Covert age-related differences in agility are related to both muscle strength and integrity of the corticospinal tract

by © Evan G. MacKenzie, A Thesis submitted

to the School of Graduate Studies in partial fulfillment of the

requirements for the degree of

Master of Science in Medicine (Neurosciences), Faculty of Medicine

Memorial University of Newfoundland

May 2025

St. John’s Newfoundland and Labrador

Abstract

Background: Agility involves moving efficiently without losing balance, requiring muscular strength and neuromuscular capacity. Maintaining agility promotes aging with vitality, living without frailty, and reduced fear of falling. Factors that influence age-related differences in agility are unknown.

Methods: Participants were recruited to determine whether quadriceps strength or integrity of the corticospinal tract (CST) influenced age-related differences in agility. Participants underwent Transcranial Magnetic Stimulation to measure CST integrity and completed a lower limb agility hopping task. CST excitability was calculated as active motor threshold intensity, the lowest stimulator output that produced a motor evoked potential. We used regression modelling to predict the contribution of quadriceps strength and CST integrity to lower limb agility, when controlling for sex.

Results: Greater quadriceps strength correlated with longer hop length (r = .581,p <.001) and reduced hop length variability (r=-.384,p=.039). Lower active motor threshold correlated with longer hop length (r=-.364,p=.048) and reduced hop length variability (r=.478,p=.007). Decreased quadriceps strength significantly predicted shorter hop length (R^2=.393,p=.002) while higher active motor threshold predicted greater hop variability (R^2=.182,p=.036).

Conclusions: Agility involves a combination of muscle power and coordination, which can be tested with a hopping agility task. CST integrity predicted coordination on the task, but not strength, even when controlling for sex.

Lay Summary

Agility involves performing complex movements smoothly and effortlessly. During aging, agility, including strength, speed, balance, and coordination, decline. Such age-related changes lead to increased risk of falls, reduced independence, and lower quality of life. Lower agility involves changes at the muscle and brain levels (i.e., corticospinal tract (CST) – the main motor connection from the brain to the muscles). However, which system is primarily responsible for worsening agility is unknown. Existing agility measures preclude quality of movement, focusing on temporal measures and used in athletics. Propulsive bipedal hopping is a new spatial measure of agility that distinguishes younger and older adults. We used propulsive bipedal hopping to identify age-related changes in agility and predictors like quadricep strength and the CST measured using Transcranial Magnetic Stimulation. We report quadricep strength predicts the hopping strength (distance) while reduced brain-muscle connection quality predicts poorer coordination on the agility task.

Acknowledgements

First and foremost, I would like to express my deep gratitude to my supervisor, Dr. Michelle Ploughman, for her invaluable guidance, insightful feedback, and unwavering support during my degree. Dr. Ploughman is an inspiration, and I am truly honored that she provided me with this incredible experience. I am grateful to my committee members, Drs. Diana De Carvalho and Ben Zendel, for reviewing my thesis and providing beneficial and valuable feedback.

I also want to send out huge thanks to all the staff and students at the Recovery and Performance Lab. I am incredibly lucky to have spent these past few years working with incredibly smart and kind individuals daily and learning so much from everyone. A sincere thank you to all the participants who volunteered their time to contribute to this project. This research would not have been possible without your support and dedication. Additionally, I would like to thank Memorial University of Newfoundland and CIHR for providing me with funding during the first year of my degree.

Lastly, I would like to thank my family and friends for their unconditional love and patience throughout my academic journey. Specifically, I would like to thank my parents, Jackie and Neil MacKenzie, who continuously supported me throughout my academic journey ever since my first day of my undergraduate degree. Finally, to my partner, Erica McShane, without your love and encouragement, I would not have been able to balance my master's degree and medical school at the same time, and I am forever grateful to have you by my side.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

CSP	Cortical Silent Period
CST	Corticospinal Tract
EMG	Electromyography
MEP	Motor Evoked Potential
REC	Recruitment Curve
TMS	Transcranial Magnetic Stimulation

Chapter 1: Introduction and Literature Review

1.1 General Introduction

The central nervous system (brain and spinal cord), the peripheral nervous system (nerves that connect the central nervous system to muscles, organs, and sensory receptors), and the musculoskeletal system (muscles, tendons, joints, and bones) work together as the neuromuscular complex. These neuromuscular components work harmoniously to initiate, control, and execute various body movements. Why is the neuromuscular system so crucial to one's overall functioning? It is constantly activated without awareness and is necessary to move and navigate the external environment to fulfill basic survival needs. Accidental falls would be frequent without proper functioning of the neuromuscular system. The individual's quality of life would be significantly diminished, and their ability to perform activities of daily living would be decreased, leading to a reduced level of independence. Like all body systems, age-related changes of the neuromuscular system are normal. However, whether components age in the same way and the impacts of those changes on everyday movement is an area of intense scrutiny.

Understanding the connection between the nervous system and the muscles they innervate is crucial for determining the level of neuromuscular functioning. The corticospinal tract, the main pathway that influences our ability to move in our environment, deteriorates with age. With that, an individual's level of agility is negatively affected, leading to a more sedentary lifestyle. The degree of impact the corticospinal tract, which is measured using transcranial magnetic stimulation to assess the integrity of the neuromuscular system, and its effect on one's agility level is poorly understood.

This thesis is prepared in manuscript format with three chapters. Chapter One provides an overview of aging and its effect on the neuromuscular system, followed by an explanation of agility using bipedal hopping and its previous use in other diseases. Transcranial magnetic stimulation is explained as a tool for detecting age-related changes in the corticospinal tract. Chapter Two is a manuscript assessing age-related changes in agility by measuring the contributions of quadriceps strength and the integrity of the corticospinal tract. This manuscript is written in the format for publication in the *Journal of Applied Physiology*, which was submitted on December 2nd, 2024. Finally, Chapter Three concludes with an expanded discussion on the implications of hopping in everyday life and the contributions of various neuromuscular system components. Study limitations will be discussed followed by suggestions for future directions in hopping as an agility measure for healthy older adults.

