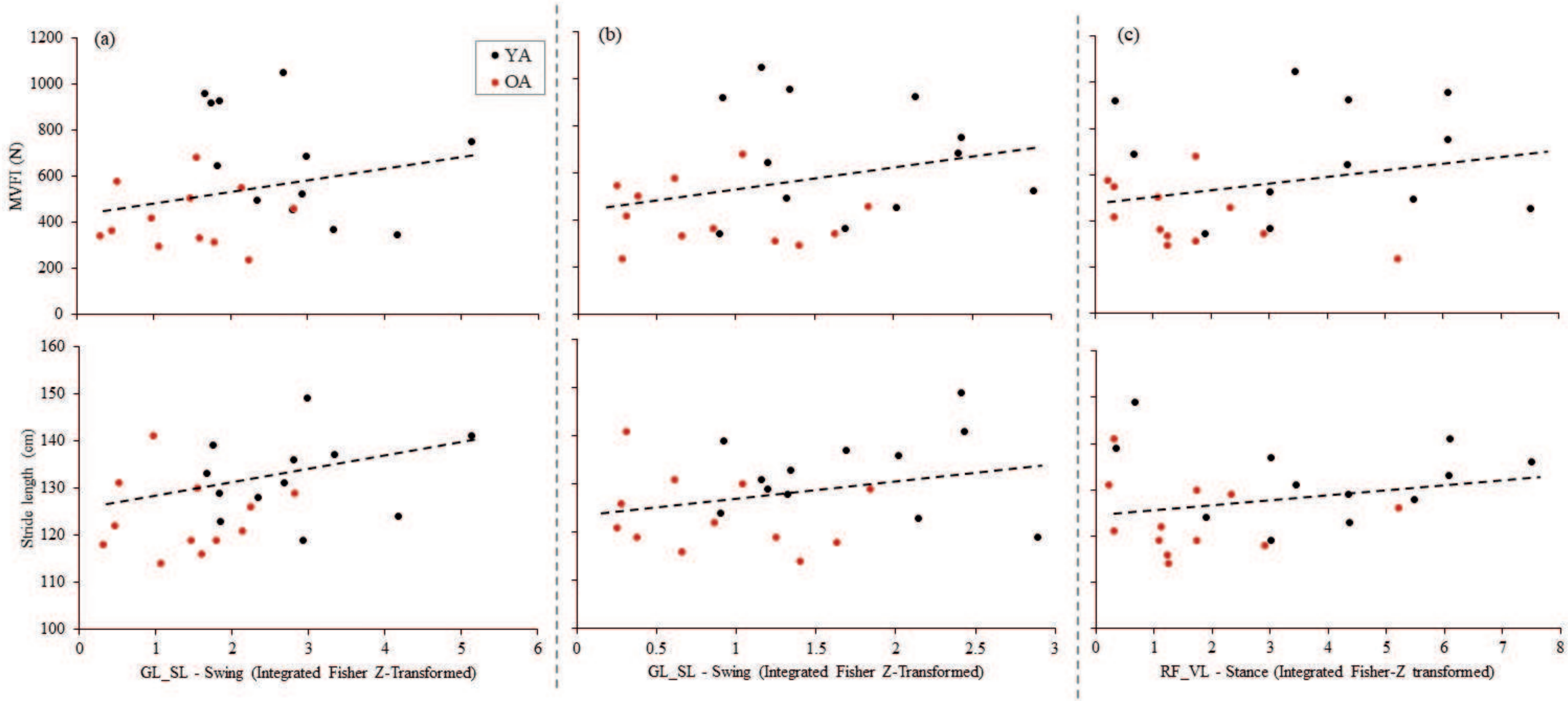


Supplementary Fig 1. Means (lines) and standard errors (shaded areas) of intermuscular coherence for all muscle pairs during 100 swing phase events. Younger adults (YA) = black; Older adults (OA) = red; Before = continuous lines; after rSTS = dashed lines. Shaded rectangle = beta-band frequency (15 to 35hz).

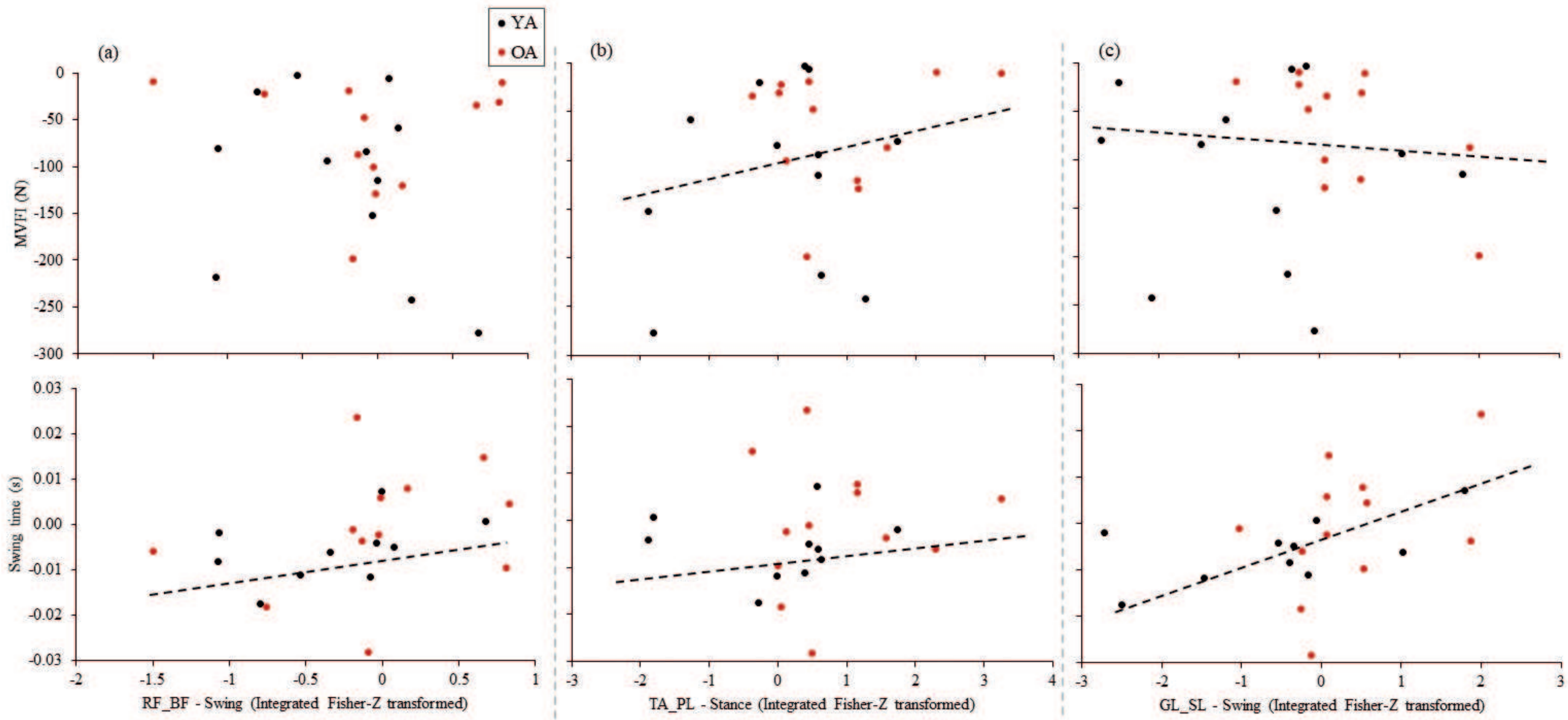


Supplementary Fig 2. Means (lines) and standard errors (shaded areas) of intermuscular coherence for all muscle pairs during 100 stance phase events. Younger adults (YA) = black; Older adults (OA) = red; Before = continuous lines; after rSTS = dashed lines. Shaded rectangle = beta-band frequency (15 to 35hz).

5



Supplementary Figure 3. Distributions plots of the association between beta-band coherence in GL-RF in swing (a), and TA-PL (b) and RF-VL (c) in stance with maximum voluntary isometric force (MVIF), and stride length, outcomes that indicated age differences before rSTS.



Supplementary Figure 4. Distributions plots of the association between absolute changes (after – before rSTS) in beta-band coherence in RF-BF in swing (a), TA-PL in stance (b), and RF-VL (c) in swing with maximum voluntary isometric force (MVIF) and swing time.