1.2 Overview of the Aging Population

1.2.1 Epidemiology

The average age of the world's population is increasing. Approximately 13% (962 million) of the total population is over 60; by 2050, the rate is expected to quadruple due to increased life expectancy (United Nations, 2015). In Canada, 25% (10.4 million) of Canadians will be over 65, and 1 in 10 Canadians will be over 80 years of age (Sheets & Gallagher, 2013). The shift in increased aging rates will profoundly impact individuals, housing, employment, retirement, and healthcare, and it will be accompanied by increased burden and severity of disease (Zhang et al., 2024). The impact of an aging society directly leads to increased prevalence of frailty and all-cause morbidity, profoundly affecting an individuals' quality of life.

1.2.2 Frailty

Frailty is a complex process to define, although clinicians report it as observable upon admission (Keevil et al., 2020). Frailty is considered a clinical state associated with an increased risk of poor health outcomes (e.g., hospitalizations, postoperative complications, disability, mortality, and risk of falls) (Keevil & Romero-Ortuno, 2015; Xue, 2011) and increased healthcare costs (Kojima, 2019). It is a progressive syndrome, characterized first by a latent (undetectable) phase and continues through three stages: pre-frail, frail, and health complications resulting from a loss of physical and cognitive performance (Buch et al., 2016). The advancement of frailty leads to several hallmarks of physical decline such as decreased muscle strength, power, and mass (e.g., sarcopenia, dynapenia), leading to reduced gait, balance, and increased fall risk (Cadore et al., 2019). Clinical frailty screening tools vary between countries (Deng & Sato, 2024). In Canada, common tools include the Fried Frailty Phenotype, the FRAIL scale, General Medical Services, Short Physical Performance Battery, Clinical Frailty Scale, PRISMA-7, and the Frailty Index (Deng & Sato, 2024). The effects of frailty can be observed at the neuromuscular level. For instance, using electromyography (EMG), smaller muscle action potentials are associated with a higher likelihood of frailty based on the Frailty Phenotype and Frailty Index measures (Swiecicka et al., 2019). With the average living age increasing, frailty rates continue to rise globally with a greater incidence of prefrail community-dwelling older adults (Ofori-Asenso et al., 2019). In 2013-2014, Canadian frailty rates are estimated to be 22% (1.1 million), while 32% (1.6 million) are considered pre-frail (Gilmour & Ramage-Morin, 2021). The prevalence is likely increased in institutional settings (e.g., long-term care homes).

Consequently, increased frailty rates lead to poor health outcomes, but steps are being taken to address frailty earlier to reduce its impact on individuals and communities.

1.2.3 Fall Risk

Falls in older adults are emerging as an epidemic. Due to multi-factorial (extrinsic, intrinsic, situational) causes, falls are leading to severe head and fracture injuries (Vaishya & Vaish, 2020). Approximately one in every five older adults over 65 report declining balance (Lin & Bhattacharyya, 2012). In 2017, the global prevalence of falls was reported as 5,186 per 100,000 people, while the mortality rate was 9.2 per 100,000 (James et al., 2020). Half of Canadian older adults living in long-term care have a fall each year, leading to reduced independence and quality of life (Kuhnow et al., 2022). Several independent risk factors can increase the probability of falls. In order of evidence strength, factors include previous history of falls, balance impairments, decreased muscle strength, visual deficits, polypharmacy (four or more medications), gait impairment, dizziness, cognitive impairment, and arthritis (Tinetti & Kumar, 2010). Common indoor environmental objects such as furniture, flooring, and other objects that pose a tripping hazard in the living room, kitchen, and bathroom can increase fall risk (Lee, 2021). Outdoor hazards include uneven surfaces, deteriorated steps, and clutter on sidewalks and streets (Lee, 2021). Interestingly, women exposed to indoor environmental hazards had a higher risk of falls, while men were more likely to fall due to outdoor environmental hazards (Lee, 2021). With an increased proportion of falls in older adults, it is critical to identify regions within the human body responsible for deteriorated movement, most notably the neuromuscular system (Ward et al., 2019). Additionally, interventions should be targeted at all elements of fall risk (i.e., intrinsic, extrinsic).

1.3 Neuromuscular System

1.3.1 Overview of the Neuromuscular System

The neuromuscular system is one of the most critical pathways responsible for navigating our environment daily. The brain regions important for movement are in the frontal and parietal cortexes, cerebellum, and striatum (Grèzes & Decety, 2001; Laforce & Doyon, 2001). Sensory information from the eyes, ears, vestibular organs, and skin provides critical input to the parietal and temporal lobes to direct and fine-tune motor responses (Hupfeld et al., 2022). The premotor cortex and supplemental motor area control movement planning and initiation (Haslband et al., 1993). In contrast, movement production involves the primary motor cortex, which receives input from the brain's various parts (typically from sensory systems) and sends information via motor neurons to the spinal cord (Teka et al., 2017). The cortical homunculus in the primary motor cortex extending caudal to the precentral gyrus contains somatotopic areas responsible for movement from the feet to the face (Gordon et al., 2023). Activation of this region is the starting point for producing simple and complex movements. The cerebellum also plays a critical role in coordination and movement timing. It acts as an error detection and correction system that initially receives information from the motor cortex and then sends it back with updates on the requirements to complete the movement (Narayanan & Thirumalai, 2019). Subcortical structures, like the basal ganglia and red nucleus, and parts of the brainstem support more automatic movements, such as movement initiation and basic reflexes (Lanciego et al., 2012).

Once the movement has been processed in the brain, neural signals move through a descending tract called the pyramidal/corticospinal tract (CST), originating primarily from the primary motor cortex and other nearby cortical regions (Jang & Seo, 2015). This tract travels down through the brainstem, assisting with motor control, and decussates at the medulla

oblongata, crossing from one side of the spinal cord to the other. The main descending pathway is the lateral CST, which is the lateral column of white matter inside the spinal cord, producing voluntary movement of the extremities (Jang & Seo, 2015). The foundation of the neuromuscular system is built on motor units, skeletal muscle fibers, and the nerves that innervate them (Hunter et al., 2016). Peripheral nerves exit the spinal cord and innervate skeletal muscle at the neuromuscular junction, the synapse site between the nerve terminal and skeletal muscle. The electrical signal (action potential) transfers to the nerve terminal, which releases a chemical signal via the neurotransmitter acetylcholine that crosses the synaptic cleft and binds to receptors on the muscle fibers. This stimulates an action potential along the T-tubule inside the sarcolemma (cell membrane surrounding a skeletal muscle fiber), releasing calcium from the sarcoplasmic reticulum and activating the cross-bridge cycle to create muscle contraction and movement (Hernandez-Ochoa & Schneider, 2018). Myosin and actin filaments attach to form cross-bridges, allowing the myosin filament to slide past actin to create a muscle contraction (Herzog et al., 2015). The filamentous protein titin binds with calcium prior to actin to provide stability, stiffness, and regulate force production during muscle contraction (Herzog et al., 2015).

1.3.2 Physiological Changes with Aging

Physiological alterations to the central nervous system, specifically those in the neuromuscular system, occur throughout life. Aging negatively affects the body, particularly the musculoskeletal system. For instance, age-related reduction in muscle fiber mass (i.e., sarcopenia) (McNeil & Rice, 2018; Nilwik et al., 2013; Power et al., 2013), decreased mitochondrial functioning (Rygiel et al., 2016), and neuromuscular junction efficiency (Dobrowolny et al., 2021; Hunter et al., 2016) suppress optimal neuromuscular system

effectiveness. There are two types of muscle fibers: slow twitch (Type Ia) and fast twitch (Type IIa and IIb). Slow twitch fibers are essential for endurance activities and are highly resistant to fatigue, producing slower contractions (Plotkin et al., 2021). Fast twitch fibers generate fast contractions are more prone to fatigue and predominately used during forceful movements (Plotkin et al., 2021). Type IIa has slightly less endurance capabilities than Type I but more than Type IIb (Plotkin et al., 2021). With age, the CST degenerates, resulting in reduced neural muscle drive and changing muscle fiber characteristics, leading to muscle atrophy and weakness (Jang & Seo, 2015; Salat et al., 2005). Importantly, reduced number of motor neurons, motor unit discharge and recruitment rates, and voluntary activation are present in older adults (Hunter et al., 2016). Motor units include motorneurons and the skeletal muscle fibres they innervate, which is the central nervous systems final output and responsible for motor control (Monti et al., 2001). Neuromuscular junction changes include decreases in pre-synaptic vesicles including their strength and maintaining active synapses. (Dobrowolny et al., 2021; Hunter et al., 2016). Type I and II muscle fibers experience age-related decreases in fiber numbers and size, calcium content and sensitivity, contractile velocity, maximum peak force/power, rate of force development, and increased muscle fatigability (Straight et al., 2018). Sarcopenia reduces maximal strength and power and decreases motor neurons, leading to motor unit loss and reduced cross-bridges (Hunter et al., 2016). Compared to younger people, older adults have decreased agonist and increased antagonist muscle activation and neural drive patterns (Hoffren-Mikkola et al., 2015). This results in muscle co-activation, when the agonist and antagonist are activated simultaneously and stabilize nearby joints (McNeil & Rice, 2018). Measuring changes in neuromuscular functioning requires advanced and expensive equipment that may only be affordable for some laboratories and clinics to acquire. Furthermore, research that measures all

elements of the neuromuscular complex (brain, spinal cord, nerve, and muscle) and its relationships to lower limb movement and control is sparse. Even less is known about how aging of the neuromuscular system impacts lower limb control.

1.3.3 Alterations in Balance and Coordination

As people age, they often have difficulty with balance and coordination, affecting their independence and ability to carry out activities of daily living. Three sensory systems control balance: visual, vestibular, and somatosensory (Hupfeld et al., 2022). The visual system provides the environmental input necessary for obstacle avoidance and navigation (Redfern et al., 2001). The vestibular system is controlled by structures within the inner ear, which sense alterations in angular/linear velocity due to gravity and modify eye and head movements to provide spatial orientation (Allen et al., 2016). Finally, the somatosensory system detects the location of the body in space based on environmental cues to control human movement and force production (Steindl et al., 2006). While it is difficult to pinpoint which specific sensory system is responsible for balance and coordination impairments, it typically varies depending on the individual and their clinical history (e.g., medication use, dizziness), and can sometimes be a combination of issues in two or more sensory systems (Hupfeld et al., 2022). Balance impairments and falls arise in older adults when one or multiple sensory systems are discoordinated. For example, visual deficits affecting gaze in older adults lead to delayed reactions, slow movements, and postural sway (Paquette & Fung, 2011). Balance impairments and overall motor decline have been linked with the aging of the cerebellum, likely contributing to an increased risk of falls in this population (Bernard & Seidler, 2014).

Coordination is critical for many forms of movement and is essential for carrying out activities of daily movement. The foundation of coordination involves communication between the brain hemispheres to synchronize both sides of the body effectively. This communication between hemispheres usually happens through the corpus callosum. However, other brain regions also coordinate bimanual movements, such as the cerebellum, supplementary motor area, cingulate motor cortex, and premotor cortex (Seidler et al., 2010). As people age, atrophy of the corpus callosum and other cortical regions may lead to, or directly cause, reduced coordination and other motor impairments such as gait and balance (Seidler et al., 2010). Walking is a bilateral coordinated movement, but it is difficult to pinpoint if the corpus callosum is primarily responsible as other cortical and spinal regions are responsible for declines in coordination (Zandvoort et al., 2022). Thus, a more demanding and less automated bilateral motor coordination activity involving the lower limbs, like hopping, could reveal early signs of corpus callosum tract damage in older adults.