6

General Discussion

This thesis examined the effects of age on gait adaptability following experimentally induced fatigue. Figure 1 illustrates the experimental design and summarizes the main findings by chapter. In chapter 2, the systematic review revealed that although fatigability affects spatial and temporal features of gait according to the type of fatigue, the underlying mechanism of muscle and mental fatigability remains unclear. In chapter 3, we found that muscle and mental fatigability minimally affected healthy young and older adults' gait, possibly because treadmill walking made gait uniform. We interpret the data to mean that: 1) mental fatigability might elicit effects whenever walking is coupled with higher cognitive involvement (e.g., dual-task walking); 2) age-dependent neuromuscular modulation might compensate for the fatigability effects to maintain gait performance; and/or 3) the repetitive sit-to-stand task might not specifically induce substantial changes in key elements of gait, thereby limiting the scope of this protocol to examine age-related gait adaptations to fatigue. In chapter 4, we examined the effects of age and exhaustive repetitive sit-to-stand on muscle activation during ascent and descent phases of the sit-to-stand task. We found that by performing remarkably fewer sit-to-stand trials, older adults had minimized fatigability effects on muscle activation, voluntary force, and motor function, producing minimal changes in stride outcomes and gait dynamics after repetitive sit-to-stand seen in Chapter 3. However, Chapter 5 shows that notwithstanding the subtle modifications in muscle activation and voluntary force, repetitive sit-to-stand produced an age-specific compensatory strategy in the neural drive to maintain gait performance.

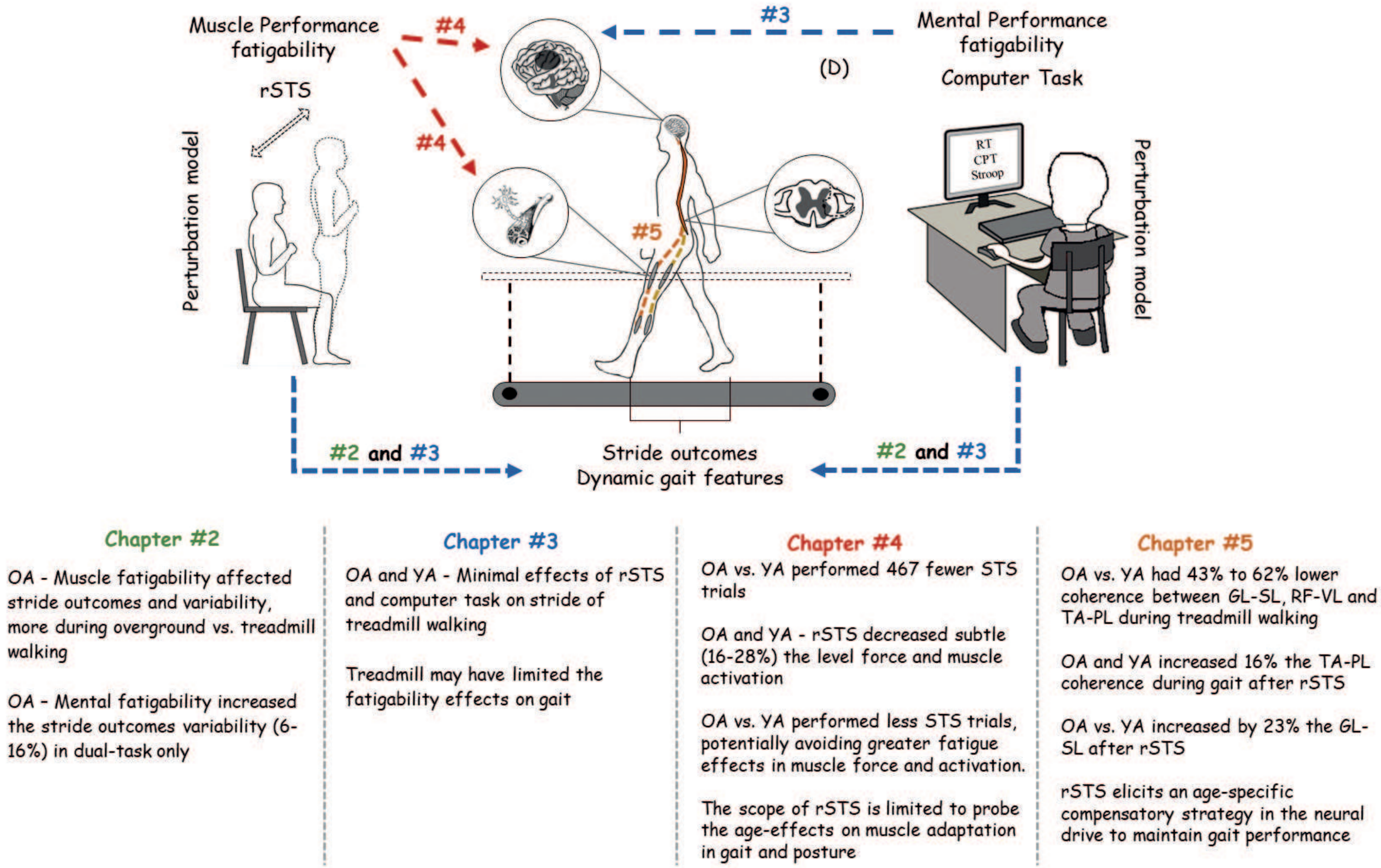


Figure 1. Schematic representation of the experimental set-up with a summary of the main finding in each chapter. OA=Older adults; YA = Younger adults; STS=Sit-to-stand; rSTS= repetitive STS; TA=Tibialis anterior; PL=Peroneus longus; GL=Gastrocnemius lateralis; SL=Soleus; RF=Rectus femoris; VL=Vastus lateralis

1. FATIGUE AND AGE EFFECTS ON STRIDE OUTCOMES AND DYNAMIC FEATURES OF GAIT

After experimentally induced fatiguability, the most often observed changes occurred in stride outcomes and gait dynamics (Chapter 2, Table 2 [1–7]), both becoming more pronounced for induced fatigue-type specificity (specific vs. non-specific gait fatigability protocols) and for gait assessment (overground vs. treadmill walking) (Chapter 2, [1,3,4]).

From the perspective of fatigue-type specificity, although fatigability evokes adaptations in spatial and temporal stride outcomes and dynamics gait features, those adaptations were moderate or even subtle depending on how specific the fatigability protocol and the gait conditions were [1]. Local specific muscle fatigability evokes only small adjustments of stride outcomes during treadmill walking (e.g., 2cm (2%) of decreased stride length (Chapter 3 [8])) and overground walking (e.g., 4 to 5 cm (3-5%) of increased stride length [6,7]), even in a protocol that targeted a decrease of 50% in the relative maximum knee torque [7]. Such small results indicated that non-specific gait fatigability, such as repetitive sit-to-stand and dynamometer exercise, might not be optimal to perturb the gait necessitating substantial adaptations.

Presumably, non-specific gait fatigability protocols do not target specific key elements of gait, such as those pertaining to rhythm/temporal activation control (central pattern generators) and the magnitude of muscle activation driven by cortical inputs [9]. Thus, gait would not be perturbed because the key elements of gait control can operate within a normal range. This hypothesis is partially supported by the literature that indicates substantial changes in stride outcomes after fatigability induced by specific gait protocol (e.g.,18% increase in stride velocity after fatiguability induced by incremental walking task) [5]. On the other hand, despite some substantial gait adaption to specific gait fatigability protocols [2], the gait adaptability to fatigability remains inconclusive in healthy older adults [10,11]. For example, long-distance walking for 30 min increased asymmetry on ankle and knee angular velocity variabilities, but inexplicably, those increases were mitigated after 60 min of treadmill walking [11].

Concerning mental performance fatigability, interference with cognitive resources due to fatigability indicated to be a useful model to perturb gait in dual-task overground walking [1,12]. This concept is indeed supported by previous evidence that suggested that mental-fatigability affected gait variability (e.g., increase by 4 to 16% in coefficients of variations in stride metrics) during dual- but not single-task in older adults' overground walking [12]. Therefore, age-related adaptability to mental performance fatigability is likely apparent only during walking conditions with high cognitive involvement. Such apparent effects of mental fatigue on gait performance during dual-task walking in older adults might be evident because, when gait control is perturbed, older adults prioritize gait adaptation at the expense of cognitive performance [13].

Fatigability effects on gait appear to be influenced by conditions in which gait is assessed. More overt effect of experimentally induced fatigability was observed during gait protocol in overground vs. treadmill walking situation. Presumably, the invariant pattern imposed by the treadmill [14,15] minimizes any potential age-related adaptation to experimentally induced fatigability. In contrast, walking situations that simulate real-life walking (e.g., overground walking), or even more complex condition (e.g., combine fatigue with external walking perturbation, obstacle avoidance, stair gait) require more active gait control and may represent higher susceptibility to the fatigability effects compared to treadmill walking [14,16].