1.4 Agility in Older Adults

1.4.1 Overview of Agility

Agility is a term with various definitions (Sheppard & Young, 2006) but can be broadly defined as controlled whole-body movement involving speed, strength, power, balance, coordination, and both acceleration and deceleration (Young et al., 2021). Several tools exist to map functional declines in lower limb mobility and balance. Most involve asking people to rise from a chair, walk quickly, or balance on one foot. Notably, such tasks have ceiling effects in that older people can easily complete them, so subtle age-related changes are not measurable (Balasubramanian, 2015). For instance, the timed-up-and-go test is a simple measure that

assesses how long it takes an individual to sit up from a chair, walk 10 feet, turn around, and sit back in the original chair (Barry et al., 2014; Coelho-Junior et al., 2018). Although it is commonly used to assess lower limb function in community-dwelling older adults, it is not a significant measure of fall risk (Barry et al., 2014). Agility outcome measures are predominately reported as time using a stopwatch, which does not account for spatial measures of agility, and interrater reliability is reduced due to error (Chen et al., 2021). For walking, the safe ambulatory speed for community-dwelling older adults is between 80 cm/s and 120 cm/s (Middleton et al., 2015). However, simple walking and balance measures cannot detect subtle underlying age-related neuromuscular deficits that occur well before visible walking impairments (Balasubramanian, 2015; Barry et al., 2014). In multiple sclerosis, a disease of advanced neurodegeneration, the timed-25-foot-walk test was not a predictor of falls in people with no observable gait abnormalities (Abasiyanik et al., 2020).

Similarly, in community-dwelling older adults, the timed up and go was not a valuable predictor of falls and was not recommended as a primary clinical outcome measure (Barry et al., 2014). There is a need for more robust measures of functioning to uncover subtle changes in physical performance affected by aging. An agility test (propulsive bipedal hopping) has recently emerged as a promising assessment of lower limb functioning in multiple sclerosis, revealing hidden neuromuscular decline (Kirkland et al., 2017). Agile older adults have reported improved balance confidence and reduced fall risk (Donath et al., 2016; Liu-Ambrose et al., 2004; Rodrigues et al., 2023; Tollar et al., 2019), providing evidence of the importance of maintaining and enhancing agility with age (Donath et al., 2016). Older adults who complete agility exercise programs report overall increased strength (Castillo de Lima et al., 2023; Lichtenstein et al., 2020; Rodrigues et al., 2023), balance (Castillo de Lima et al., 2023), mobility (Reed-Jones et

al., 2012; Tollar et al., 2019), short-term memory and cognitive functioning (Castillo de Lima et al., 2023; Morat et al., 2020), and may also experience improved cardiovascular function (Morat et al., 2020). However, which agility test is best for identifying these beneficial effects and is useable as a clinical measure is yet to be determined.

1.4.2 Types of Agility Tests

Several agility tests exist to challenge humans with complex movements requiring the use of muscles, joints, and ligaments. While these measures of agility provide a higher degree of difficulty compared to simple walking tasks, most of these outcome measures are only temporal and recorded with a stopwatch, disregarding variables that correspond to strength and coordination that require more sophisticated methods of measurement (Balasubramanian, 2015). For instance, the ten-step test assesses the time it takes to alternately step on a raised block with each foot for ten rounds (Miyamoto et al., 2008). Another test, the 8-foot up-and-go test, measures the time to stand from a chair, walk to a target 8 feet away, turn around, walk back to the starting chair, and sit down (Rolenz & Reneker, 2016). Similarly, the agility challenge for the elderly is a more demanding test involving participants walking as fast as possible with acceleration, deceleration, changing directions, and stop-and-go movement in linear and diagonal directions (Lichtenstein et al., 2019). While the previously mentioned agility tests have strengths and weaknesses, it is essential to identify subtle lower limb deficits through challenging tests incorporating spatial measures. A new agility test (bipedal hopping) is capable of measuring performance based on spatial variables such as hop length distance and variability, and has exhibited potential as a clinical outcome measure of reduced agility in older adults and people

with multiple sclerosis (Kirkland et al., 2017). To date, there has yet to be a clear consensus on which agility test is best to use for assessing subtle lower limb deficits in older adults.

1.5 Bipedal Hopping

1.5.1 Neuromuscular Components of Bipedal Hopping

Bipedal hopping is a demanding task involving neuromuscular contributions of strength and neural control of balance and coordination through activation and inhibition of various lower limb muscles (Kirkland et al., 2017). At the muscular level, skeletal muscles undergo the stretch-shortening cycle quickly and intensely at various stages to propel the body forward during the hop (Kirkland et al., 2018; Kirkland et al., 2017; Kirkland et al., 2020). Secondly, balance symmetry is necessary to maintain the center of pressure within the base of support during the landing phase (Kirkland et al., 2020). Coordination of hopping requires the accurate firing of appropriate agonist and antagonist muscles in an efficient manner to counteract the task demands.

1.5.2 Biomechanical Hopping Stages

Bipedal hopping is a complex movement involving forward propulsion as both feet leave the ground during takeoff, followed by a return during the landing phase. There are five stages of movement during hopping, as depicted in Figure 1.1: isometric, concentric, airborne, eccentric, and landing phases (Kirkland et al., 2017; Smith, 2014). The isometric phase (shortest phase) transitions from eccentric to concentric contraction with no change in muscle fiber length. When the muscle fibers are stretched, afferent signals are sent to the spinal cord, which sends efferent signals to relieve the stretch, producing a muscle contraction. The concentric phase involves muscle fiber shortening, leading to the initiation of forward propulsion (airborne phase) during

hopping. This involves extension at the hips, knees, and ankles until the body reaches its highest point during the hop, acting as an indicator of lower limb muscle strength (Kirkland et al., 2018; Kirkland et al., 2017; Kirkland et al., 2020). The airborne phase occurs when both feet leave the ground before forward movement and ends when they return to the ground. The eccentric phase involves muscle fiber lengthening, leading to hip, knee, and ankle flexion through tonic muscle contraction of the gluteal, quadriceps, and calf (gastrocnemius and soleus) muscles, decelerating the lowering of center of gravity (absorption of energy) as the body returns towards the ground. The landing phase concludes the hop with both feet landing on the ground and transitioning back to the isometric phase to repeat the hopping cycle.

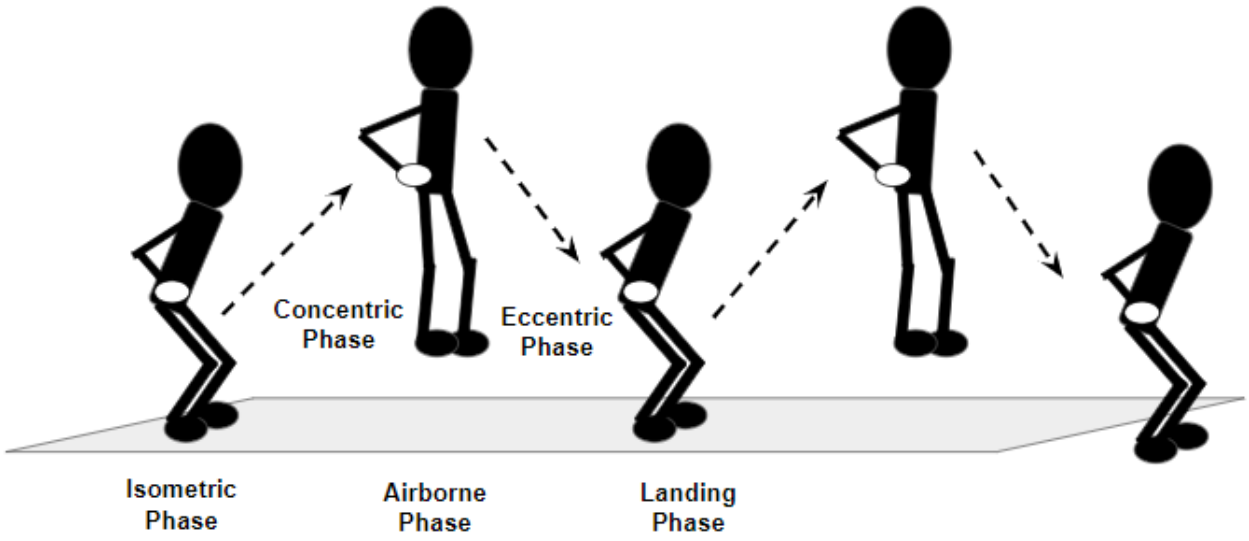

Figure 1.1 Biomechanical Hopping Stages

Representation of the biomechanical phases of hopping. The five hopping phases (isometric, concentric, airborne, eccentric, and landing) are completed for all hops along the instrumented walkway. Once participants hop off the walkway at one end, they turn around and hop back on the walkway to the end they started on. Original figure © Evan G MacKenzie.

1.5.3 How to Measure Bipedal Hopping

An efficient and accurate method of measuring hopping can be conducted on an instrumented walkway [i.e., ProtoKinetics Walkway (ProtoKinetics, Havertown, USA)]. A walkway contains load cells along the mat, forming a grid where increased activation and pressure of load cells from the feet during a hopping task transmit information to a computer. Depending on which cells become activated, footfalls are produced, and various hopping variables can be recorded and interpreted. Components of bipedal hopping that can be observed and measured on an instrumented pressure-sensitive walkway include hop length (cm), width (cm), time (s), symmetry/asymmetry index, consistency, and center of pressure (Kirkland et al., 2017; Kirkland et al., 2020). The hop length, a measure of lower limb strength, is the average distance from the heel strike of one hop (whichever heel lands first) to the location of the subsequent heel strike. Hop length coefficient of variation measures hopping consistency and coordination, taking the hop lengths performed during a trial and dividing them by the standard deviation of all hops. Both variables are depicted in Figure 1.2.