While numerous studies focused on age-associated adaptability in stride outcomes in response to performance and perceived fatigability (Chapter 2, [1–3,5,7,17–20]), the underlying neural mechanism of gait adaptability due to fatigability remain mostly unanswered. Curiously, these studies indirectly attributed changes in stride outcomes to the effects of induced fatigability on neuromuscular control [2,3,5,7,17–20], but failed in analyzing it. Specifically considering the present data, we suggest that age-dependent modulations in the common neural drive (intermuscular coherence) might have compensated for the muscle performance fatigability effects on gait. Thus, the participants could keep the stride metrics of gait performance unchanged after repetitive sit-to-stand.

In chapter 5, we examined if age-dependent modulation in neuromuscular control may be mediating the fatigability effects on gait metrics. The first new observation was that age-related reduction (45 to 68%) in beta-band coherence extended the previous findings [21–23] to be present not only in ankle dorsiflexor (Tibialis anterior and Peroneus longus) but also in gastrocnemius lateralis-Soleus and Rectus femoris-Vastus Lateralis muscle pairs. Reduced beta-band coherence, indicative of corticomuscular communication, in older adults might be indicative of inefficiency in the central nervous system to reduce the dimensionality by sending common drives to muscles that exert similar functions [24]. This assumption is plausible because it is widely assumed that intermuscular beta-band coherence may happen from pooled inputs via branched corticospinal tracts [24–27]. This inefficiency in the central nervous system in reducing the dimensionally motor control would impair the synchronization of muscle units firing [28], affecting motor coordination. It explains the poor gait performance in older adults (Chapter 3 and Chapter 5) and would signalize higher energy cost to control coordinated movement, as gait [29]. Age-specific modulation in coherence before repetitive sit-to-stand point to the necessity of further compensatory neural modulation due to fatigability, mainly in the old group.

Indeed, our data indicated an age-specific modulation in neuromuscular control during gait after fatigability (Chapter 5). Such age-modulation was mostly observed by a specific increase (~23 to 49 %) in Gastrocnemius Lateralis-Soleus coherence in swing and Tibialis Anterior-Peroneus Longus in stance phases in older adults. While in younger, a decrease in Gastrocnemius Lateralis-Soleus coherence (~23%) and only a slight increase in the Tibialis Anterior-Peroneus Longus (1%) was witnessed. This modulation suggests that older adults evoked compensatory neural strategy to compensate muscle fatigability, indicated by a strengthening in common neural inputs via branched corticospinal tracts. Strengthened coherence is described as a compensatory attempt of the central nervous system in reducing the dimensionality of the motor system to send shared drives to two close synergistic muscles during gait [9,30]. Presumably, age-specific neuromuscular gait modulation due to muscle fatigability might occur because of age-specific neuromuscular deterioration. Such neuromuscular deterioration contributes to age-related changes in mechanical output during gait [31], causing older adults to evoke a compensatory neural strategy due to muscle fatigability to keep the stride metrics of treadmill walking unchanged (Chapter 3 and Chapter 5).

2. FATIGUE AS A MODEL TO UNDERSTAND AGE-RELATED GAIT ADAPTABILITY

Experimentally induced fatigability as a perturbation model has been extensively used to examine age-related adaptability in functional tasks (e.g., postural and gait [12,32,33]). Those studies explained alterations in behavioral outcomes of a subsequent gait and posture through the physiologic and psychological effects of the perturbation model. However, these protocols failed in measuring the perturbation model per se, which unsubstantiated all the explanation for the age-related adaptability to fatigability. In chapter 4, we verified the age-specific changes in muscle activation due to repetitive sit-to-stand, muscle fatigability model. Additionally, although we did not test, we also explored the literature to understand how demanding mental tasks would impair movement control.

2.1. Repetitive sit-to-stand as a perturbation model

While numerous studies used repetitive sit-to-stand as a perturbation model to examine age-related adaptability in gait [4,6,8,19,34], the reason for the use of the repetitive sit-to-stand as fatigability perturbation is unclear. Our suspicion for this widespread usage of repetitive sit-to-stand is because sit-to-stand is one of the most muscle demanding functional tasks [35–37], which requires relatively higher muscle effort compared even with ascent or descent of stairs [1]. In addition, repetitive sit-to-stand is particularly harder for older vs. younger adults to execute due to the age-typical degenerative process in neuromuscular function [38].

In chapter 4, we determined the effects of repetitive sit-to-stand on muscle activation during initial- and late-stages of sit-to-stand and on maximum force to probe the repetitive sit-to-stand as a perturbation model to examine age-related gait adaptability. The most notable evidence was an overwhelmingly increasing in rate of perceived exertion that accompanied 467 fewer sit-to-stand trials in older (134) vs. younger adults (601). While older and younger adults signalized to be unable to continue with sit-to-stand, the reduction in the maximum voluntary isometric force and knee and dorsiflexor activation, in both age groups, were limited to 16% and 25%, respectively. The relatively subtle decrease in the level of maximal force and electromyography activation after hundreds of sit-to-stand trials point to the potential limitation of this task as a perturbation model to explore age-effects on gait adaptability.

Combining repetitive sit-to-stand performance, and its effects on muscle force and activation, it seems plausible that older adults, to perform a drastically reduced number of sit-to-stand trials, had spared knee extensors from becoming dysfunctional. This observation is endorsed by other studies that verified even small effects of repetitive sit-to-stand on the maximal torque (7 to 10%) [18,19]. Such sparing effects of repetitive sit-to-stand on muscle function may underlie the trivial changes in gait biomechanics in obstacle crossing tasks [19] and minimal effects of repetitive sit-to-stand on treadmill walking performance (Chapter 2 and 3 [1,8]).

Curiously, even with limited effects, repetitive sit-to-stand elicits an age-specific compensatory strategy in the neural drive to maintain unchanged gait performance. The age-specific modulations in the neural drive during treadmill walking were accompanied by the repetitive sit-to-stand effects on muscle force and activation. However, it is perhaps pretentious to assume that age-specific modulation in Tibial anterior-Peroneus Longus, Gastrocnemius Lateralis-Soleus and Rectus Femoris-Vastus Lateralis is entirely consequences of repetitive sit-to-stand since changes between repetitive sit-to-stand outcomes and coherence did not correlate (r=0.20 to 0.38; p>0.05, Chapter 5). Instead, it seems reasonable that the age-specific modulation in common neural drive during treadmill walking after repetitive sit-to-stand may arise from a combination of subtle changes in muscle activation, maximum torque [39,40], the overwhelming increase in rate of perceived exertion due to fatigability (signal of central fatigue) [41], age-related degeneration in neuromuscular control [21,23], and possible changes in somatosensorial feedback due to repetitive sit-to-stand (not assessed here) that impair the neural control of gait [9]. Altogether, the arguments indicate a limitation of repetitive sit-to-stand as a perturbation model to examine age-related gait adaptabilities.

2.2. Demanding mental task as a perturbation model

Mental performance fatigability is described as a psychophysiological state due to prolonged exposure to a demanding mental task [42,43]. While psychologically this state is associated to a decline in motivation accompanied by increased self-reported fillings of tiredness [44], physiologically mental performance fatigability is, for example, related to changes in brain activity across Alpha, Beta and Theta bands in frontal, central and posterior brain areas [45]. Together, it is reasonable to believe that mental performance would affect the top-down control of movement [46], but, mainly, in a task in which the allocation of cognitive resources/functions is highly required [12]. In this sense, experimental protocol as a single task treadmill walking or standing postural task in which the cognitive involvement is small, the effects of mental performance fatigability may be minimal or even absent [8,33]. Conceivably, demanding mental tasks would be an appropriate model to examine age-related adaptation to mental fatigability in dual-task walking task [12], preferably in more active gait conditions, such as overground walking.

3. LIMITATION AND FUTURE DIRECTIONS

Collectively the results suggest that protocols of induced fatigability may evoke adaptations in a fatigability-type specific way. For this reason, high muscle demanding fatigability protocols that target specific key elements of gait might be useful to examine the effects of age and fatigue on gait adaptability [10]. In addition, there is a need to determine the effects of muscle performance fatigability on motor outcomes that are both specific and not specific to the fatiguing task, an approach that would improve experimental control and the validity of conclusions. Further studies should drive the hypothesis not only for the strides outcomes but focus on understanding the underlying neural mechanism related to muscle fatigability effects in older adults' gait mechanics.

Using a treadmill to examine the effects of age and fatigue in gait adaptability can minimize such effects because treadmill walking minimizes gait variability [14,47]. Possibly, this treadmill influence may have mitigated the mental and muscle fatigability effects on gait. Thus, assessing gait adaptability to experimentally induced fatigability during more reactive gait control, such as overground walking, or even more complex gait conditions (e.g., perturbed gait, obstacle crossing, dual-task walking, step up and down in a curb) can augment the potential effects of fatigability in gait [1]. Since age-related changes in gait are pronounced in these gait conditions [48–50], such complex gait would also increase the niche for examining the age and fatigability effects on gait.