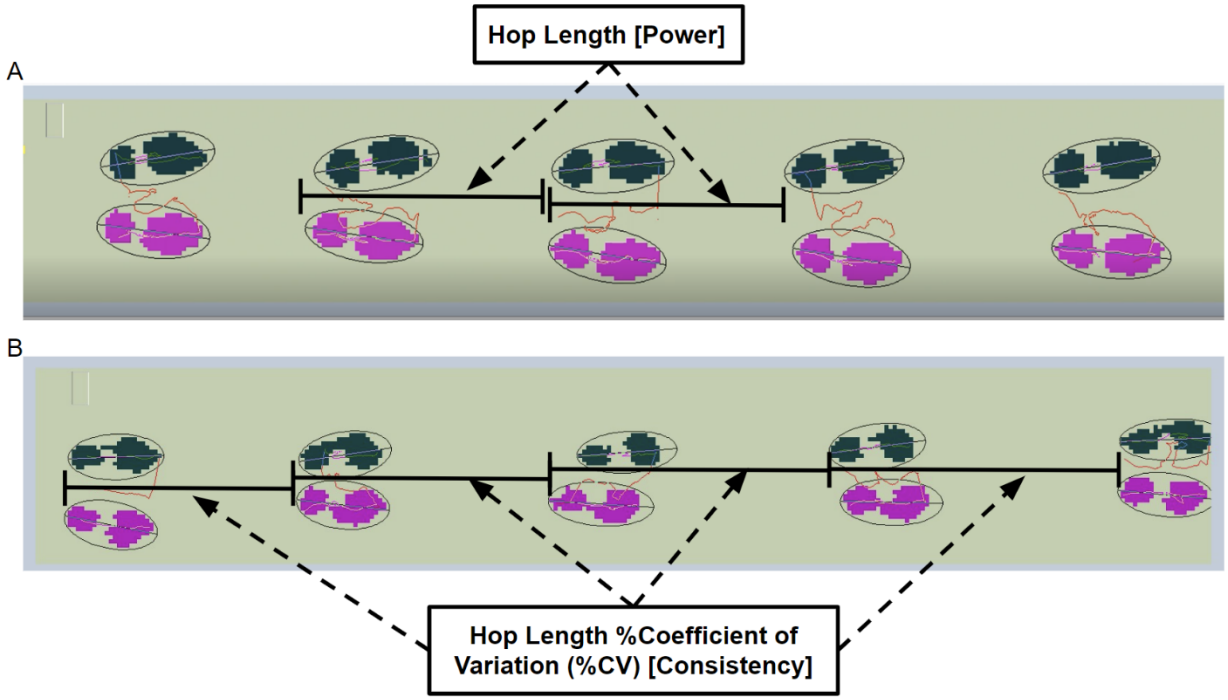

Figure 1.2 Bipedal Hopping Variables

Representative hopping footfalls derived from an instrumented walkway [i.e., ProtoKinetics Walkway (ProtoKinetics, Havertown, USA)]. The green and pink footprints represent the left and right feet, respectively. Panel A displays footfalls visually representing hop length (strength). This is a measure of distance (cm) from the heel of the first hop to the heel of the subsequent hop. All hop lengths are averaged to give a value of all hop lengths completed during the trial. Panel B provides a visual representation of hop length percent coefficient of variation. This is a measure of consistency and coordination of hopping, which calculates the variation of all hop length distances completed during the trial. Both Panel A and Panel B are the same scale and are from two different research participants to give a representation of each hopping variable. The thin lines within each foot and in between represent centre of pressure variables. Original figure © Evan G MacKenzie.

1.5.4 Hopping as a Measure of Agility

Hopping is a complex task that requires significant recruitment of neuromuscular resources instantaneously. Possessing the ability to hop is crucial as it is not always needed, but when it is, it prevents falls and other severe injuries. For instance, avoiding getting splashed by a car while walking on the sidewalk. As a result, it is critical that children learn and develop gross motor functional skills like hopping early in life. However, children with motor impairment demonstrate difficulty in hopping, so bilateral and unilateral hopping tests are typically performed as outcome measures (e.g., Movement Assessment Battery for Children) (Hands et al., 2015). Another example of hopping used as a measure is the Gross Motor Function Measure for children with physical impairments caused by cerebral palsy (Russell et al., 1989).

Additionally, hopping is used for various rehabilitation outcome measures. Children and adults in athletics recovering from anterior cruciate ligament injury or surgery frequently use jumping tasks to determine their capacity for return to sports (Davies et al., 2017; Myer et al., 2011). Patients recovering post-stroke perform the Chedoke-McMaster Stroke Assessment and complete one-legged hopping on the more affected side to assess the severity of impairment (Gowland et al., 1993). Similarly, the Community Balance and Mobility Scale involves hopping on one foot multiple times, which is validated as an outcome measure for those with a traumatic brain injury (Howe et al., 2006). As a result, hopping has been utilized to assess optimal lower limb functioning and possess the ability to assist in rehabilitation and improve outcomes. The previously mentioned tests that involve hopping are for conditions with evident lower limb impairments. Still, there is a need to identify subtle deficits in community-dwelling older adults at risk for eventual sharp decline in mobility and fall risk.

1.5.5 Effect of Age on Hopping

Age-related changes in neuromuscular functioning predominantly affect physically demanding gross motor tasks, such as hopping. Unsurprisingly, older adults demonstrate lower vertical jumping heights than younger people (Hoffren-Mikkola et al., 2015; Kirkland et al., 2022). Previously, work showed that horizontal hop length and hopping speed during a bipedal hop test are lower in people over 70 than in participants in their 40s (Kirkland et al., 2020). A recent study assessed the differences in bipedal hopping between young and older adults and people with low-severity multiple sclerosis (disease of advanced nervous system aging). Interestingly, they found that hop length decreased from younger adults to people with multiple sclerosis and older adults, while hop length variability (hop consistency and coordination) increased (worsened) (Kirkland et al., 2017). Similarly, when the same groups as the previous study hopped while using a metronome at 40 or 60 beats per minute, older adults still had shorter hop lengths and increased hop length variability (Kirkland et al., 2018). Additionally, hopping velocity was significantly increased, meaning older adults took longer and shorter hops when compared to younger adults and people with multiple sclerosis (Kirkland et al., 2018).

The underlying mechanisms relating to poorer hopping performance with age might be explained by the decreased muscle fiber cross-sectional area that cannot maintain explosive force production, leading to a shorter hop (Hoffren-Mikkola et al., 2015). Additionally, muscle stretching and shortening reduction are present in older adults, resulting in deficits during the concentric and eccentric phases of hopping (Elam et al., 2021). The knee extensors, necessary for the eccentric phase of hopping, experience increased fatigability and reduced strength in older adults due to disruptions in excitation-contraction coupling and cross-bridge formation (Greenberger & Paterno, 1995; Sundberg et al., 2018). With age, the connection and activation

of agonist and antagonist muscles are negatively affected. Older adults display inadequate agonist muscle activation during forceful and explosive movements, with increased antagonist activity (Narici & Maganaris, 2006). The dysfunction of muscle activation is prevalent during the landing phase of hopping as older adults have inadequate agonist muscle activity, resulting in reduced muscle force capacity to maintain optimal hopping (Hoffren et al., 2011).

Interestingly, physically active older adults performed similarly to non-active younger adults, demonstrating the effect of training on reducing the adverse effects of aging on hopping and lower limb functioning (Sanchez-Trigo et al., 2022). Those who complete hopping training reported improved gastrocnemius medialis muscle and Achilles tendon functioning. As a result, older adults demonstrate greater rapid force production capacity and better hopping ability (Hoffren-Mikkola et al., 2015; Hoffrén et al., 2012; Hoffren et al., 2011). Whether or not hopping as an agility test helps measure subtle changes in lower limb power, coordination, and balance as one ages is unknown.

1.6 Transcranial Magnetic Stimulation (TMS)

1.6.1 Neurophysiology of TMS

Transcranial magnetic stimulation (TMS) has developed into a promising tool capable of probing the integrity of the neuromuscular system, specifically the CST, to assess human performance (Matamala et al., 2013). TMS is a non-invasive neurophysiological technique used to stimulate the human brain and measure corticospinal excitability and the integrity of the CST within the spinal cord (Chaves et al., 2021; Rossini et al., 2015). This technique involves the application of a single, paired, or repetitive stimulus through a magnetic coil on certain parts of the brain, such as the primary motor cortex (Bashir et al., 2014; Opie et al., 2020). Electrical

currents flow through the coil, generating a perpendicular magnetic field that passes through the scalp and stimulates the corticospinal neurons in the primary motor area (Chaves et al., 2021). The descending CST is triggered, directly activating pyramidal tract neurons or indirectly through interneurons. Finally, a signal elicits a motor-evoked potential (MEP) in a targeted muscle. TMS is often paired with electromyography (EMG) to record the resulting muscle(s) activity. The neurophysiology of TMS is shown in Figure 1.3.

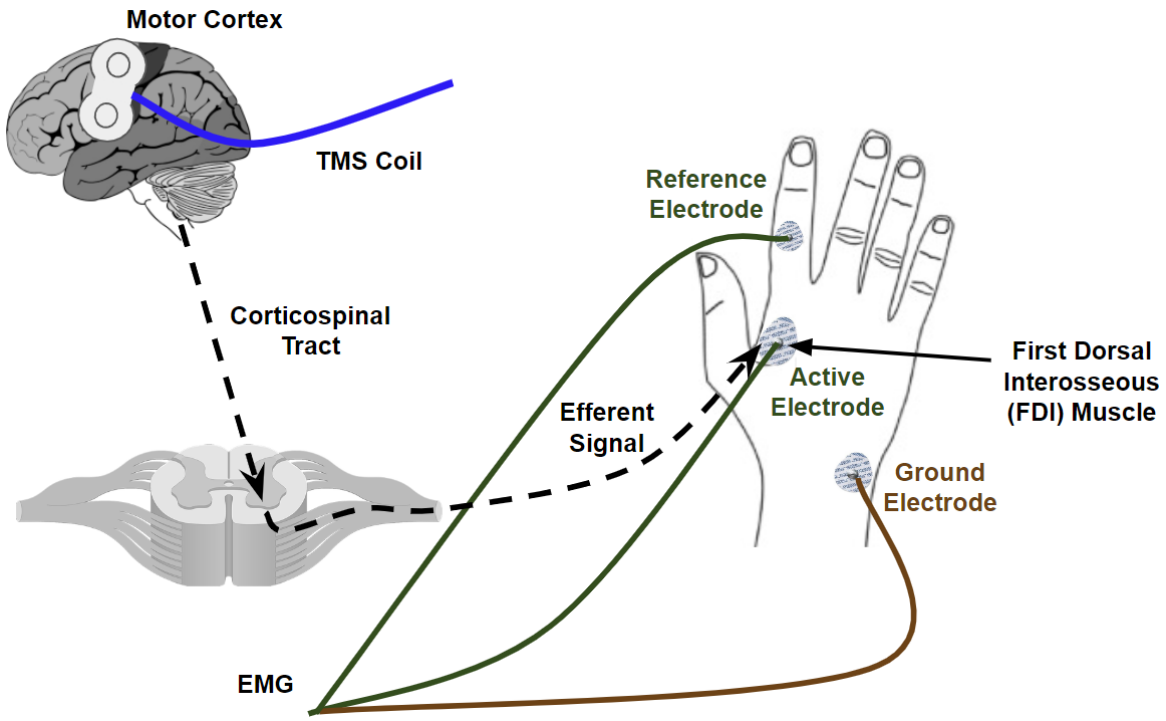

Figure 1.3 Neurophysiology of Transcranial Magnetic Stimulation

A visual representation of the physiological mechanisms behind the delivery of TMS. First, the TMS coil is placed along the motor cortex in the location that delivers the most reliable and efficient signal to the first dorsal interosseous (target muscle). Stimulation of the motor cortex elicits a signal that travels down the CST and delivers efferent signals through peripheral nerves to the first dorsal interosseous muscle, which produces a muscle contraction recorded through EMG by the active electrode. The reference electrode is placed on the interphalangeal joint of the first digit and acts as a reference to the values recorded by the active electrode. The ground electrode is placed on the ulnar styloid process, which improves the signal to noise ratio. Original figure © Evan G MacKenzie.

Practitioners can measure the speed at which neural signals are transmitted from the targeted motor cortex area, down through the spinal cord using the descending CST, and finally, to the muscle (Rossini et al., 2015). Through brain mapping, TMS facilitates the exploration of motor regions to determine areas responsible for sending signals and creating movement (McGregor et al., 2012). As the TMS coil moves across the primary motor cortex, specific muscles, such as those in the hand, arm, shoulder, and legs, become activated (Chaves et al., 2021). Trial-to-trial variability can occur if proper coil positioning and orientation are not maintained for each stimulated location (Rossini et al., 2015). TMS can measure differences between age groups, sexes, and those with neuromuscular disorders (e.g., multiple sclerosis, Parkinson's disease) (Brown et al., 2014; Chaves et al., 2021). However, age is only one of several factors that influence the trajectory of cortical plasticity, along with genetic, biological, and environmental factors (Pascual-Leone et al., 2011). The extent and severity of specific neurophysiological changes in CST functioning in older adults, measured using TMS, is unknown.