Especially regarding mental performance fatigability, although demanding mental tasks effectively induced mental performance fatigability (Chapter 3), the adaptability on gait evoked by this protocol was minimal. Probably, healthy subjects would walk without any effect of mental fatigability because small cognitive resources are required during single treadmill walking. Future studies that intend to understand the effects of mental performance fatigability during gait should consider examining dual-task walking. We also suspect that if such fatiguing protocols focus on a specific cognitive function, e.g., attention, the secondary task during dual-task walking should also have high involvement of the specific cognitive function (attention). These specifics aspects of the task are likely determinant to examine mental fatigability effects on gait adaptability.

Limitations of this thesis also involve the characteristics of the participants. The two age groups were functionally similar (as observed by physical performance tasks, global cognition, and trait of fatigue), representing an unusually healthy segment of older adults. However, the similarity between the two age groups eliminated "confounders" functional differences, permitting us to examine a "purer" age-effect. Studies with fatigability protocols applied for a "typical" segment of older adults would broaden the scope and can be more representative of this population. It would also magnify the age-specific modulation for fatigue. Still considering population selection, perhaps, the most critical gap in knowledge is related to comparative studies of gait adaptation in older adults with and without self-reported fatigue. Such studies would provide meaningful insights into adaptations in healthy older adults after experimentally induced muscle or mental fatigability.

4. CONCLUSIONS

This thesis examined the effect of age and experimentally induced mental and muscle fatigability on gait. Muscle and mental fatigability had minimal effects on stride outcomes and dynamic gait features in younger and healthy older adults, possibly because treadmill walking makes gait uniform. We surmised that the overwhelming increase in perceived fatigue produced by repetitive sit-to-stand in older adults was accompanied by only subtle modifications in muscle force and activation, limiting the scope of this perturbation model to probe the age-effects on muscle adaptation in gait and posture. The effects of age and fatigability might be more overt during real-life or complex walking tasks (dual-task, perturbed walking) compared with treadmill walking and, perhaps, more effective model for examining gait and age adaptability to fatigability should considering specific gait fatigue-type. However, even with limited effects, repetitive sit-to-stand elicits age-specific changes in the neural drive, which could be interpreted as compensation for fatigue to maintain gait performance.

REFERENCES

[1] Santos PCR, Barbieri FA, Zijdewind I, Gobbi LTB, Lamoth C, Hortobágyi T. Effects of experimentally induced fatigue on healthy older adults' gait: A systematic review. PLoS One 2019;14:e0226939. doi:10.1371/journal.pone.0226939.

[2] Arvin M, Hoozemans MJM, Burger BJ, Rispens SM, Verschueren SMP, van Dieën JH, et al. Effects of hip abductor muscle fatigue on gait control and hip position sense in healthy older adults. Gait Posture 2015;42:545–9. doi:10.1016/j.gaitpost.2015.08.011.

[3] Toebes MJP, Hoozemans MJM, Dekker J, van Dieën JH. Effects of unilateral leg muscle fatigue on balance control in perturbed and unperturbed gait in healthy elderly. Gait Posture 2014;40:215–9. doi:10.1016/j.gaitpost.2014.03.194.

[4] Helbostad JL, Leirfall S, Moe-Nilssen R, Sletvold O. Physical Fatigue Affects Gait Characteristics in Older Persons. Journals Gerontol Ser A Biol Sci Med Sci 2007;62:1010–5. doi:10.1093/gerona/62.9.1010.

[5] Morrison S, Colberg SR, Parson HK, Neumann S, Handel R, Vinik EJ, et al. Walking-Induced Fatigue Leads to Increased Falls Risk in Older Adults. J Am Med Dir Assoc 2016;17:402–9. doi:10.1016/j.jamda.2015.12.013.

[6] Barbieri FA, Santos PCR, Simieli L, Orcioli-Silva D, van Dieën JH, Gobbi LTB. Interactions of age and leg muscle fatigue on unobstructed walking and obstacle crossing. Gait Posture 2014;39:985–90. doi:10.1016/j.gaitpost.2013.12.021.

[7] Granacher U, Wolf I, Wehrle A, Bridenbaugh S, Kressig RW. Effects of muscle fatigue on gait characteristics under single and dual-task conditions in young and older adults. J Neuroeng Rehabil 2010;7:56. doi:10.1186/1743-0003-7-56.

[8] Santos PCR, Hortobágyi T, Zijdewind I, Bucken Gobbi LT, Barbieri FA, Lamoth C. Minimal effects of age and prolonged physical and mental exercise on healthy adults' gait. Gait Posture 2019;74:205–11. doi:10.1016/j.gaitpost.2019.09.017.

[9] NIELSEN JB. How We Walk: Central Control of Muscle Activity during Human Walking. Neurosci 2003;9:195–204. doi:10.1177/1073858403251978.

[10] Wai-Chi Wong D, Lam W-K, Chiu-Chun Lee W. Gait asymmetry and variability in older adults during long-distance walking: Implications for gait instability 2019. doi:10.1016/j.clinbiomech.2019.11.023.

[11] Da Rocha ES, Kunzler MR, Bobbert MF, Duysens J, Carpes FP. 30 min of treadmill walking at self-selected speed does not increase gait variability in independent elderly. J Sports Sci 2018;36:1305–11. doi:10.1080/02640414.2017.1375139.

[12] Behrens M, Mau-Moeller A, Lischke A, Katlun F, Gube M, Zschorlich V, et al. Mental Fatigue Increases Gait Variability During Dual-task Walking in Old Adults. J Gerontol A Biol Sci Med Sci 2018;73:792–7. doi:10.1093/gerona/glx210.

[13] Vervoort D, den Otter AR, Buurke TJW, Vuillerme N, Hortobágyi T, Lamoth CJC. Effects of Aging and Task Prioritization on Split-Belt Gait Adaptation. Front Aging Neurosci 2019;11:10. doi:10.3389/fnagi.2019.00010.

[14] Lee SJ, Hidler J. Biomechanics of overground vs. treadmill walking in healthy individuals. J Appl Physiol 2008;104:747–55. doi:10.1152/japplphysiol.01380.2006.-The.

[15] Hollman JH, Watkins MK, Imhoff AC, Braun CE, Akervik KA, Ness DK. A comparison of variability in spatiotemporal gait parameters between treadmill and overground walking conditions. Gait Posture 2016;43:204–9. doi:10.1016/j.gaitpost.2015.09.024.

[16] Dingwell JB, Cusumano JP, Cavanagh PR, Sternad D. Local dynamic stability versus kinematic variability of continuous overground and treadmill walking. J Biomech Eng 2001;123:27–32.

[17] Helbostad JL, Sturnieks DL, Menant J, Delbaere K, Lord SR, Pijnappels M. Consequences of lower extremity and trunk muscle fatigue on balance and functional tasks in older people: A systematic literature review. BMC Geriatr 2010;10:56. doi:10.1186/1471-2318-10-56.

[18] Barbieri FA, dos Santos PCR, Simieli L, Orcioli-Silva D, Van Dieën JH, Gobbi LTB. Interactions of age and leg muscle fatigue on unobstructed walking and obstacle crossing. Gait Posture 2014;39:985–90. doi:10.1016/J.GAITPOST.2013.12.021.

[19] Hatton AL, Menant JC, Lord SR, Lo JCM, Sturnieks DL. The effect of lower limb muscle fatigue on obstacle negotiation during walking in older adults. Gait Posture 2013;37:506–10. doi:10.1016/j.gaitpost.2012.09.004.

[20] Li Q, Kobayashi M, Kumeda S, Ochiai T, Miura T, Kagawa T, et al. Effects of Forest Bathing on Cardiovascular and Metabolic Parameters in Middle-Aged Males. Evidence-Based Complement Altern Med 2016;2016:1–7. doi:10.1155/2016/2587381.

[21] Gennaro F, Bruin ED. A pilot study assessing reliability and age-related differences in corticomuscular and intramuscular coherence in ankle dorsiflexors during walking. Physiol Rep 2020;8. doi:10.14814/phy2.14378.

[22] Roeder L, Boonstra TW, Kerr GK. Corticomuscular control of walking in older people and people with Parkinson’s disease. Sci Rep 2020;10:2980. doi:10.1038/s41598-020-59810-w.

[23] Spedden ME, Choi JT, Nielsen JB, Geertsen SS. Corticospinal control of normal and visually guided gait in healthy older and younger adults. Neurobiol Aging 2019;78:29–41. doi:10.1016/j.neurobiolaging.2019.02.005.

[24] Semmler JG, Kornatz KW, Meyer FG, Enoka RM. Diminished task-related adjustments of common inputs to hand muscle motor neurons in older adults. Exp Brain Res 2006;172:507–18. doi:10.1007/s00221-006-0367-0.

[25] Spedden ME, Nielsen JB, Geertsen SS. Oscillatory Corticospinal Activity during Static Contraction of Ankle Muscles Is Reduced in Healthy Old versus Young Adults. Neural Plast 2018;2018. doi:10.1155/2018/3432649.

[26] Jensen P, Frisk R, Spedden ME, Geertsen SS, Bouyer LJ, Halliday DM, et al. Using Corticomuscular and Intermuscular Coherence to Assess Cortical Contribution to Ankle Plantar Flexor Activity During Gait. J Mot Behav 2019;51:668–80. doi:10.1080/00222895.2018.1563762.

[27] Norton JA, Gorassini MA. Changes in Cortically Related Intermuscular Coherence Accompanying Improvements in Locomotor Skills in Incomplete Spinal Cord Injury. J Neurophysiol 2006;95:2580–9. doi:10.1152/jn.01289.2005.

[28] Del Vecchio A, Germer CM, Elias LA, Fu Q, Fine J, Santello M, et al. The human central nervous system transmits common synaptic inputs to distinct motor neuron pools during non-synergistic digit actions. J Physiol 2019;597:5935–48. doi:10.1113/JP278623.

[29] Hortobagyi T, Finch A, Solnik S, Rider P, DeVita P. Association Between Muscle Activation and Metabolic Cost of Walking in Young and Old Adults. Journals Gerontol Ser A Biol Sci Med Sci 2011;66A:541–7. doi:10.1093/gerona/glr008.

[30] Semmler JG, Ebert SA, Amarasena J. Eccentric muscle damage increases intermuscular coherence during a fatiguing isometric contraction. Acta Physiol 2013;208:362–75. doi:10.1111/apha.12111.

[31] Hortobágyi T, Rider P, Gruber AH, DeVita P. Age and muscle strength mediate the age-related biomechanical plasticity of gait. Eur J Appl Physiol 2016;116:805–14. doi:10.1007/s00421-015-3312-8.

[32] Monjo F, Terrier R, Forestier N. Muscle fatigue as an investigative tool in motor control: A review with new insights on internal models and posture-movement coordination. Hum Mov Sci 2015;44:225–33. doi:10.1016/j.humov.2015.09.006.

[33] Morris AJ, Christie AD. The effect of a mentally fatiguing task on postural balance control in young and older women 2020. doi:10.1016/j.exger.2020.110840.

[34] Santos PCR, Gobbi LTB, Orcioli-Silva D, Simieli L, van Dieën JH, Barbieri FA. Effects of leg muscle fatigue on gait in patients with Parkinson's disease and controls with high and low levels of daily physical activity. Gait Posture 2016;47:86–91. doi:10.1016/j.gaitpost.2016.04.002.

[35] Alcazar J, Losa-Reyna J, Rodriguez-Lopez C, Alfaro-Acha A, Rodriguez-Mañas L, Ara I, et al. The sit-to-stand muscle power test: An easy, inexpensive and portable procedure to assess muscle power in older people. Exp Gerontol 2018;112:38–43. doi:10.1016/j.exger.2018.08.006.

[36] Jeon W, Jensen JL, Griffin L. Muscle activity and balance control during sit-to-stand across symmetric and asymmetric initial foot positions in healthy adults. Gait Posture 2019;71:138–44. doi:10.1016/j.gaitpost.2019.04.030.

[37] Netz Y, Ayalon M, Dunsky A, Alexander N. "The multiple-sit-to-stand" field test for older adults: What does it measure? Gerontology 2004;50:121–6. doi:10.1159/000076769.

[38] Bryanton M, Bilodeau M. The role of thigh muscular efforts in limiting sit-to-stand capacity in healthy young and older adults. Aging Clin Exp Res 2017;29:1211–9. doi:10.1007/s40520-016-0702-7.

[39] Boonstra TW, Daffertshofer A, van Ditshuizen JC, van den Heuvel MRC, Hofman C, Willigenburg NW, et al. Fatigue-related changes in motor-unit synchronization of quadriceps muscles within and across legs. J Electromyogr Kinesiol 2008;18:717–31. doi:10.1016/j.jelekin.2007.03.005.

[40] Danna-Dos Santos A, Poston B, Jesunathadas M, Bobich LR, Hamm TM, Santello M. Influence of fatigue on hand muscle coordination and EMG-EMG coherence during three-digit grasping. J Neurophysiol 2010;104:3576–87. doi:10.1152/jn.00583.2010.

[41] Guo F, Sun YJ, Zhang RH. Perceived exertion during muscle fatigue as reflected in movement-related cortical potentials: An event-related potential study. Neuroreport 2017;28:115–22. doi:10.1097/WNR.0000000000000732.

[42] Van Cutsem J, Marcora S, De Pauw K, Bailey S, Meeusen R, Roelands B. The Effects of Mental Fatigue on Physical Performance: A Systematic Review. Sport Med 2017;47:1569–88. doi:10.1007/s40279-016-0672-0.

[43] Boksem MAS, Tops M. Mental fatigue: Costs and benefits. Brain Res Rev 2008;59:125–39. doi:10.1016/j.brainresrev.2008.07.001.

[44] Boksem MAS, Meijman TF, Lorist MM. Mental fatigue, motivation and action monitoring. Biol Psychol 2006;72:123–32. doi:10.1016/j.biopsycho.2005.08.007.

[45] Tran Y, Craig A, Craig R, Chai R, Nguyen H. The influence of mental fatigue on brain activity: Evidence from a systematic review with meta-analyses. Psychophysiology 2020. doi:10.1111/psyp.13554.

[46] Lorist MM. Impact of top-down control during mental fatigue. Brain Res 2008;1232:113–23. doi:10.1016/j.brainres.2008.07.053.

[47] Hollman JH, Kovash FM, Kubik JJ, Linbo RA. Age-related differences in spatiotemporal markers of gait stability during dual task walking. Gait Posture 2007. doi:10.1016/j.gaitpost.2006.08.005.

[48] Galna B, Peters A, Murphy AT, Morris ME. Obstacle crossing deficits in older adults: A systematic review. Gait Posture 2009;30:270–5. doi:10.1016/J.GAITPOST.2009.05.022.

[49] Chandran VD, Calalo JA, Dixon PC, Dennerlein JT, Schiffman JM, Pal S. Knee muscle co-contractions are greater in old compared to young adults during walking and stair use. Gait Posture 2019;73:315–22. doi:10.1016/J.GAITPOST.2019.07.501.

[50] Hortobágyi T, Mizelle C, Beam S, DeVita P. Old adults perform activities of daily living near their maximal capabilities. J Gerontol A Biol Sci Med Sci 2003;58:M453-60.

A

Appendix

ACKNOWLEDGEMENTS

This thesis is made possible by the support, guidance, and patience of many individuals over several years. For those, I appreciate all the support, words, and teachings. I really thank you all.

Unquestionably, my steady growth in science was only possible by the unwavering support by my promotion team. I am especially appreciative of their effort and suggestions during meetings, working time, coffee time, etc. I am grateful for each particular piece of advice, which helped in the growth of my skills as a researcher. Especially, I would like to thank those who were closest to me during this process. To my promotion team, I am so grateful for all your time and knowledge invested in this thesis. I can guarantee that I carefully listened and tried to learn as much as I could with all of you.

I would like to start by thanking Prof. Dr. Tibor Hortobágyi for giving me the opportunity to come to Groningen as a sandwich PhD student. It was an excellent challenge and a tremendous opportunity to learn and grow, both on the personal and professional fronts. I especially appreciate having you, Tibor, as my promotor, for I was able to witness your immense knowledge, not only about aging, gait, neuromuscular control but about science. Until today, I am positively surprised that whenever I send you a manuscript even if it is at the end of the day, your prompt response with your many good suggestions and invaluable feedback arrives in my email inbox. From the many instances where I have been impressed with your intellect, I would like to take the liberty of mentioning a dinner that we had, together with Brazilian professors. That evening, you were talking about the most incredible mentor you have ever had, Prof. Walter P. Kroll (1930, Chicago, IL – 2011, Hadley, MA). You mentioned that when you sat down with him to discuss data based on physiology, he put the physiology 'cap' on. If the discussion changed to aspects of psychology, he took off his 'cap' from physiology and put on his 'cap' from psychology. You concluded that story saying that it was so impressive your (mentor's) capacity to know/discuss the subject with such a diverse range of knowledge. However, that evening, I was sitting facing you, and I found myself identifying with the story. I really appreciate all your 'caps', thank you!

Prof. Dr. Claudine Lamoth. Claudine, thank you for being so close throughout my journey in Groningen. Your teachings and advice go beyond the edges of science. You always showed great care towards international students, and towards me staying in Groningen, proposing ways to integrate students, seeking an understanding of the cultural differences, and trying to provide a nice environment for my wellbeing. In that sense, I would like to mention one specific talk we had, after which I found myself feeling much more comfortable and confident. It was supposed to be a regular meeting meant for us to discuss data analysis. However, the direction took another turn, somehow at that moment, you seemed to have guessed exactly what I was needing. We talked about personal aspects, and you gave me really good advice that made me feel comfortable, supported, and made me change my behavior positively, particularly in relation to the promotion team and other colleagues. I cannot even begin to describe how valuable your tremendous support and patience were in helping me with data management and analysis in Matlab. Nowadays, before starting anything (writing, analysis, etc.), I can hear your voice in my mind saying: “make a clear and structured plan”, words that I appreciate.

I would also like to thank Dr. Inge Zijedwind. Inge, thank you very much for your kindness. You were always open and available to discuss my endless doubts about fatigability concepts, assessments, and tools. I also appreciate all those times when you encouraged me to search for solutions, explore different ways to apply and understand my data and all the concepts behind my project. I also appreciate the care and attention you gave during every presentation and piece of writing where you were involved.

Dr. Fabio A. Barbieri. Fabio, thank you for all the support. Fabio, besides being part of my promotion team, you are a close friend, and responsible for all my steps inside of academia that have resulted in this document. Since 2008, the year we started working together, we have shared numerous moments, as friends, as workmates, and as promotor and student. It was in your thesis that I got involved for the first time in a scientific project. A few years later, I remember how proud of you I was when you became the first PhD of our department (maybe of the whole University) to graduate as a Double PhD. Now here I am following the same journey. I do not have enough words to thank you! I am not able to choose a specific instance as there are several (Norway, Belgium, Netherlands, Spain, Check Republic, Alagoas, Londrina, Belo-Horizonte, Ubatuba, InterUnesps and hundreds, maybe thousands, with the futsal team). Meu muito obrigado!

Prof. Dra. Lilian T. B. Gobbi. Lilian, thanks for the opportunity you gave me to start my academic journey in your Lab (LEPLO). I really appreciate all the possibilities that opened up for me because of that. These possibilities extrapolated the scientific field and allowed me to develop my management, teaching, leadership skills. I am thankful for the administrative and logistic support that you provided to all the students and to me. You have also believed in me, embracing my projects' ideas and making them possible, no matter how expensive or difficult developing the ideas were, and for that, I am deeply appreciative. Thank you very much!

I am grateful to all staff members, PhD students, and colleagues at the Center for Human Movement Science, especially those whom I shared a special friendship with Ana Paula, Rucia, Alfredo, Matheus Pacheco, Margot, Sander, Iris. Special thanks to Iris. I appreciate how you care about your friends' wellbeing and are so congenial and inclusive. Thank you for the particular support and friendship you gave me. I am also pleased to have the company of all the IT members (Wim, Anniek, Dirk, and Emyl). Thank you for your support and for those enjoyable conversations.

I am also thankful to the talented students involved in my project; without them, it would have been impossible to develop this thesis. Nick Fennema, thank you very much for all the support, nice conversations, and for the good coffees you introduced me to here in Groningen. I really appreciate all the help you gave me, from data acquisition to recruitment of participants, data analysis, and to helping me settle here in Groningen. However, what I most appreciate in you is your goodness and readiness with which you support new ideas. I also share a similar sentiment and bond with Inge Kenter. We shared several hours in the lab, and you were always there in a good mood to make those hours pleasant and to facilitate the communication with the participants, besides, of course, providing unrelenting support during the procedures. You helped me in developing my teaching (supervision) skills. Wherever I will be, I will be cheering for the success of both you and Nick.

To my housemate and my newest friend, Sumiran Rastogi, thank you very much for helping me with my endless English doubts, sharing good moments, food, ice cream, and joining me to make fun of Ana (LOL!). I am grateful to share all the good moments, my anxiety and my impatience to finish my thesis with you, Sumi. Thanks for your smart words!

To my Brazilian community here, thank you for letting me have a piece of Brazil here in Groningen, thanks to Danilo, Isa, Kiko, and Matheusinho. Regarding feeling, I have a special place here to acknowledge Sergio and Dena. I do not have words to say how important to me (or us, I am sure Ana will agree) you both were and still are. I appreciated all the moments we spent together, and all of them will always be present in my memory. Prepare yourselves to receive us in Brazil, because now, you are part of our life and we will meet sooner to have more fun, good food, and moments together. From LEPLO, I would like to thank all members that are/were part of the Posture and Gait studies lab (LEPLO) for all the moments together, learning partnerships, and friendships. In particular, I would like to thank Diego Orcioli-Silva and Victor Spiandor Beretta. You both are extremely talented and special friends, with whom I have had the pleasure to share a good professional and personal friendship. Thanks for making science not only serious and responsible, but also pleasant, funny, and enjoyable, for the innumerous group calls we made to talk about everything. I hope our partnership in science endures. A special thanks to Paulo Pelicioni, I already told you, you are an inspiring and extremely reliable person. Thanks for our communication during this period.

To my family and childhood friends, I will write in Portuguese. Primeiramente, aos meus pais e minha irmã Paula. Eu não tenho palavras para agradecer o que vocês são e representam para mim e `a esta tese. Quando eu penso na minha trajetória, em quem eu sou, na minha essência, nos meus valores, vocês são parte íntegra destes pensamentos. Se precisei de motivação, de força, ou perseverança, vocês também estavam em meu pensamento. Enfim, agradeço imensamente por me darem chance e condições para que meus sonhos e metas fossem realizados. À família Cassanti meu muito obrigado. Obrigado André(s) e Ana(s)! Obrigado por me receberem tão bem na família e por me acompanharem nesta jornada. Obrigado também por todo (e foram muitos) suporte que vocês deram `a Clara e a mim. Eu sou muito grato por vocês fazerem a distância de um oceano parecer tão pequena, pelas ligações diárias (estas sem exceções), pelas visitas, e por todo carinho e amor, por acompanhar nossos passos, nos ajudar quando e necessário e por celebrar cada progresso nosso. Lazzareti, agradeço imensamente por me receberem tão bem e por todo carinho e atenção. Obrigado pela atenção e carinho e por todo amor que vocês nos deram. Fico muito feliz por ter vocês em minha vida. Guimarães, obrigado Teco, Cris e Carol! Vocês são especiais, talvez até anjos sem asas. Muito obrigado por, junto com a Paula, cuidar dos meus pais e dos outros velhos da família. Agradeço também aos meus amigos, Nando, Leo, Xande, Diego, Adriano, Rodrigo, Gabi, Rafa, Tati. Obrigado por estarem presentes neste e outros períodos que me levaram até aqui.

Finally, turning back to English, I would like to thank Ana Clara Cassanti. Nobody could imagine we would be here together. Thank you for being with me always, for making this opportunity possible, for making me believe in myself and in ourselves. We, together, are growing and achieving targets as a couple, without

missing our own aims. I am so happy to be with you. Thanks for accepting without hesitation to be with me here and for the tremendous support you give to me here and always. Love you!

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001. Additionally, this study received financial support from the Graduate School of Medical Sciences (GSMS)/ University of Groningen.

ABOUT THE AUTHOR

Paulo Cezar Rocha dos Santos was born in Osasco – SP, Brazil, on the 16th of November and grew up in Carapicuíba – SP, Brazil. In 2006, he moved to Rio Claro – SP to pursue a Bachelor's in Physical Education at São Paulo State University (UNESP), where he obtained the title in 2010. In 2013, he obtained his Master's in Human Movement Science from UNESP, where his research topic was to verify the effects of muscle fatigability and level of physical activity on gait outcomes in people with Parkinson's Disease.

Paulo's research interest and expertise lie in understanding the underlying mechanism of human movement, particularly gait. He is especially interested in understanding how older adults would adapt their gait in response to induced fatigue – the topic on which he also wrote his PhD. He started his PhD at UNESP and then moved to Groningen to pursue a Sandwich PhD program funded by the Abel Tasman Scholarship at the Department of Human Movement Science, at the University Medical Center Groningen, University of Groningen. Besides the research activities, Paulo has also supervised bachelor students at both UNESP and the University of Groningen.

Parallel to his PhD research, Paulo also worked on several other projects in different research groups (Posture and Gait Studies Lab – under supervision of Prof. Dr. Lilian T. B. Gobbi, and Human Movement Research Laboratory – under supervision of Dr. Fabio A. Barbieri), resulting in 30 papers published, 2 submitted, 7 book chapters, and several conference contributions. Currently, Paulo seeks to continue his academic career, with a focus on physical exercise and/or neural mechanisms of gait in healthy and Parkinson's Disease individuals.

JOURNAL PUBLICATIONS

Peer-review journals

1 - GOBBI, L.T.B., PELICIONI, P.H.S**.,** LAHR, J., LIRANI-SILVA, E., TEIXEIRA-ARROYO, C., **SANTOS, P.C.R.** Effects of different types of exercises on psychological and cognitive features in people with Parkinson's disease. *Annals of Physical and Rehabilitation Medicine* (**In press**).

2 - ORCIOLI-SILVA, D., BARBIERI F.A., **SANTOS, P.C.R.,** BERETTA, V.S. SIMIELI, L., VITÓRIO, R., LIRANI-SILVA E., GOBBI L.T.B. Double obstacles increase gait asymmetry during obstacle crossing in people with Parkinson's disease and healthy older adults: A pilot study. *Scientific Reports.* v. 10, p.1-8, 2020.

3 – **SANTOS, P.C.R**., BARBIERI, F.A.B., ZIJEWIND, I, GOBBI, L.T.B., LAMOTH, C., HORTOBÁGYI. T. Effects of experimentally induced fatigue on healthy older adults' gait: a systematic review. *Plos One.* v.14(12), p. 1-14, 2019.

4 - **SANTOS, P.C.R**., HORTOBÁGYI. T., ZIJEWIND, I., GOBBI, L.T.B., BARBIERI, F.A.B., LAMOTH, C. Minimal effects of age and prolonged physical and mental exercise on healthy adults' gait. *Gait & Posture.* v.74, p.205 - 211, 2019.

5 - BERETTA, V.S., VITÓRIO, R., **SANTOS, P.C.R.,** ORCIOLI-SILVA, D., GOBBI, L.T.B. Postural control after unexpected external perturbation: Effects of Parkinson's disease subtype. *Human Movement Science.* v.64, p.12 - 18, 2019.

6 - BERETTA, V.S., **SANTOS, P.C.R**., JAIMES, D.A.R., PESTANA, M.B., JIMENEZ, A.M.F., SCARABOTTOLO, C.C., GOBBI, L.T.B. Postural adjustments of active youths in perturbation and dual-task conditions. *Revista Brasileira de Medicina do Esporte,* v.25, p.428 - 432, 2019.

7 - PALUCCI VIEIRA, L.H., CUNHA, S.A., SANTIAGO, P.R.P., **SANTOS, P.C.R.,** CARDENAS, G.C., BARBIERI, R.A., BAPTISTA, A.M., BARBIERI, F.A. Dominant-non-dominant support limb kinematics and approach run parameters in futsal kicking of stationary and rolling ball. *Journal of Sports Medicine and Physical Fitness. v.*2, 2019.

8 - PEREIRA, M.P., BATISTELA, R.A., **SANTOS, P.C.R.,** SIMIELI, L., GOBBI, L.T.B. The Dual-Tasking Overload on Functional Mobility Is Related to Specific Cognitive Domains in Different Subtypes of Parkinson's Disease. *Topics in Geriatric Rehabilitation.* v.35, p.119 - 124, 2019.

9 - PEREIRA, V.A.I., BARBIERI, F.A., ZAGATTO, A.M., **SANTOS, P.C R.,** SIMIELI, L., BARBIERI, R.A., CARPES, F.P., GOBBI, L.T.B. Muscle fatigue does not change the effects on lower limbs strength caused by Aging and Parkinson's disease. *Aging and Disease.* v.9, p.952 - 962, 2018.

10 - SIMIELI, L., BARBIERI, F.A., ORCIOLI-SILVA, D., LIRANI-SILVA, E., BERETTA, V.S., **SANTOS, P.C.R**., GOBBI, L.T.B. Variability of crossing phase in older people with Parkinson's disease is dependent of obstacle height. *Scientific Reports.* v.8, p.1 - 7, 2018.

11 - BERETTA, V.S., BARBIERI, F.A., ORCIOLI-SILVA, D., **SANTOS, P.C.R.,** SIMIELI, L., VITÓRIO, R., GOBBI, L.T.B. Can postural control asymmetry predict falls in people with Parkinson's disease? *Motor Control.* v.22, p.449 - 461, 2018.

12 - ZAMPIER, V.C., VITORIO, R., BERETTA, V.S., JAIMES, D.A R., ORCIOLI-SILVA, D., **SANTOS, P.C.R.,** GOBBI, L.T.B. Gait bradykinesia and hypometria decrease as arm swing frequency and amplitude increase. *Neuroscience Letters.* v.687, p.248 - 252, 2018.

13 - ORCIOLI-SILVA, D., VITÓRIO, R., LIRANI-SILVA, E., **SANTOS, P.C.R.,** BERETTA, V.S., GOBBI, L.T.B. Objective measures of unobstructed walking and obstacle avoidance in Parkinson's disease subtypes. *Gait & Posture*. v.62, p.405 - 408, 2018.

14 - ORCIOLI-SILVA, D., BARBIERI, F.A., SIMIELI, L., **SANTOS, P.C.R**., BERETTA, V.S., COELHO, F.G.M., ANDRADE, L.P., GOBBI, L.T.B. A program of physical activity improves gait impairment in people with Alzheimer's disease. *Motriz: Revista de Educação Física.* v.24, 2018.

15 - BARBIERI, F.A., SIMIELI, L., ORCIOLI-SILVA, D., BAPTISTA, A.M., PESTANA, M.B, BERETTA, V.S., **SANTOS, P.C.R.,** GOBBI, L.T.B. Obstacle avoidance increases asymmetry of crossing step in individuals with Parkinson's disease and neurologically healthy individuals. *Journal of Motor Behavior.* v.2, p.1 - 9, 2017.

16 - SIMIELI, L., GOBBI, L.T.B., ORCIOLI-SILVA, D., BERETTA, V.S., **SANTOS, P.C.R.,** BAPTISTA, A.M., BARBIERI, F.A. The variability of the steps preceding obstacle avoidance (approach phase) is dependent on the height of the obstacle in people with Parkinson's disease. *PLoS One*. v.12, p.e0184134, 2017.

17 - ORCIOLI-SILVA, D., BARBIERI, F.A., SIMIELI, L., VITORIO, R., **SANTOS, P.C.R**., BERETTA, VICTOR S., GOBBI, L.T.B. Walking behavior over multiple obstacles in people with Parkinson's disease. *Gait & Posture.* v.58, p.510 - 515, 2017.

18 - **SANTOS, P.C.R**., GOBBI, L.T.B., ORCIOLI-SILVA, D., SIMIELI, L., VAN DIEËN, J.H., BARBIERI, F.A. Effects of leg muscle fatigue on gait in patients with Parkinson's disease and controls with high and low levels of daily physical activity. *Gait & Posture.* v.47, p.86 - 91, 2016.

19 - **SANTOS, P.C.R**., MORAIS, L., SIMIELI, L., SILVA, E., VITÓRIO, R., FERREIRA, M.D.T., CAETANO, M.J., GOBBI, L.T.B. Comparação do equilíbrio e da mobilidade funcional entre pacientes com doença de Parkinson ativos e inativos. *Revista Brasileira de Atividade Física e Saúde.* v.21, p.534 - 541, 2016.

20 - BARBIERI, F.A., BERETTA, S.S., PEREIRA, V.A.I., SIMIELI, L., ORCIOLI-SILVA, D., **SANTOS, P.C.R**., VAN DIEËN, J.H., GOBBI, L.T.B. Recovery of gait after quadriceps muscle fatigue. *Gait & Posture.* v.47, p.270 - 274, 2016

21 - LIRANI-SILVA, E., VITÓRIO, R., BARBIERI, F.A., BAPTISTA, A.M., **SANTOS, P.C.R**., GOBBI, L.T.B. Different types of additional somatosensory information do not promote immediate benefits on gait in patients with Parkinson's disease and older adults. *Motriz: Revista de Educação Física.* v.21, p.244 - 249, 2015.

22 - BARBIERI, F.A., **SANTOS, P.C.R**., SIMIELI, L., ORCIOLI-SILVA, D., VAN DIEËN, J.H., GOBBI, L.T.B. Interactions of age and leg muscle fatigue on unobstructed walking and obstacle crossing. *Gait & Posture.* v.39, p.985 - 990, 2014.

23 - VITORIO, R., LIRANI-SILVA, E., BAPTISTA, A.M., BARBIERI, F.A., **SANTOS, P.C.R.,** TEIXEIRA-ARROYO, C., GOBBI, L.T.B. Disease severity affects obstacle crossing in people with Parkinson's disease. Gait & Posture. v.40, p.266 - 269, 2014.

24 - **SANTOS, P.C.R.,** BARBIERI, F.A., ORCIOLI-SILVA, D., SIMIELI, S., GOBBI, L.T.B. Effects of Physical Activity Levels on Fatigue Perception in Patients with Parkinson's Disease and Neurologically Healthy Individuals. Health, v.06, p.2927 - 2933, 2014.

25 - MILIONI, F., ANTUNES, B.M.M., TEIXEIRA-ARROYO, C., LOURES, J.P., SCARIOT, P.P.M., **SANTOS, P.C.R.,** SILVA, M.S., LUCIANO, E. Efeitos do exercício agudo sobre biomarcadores séricos de ratos diabéticos. Revista Brasileira de Medicina do Esporte (Impresso). v.20, p.32 - 36, 2014.

26 - BARBIERI, F.A., **SANTOS, P.C.R.,** VITORIO, R., VAN DIEËN, J.H., GOBBI, L.T.B. Effect of muscle fatigue and physical activity level in motor control of the gait of young adults. Gait & Posture. v.38, p.702 - 707, 2013.

27 - BARBIERI, F.A., **SANTOS, P.C.R.,** VITORIO, R., LIRANI-SILVA, E., Gobbi, L. T. B., VAN DIEËN, J.H. Systematic review of the effects of fatigue on spatiotemporal gait parameters. Journal of Back and Musculoskeletal Rehabilitation. v.26, p.125 - 131, 2013.

28 - BARBIERI, F. A., VITORIO, R., **SANTOS, P.C.R**., GOBBI, L.T.B. Revisão sistemática do efeito do envelhecimento no andar livre e adaptativo. Revista da Educação física (UEM. Online). v.24, p.135 - 143, 2013.

29 - BARBIERI, F.A., RINALDI, N.M., **SANTOS, P.C.R.,** LIRANI-SILVA, E, VITORIO, R., TEIXEIRA-ARROYO, C., STELA, F., GOBBI, L.T.B. Functional capacity of Brazilian patients with Parkinson's disease: relationship with clinical characteristics and disease severity. Archives of Gerontology and Geriatrics. v.54, p.e52 - e58, 2012.

30 - **SANTOS, P.C.R**., BARBIERI, F.A., GOBBI, L.T.B. Relacionamento entre as variáveis da corrida de aproximação e da posição de pé de apoio com a velocidade da bola nos chutes com o membro dominante e não dominante. Revista Brasileira de Biomecânica (Impresso), v.13, p.16 - 21, 2012.

Papers under review

1 - **SANTOS, P.C.R**., LAMOTH, C., GOBBI, L.T.B., ZIJEWIND, I., BARBIERI, F.A.B., HORTOBÁGYI. T. Older compared with young adults perform 467 fewer sit-to-stand trials to minimize changes in muscle activation and voluntary force. Gait and Posture (**Under review**, English).

2 - **SANTOS, P.C.R**., BARBIERI, F.A.B., ZIJEWIND, I., GOBBI, L.T.B., LAMOTH, C. HORTOBÁGYI. T. Age-specific modulation of intermuscular beta coherence during gait before and after experimentally induced fatigue. Scientific Reports (**Under review,** English).

Book chapters

1 - **SANTOS, P.C.R**., ORCIOLI-SILVA, D., SIMIELI, L., PEREIRA, V.I.A., BARBIERI, F.A. Effects of physical activity on walking in individuals with Parkinson's disease. In: BARBIERI, F.A., VITÓRIO, R. (Org.) *Locomotion and Posture in Older Adults*. 1 ed. Cham-Switzerland: Springer, 2017, p. 177-193.

2 - GOBBI, L.T.B., BARBIERI, F.A., VITORIO, R., PEREIRA, M.P., TEIXEIRA-ARROYO, C., **SANTOS, P.C.R.,** MORAIS, L.C., PELICIONI, P.H.S., et al. Long-Term Multimodal Exercise Program Improves Motor and Non-Motor Parameters of People with Parkinson´s Disease. In: RANA, A.Q. (Org.) *A synopsis of Parkinson´s Disease*. 1 ed. Rijeka-Croatia: InTech, 2014, p. 147-160.

3 - BARBIERI, F.A., MORAIS, L. C., **SANTOS, P.C.R.** Exercício e doença de Parkinson: principais evidências do PROPARKI In: GOBBI, L.T.B., BARBIERI, L.T.B., VITÓRIO, R (Org.) *Doença de Parkinson e Exercício Físico.*1 ed.Curitiba : CRV, 2014, v.1, p. 55-76.

4 - **SANTOS, P. C. R.,** TEIXEIRA-ARROYO, C., GOBBI, L. T. B. PROPARKI: AtivaMente In: COELHO, F.G.M., GOBBI, S., COSTA, J.L.R., GOBBI, L.T.B (Org.). *Exercício Físico no Envelhecimento Saudável e Patológico: Da teoria à prática*. 1ed.Curitiba : CRV, 2013, v.1, p. 391-399.

5 - TEIXEIRA-ARROYO, C., **SANTOS, P.C.R.,** GOBBI, L.T.B. Programa de Atividade Física para Pacientes com Doença de Parkinson: PROPARKI In: COELHO, F.G.M., GOBBI, S., COSTA, J.L.R., GOBBI, L.T.B. (Org.). *Exercício Físico no Envelhecimento Saudável e Patológico: Da teoria à prática*.1 ed. Curitiba: CRV, 2013, v.1, p. 341-368.

6 - GOBBI, L.T.B., VITORIO, R., TEIXEIRA-ARROYO, C., LIRANI-SILVA, E., RINALDI, N.M., BARBIERI, F. A., PEREIRA, M.P., **SANTOS, P.C.R.,** BATISTELA, R.A. Gait Velocity, Attention and Exercise in Parkinson s Disease. In: YOSHIDA, C., ITO, A. (Org.). *Parkinson's Disease: Diagnosis, Treatment and Prognosis*. Ed. New York: Nova Science Publishers, 2012, p. 1-15.

7 - GOBBI, L.T.B., BARBIERI, F.A., VITORIO, R., PEREIRA, M.P., TEIXEIRA-ARROYO, C., ALVES, A.P.T., BATISTELA, R.A., FORMAGGIO, P.M., LIRANI-SILVA, E., MORAIS, L.C., PELICIONI, P.H.S., RAILE, V., RINALDI, N.M., **SANTOS, P.C.R.,** TAKAKI, C.B., STELA, F., GOBBI, S. Effects of a Multimodal Exercise Program on Clinical, Functional Mobility and Cognitive Parameters of Idiopathic Parkinson's Disease Patients In: DUSHANOVA, J. *Dianostics and Rehabilitation of Parkinson's Disease.* Ed. Rijeka: Intech, 2011, p. 339-352.

CONFERENCE CONTRIBUTIONS (selected only during the PhD track)

1 - **SANTOS, P.C.R.** Effects of age and fatigue on gait dynamics. *VvBN PhD day - Groningen,* 2019 (Poster Presentation, English).

2 - **SANTOS, P.C.R.,** HORTOBÁGYI, T., ZIJDEWIND, I., GOBBI, L.T.B., BARBIERI, F.A., LAMOTH, C. The Effects of age and fatigue on gait dynamics. *International Society for Posture and Gait Research World Congress,* 2019 (Poster Presentation, English).

3 - **SANTOS, P.C.R.,** GOBBI, L.T.B., BARBIERI, F.A., LAMOTH, C., ZIJDEWIND, I., HORTOBÁGYI, T. Mental and muscle fatigue does not affect stride characteristics: preliminary results. *Motor Control Summer School – XV,* 2018 (Poster Presentation, English)

4 - **SANTOS, P.C.R.,** BERETTA, V.S., ORCIOLI-SILVA, D., COLATRELLA, G.B., GOBBI, L.T.B. The relationship between fatigue and dual-task walking depends of the Parkinson's Disease subtype. *V - São Paulo meeting of motor behavior (5º Encontro Paulista de Comportamento Motor),* 2017. (Poster Presentation, Portuguese)

5 - **SANTOS, P.C.R.,** BARBIERI, F.A., BERETTA, V.S., ORCIOLI-SILVA, D., GOBBI, L.T.B. Perceived fatigue affects the gait in habitual and fast speed in people with Parkinson's Disease. *XVII Brazilian Congress of Biomechanics, 2017.* (Poster Presentation, Portuguese)

6 - **SANTOS, P. C. R.,** BERETTA, V. S., CONCEICAO, N. R., ZAMPIER, V. C., COLATRELLA, G. B., GOBBI, L. T. B. The fatigue symptom impairs the walking with cognitive overload in people with Parkinson's Disease. X International Congress of Physical Education and Human Movement Science, 2017 (Poster Presentation, Portuguese).