1.6.2 TMS Variables

1.6.2.1 Motor Thresholds

Motor thresholds are commonly measured TMS variables in older adults (Cabral et al., 2022; Hassanlouei et al., 2017; Houde et al., 2018; Rozand et al., 2019). They are considered the lowest TMS intensity (i.e., maximum stimulator output) through a magnetic field that can elicit a MEP (Chaves et al., 2021). There are two types of motor thresholds: resting motor threshold and active motor threshold. Resting motor threshold is completed during relaxation, whereas the active motor threshold is measured with light tonic activation of the targeted muscle (e.g., first

dorsal interosseous or vastus lateralis muscle) (Hassanlouei et al., 2017). To determine the resting motor threshold, we calculated the % maximum stimulator output, which is the lowest intensity that causes a peak-to-peak MEP amplitude of 50 μV or greater in at least 5/10 stimulation trials (Chaves et al., 2019; Chaves et al., 2021; Rossini et al., 2015). Active motor threshold requires a peak-to-peak MEP amplitude of 200 μV or greater as it involves a tonic muscle contraction that induces fast-conducting neurons in the CST (Chaves et al., 2021; Rossini et al., 2015). Individuals with a high resting motor threshold or active motor threshold have lower cortical excitability as it requires more intensity to elicit the MEP (Chaves et al., 2021). However, thresholds often differ between individuals and are affected by age, gender, coil placement, motor deficits, pharmacologic drug intake, hair thickness/colour, and scalp-to-cortex distance. (Alawi et al., 2023; Archer et al., 2024; Sollmann et al., 2017; Van Hoornweder et al., 2024).

Other variables derived from resting motor threshold and active motor threshold include latency (ms), a brief period of minimal activity (motor-evoked potential latency) before the motor-evoked potential can be observed from the EMG. After a motor-evoked potential, there is a cortical silent period (CSP) where the voluntary muscle contraction is interrupted, creating a long pause in EMG activity after a stimulation from TMS. This results from spinal cord and cortical ($GABA_B$ receptors) inhibition (Chaves et al., 2021). Compared to younger adults, older adults typically show a greater % maximum stimulator output to elicit a sufficient MEP response, lower MEP amplitudes, and longer latency and CSP (Bernard & Seidler, 2012; Fujiyama et al., 2012; Matamala et al., 2013; Tang et al., 2019). The usefulness of specific motor threshold variables as clinical biomarkers in older adults to examine reduced CST integrity and how that relates to agility performance are yet to be determined.

1.6.2.2 Excitatory and Inhibitory Recruitment Curves

Recruitment curves (REC), also referred to as "stimulus-response curves" or "input-output curves," measure the relationship between TMS stimulation intensity and either MEP amplitudes or CSP (Chaves et al., 2021; Rossini et al., 2015). RECs follow a sigmoidal shape, with an initial flat portion followed by a substantial rise in MEP or CSP gain and conclude with a plateau region (Chaves et al., 2021). Generally, increasing the intensity of TMS stimulation results in gradual increases in MEP amplitude and CSP (Rossini et al., 2015). RECs for hand muscles in healthy older adults exhibit strong reliability across subjects (Osnabruegge et al., 2023). Variables extracted from the RECs include slope, R^2, and area under the curve. Slope and R^2 measure corticospinal neurons' recruitment accuracy and gain, respectively (Chaves et al., 2021; Rossini et al., 2015) and are derived from the Boltzmann sigmoidal equation (TMS stimulus intensity × MEP amplitude). Area under the curve measures total excitation and inhibition of the corticospinal pathway, calculated using the trapezoidal rule ($\Delta X \times (Y1 + Y2)/2$) where X-values represent TMS intensity and Y-values represent either MEP amplitude or CSP time (Chaves et al., 2021). Area under the curve considers the total MEP amplitudes or CSP over a range of TMS intensities. Larger areas under the curve from MEPs indicate greater corticomotor output (Iyer & Madhavan, 2019). For CSP, research suggests that increased area under the curve represents a reduced capacity for long-term potentiation of the CST (Chaves et al., 2021). Generally, older adults have lower corticospinal excitability and increased inhibition (Levin et al., 2014; Opie et al., 2020; Rozand et al., 2019). However, active older adults demonstrate increased corticospinal excitability compared to age-matched inactive individuals, suggesting physical activity is a protective factor (Houde et al., 2018). Increased GABAergic

inhibition is prominent in older adults, especially those weaker and frail (Clark et al., 2015), and female subjects (Shibuya et al., 2016). Similarly, with motor thresholds, the exact excitatory and inhibitory mechanisms and testing procedures revealed through TMS and their clinical implications for agility in older adults are unknown.

1.7 Thesis Objective

The objective of this thesis was to explore the age-related changes in agility through the measurement of quadriceps strength and analyzing CST integrity. We aimed to answer the following research questions:

(1) What are the age-predicted differences in agility?
(2) Does quadriceps strength or CST integrity contribute to age-related differences in agility?

We hypothesize that increased participant age will result in decreased performance on our agility hopping task, including variables relating to power and coordination. Additionally, we expect reduced quadriceps strength and CST integrity to correlate with poorer performance on our agility hopping task caused by decreased neuromuscular capacity.

Chapter 2: Manuscript

2.1 Co-Authorship Statement

I would like to acknowledge the collaborative contributions of my fellow Recovery and Performance Laboratory members in preparation for this manuscript. Dr. Michelle Ploughman, my primary supervisor, designed and identified the research topic and proposal, and edited/revised and approved the final version of the manuscript. Dr. Nick Bray also edited and revised the manuscript and assisted with the data analysis. Syed Raza, Caitlin Newell, and Hannah Murphy assisted with participant recruitment, data collection, and data extraction. Syed Raza also assisted with analyzing the data. I conceived and designed the research topic, performed all experiments, analyzed data, interpreted results of experiments, prepared figures and tables, and prepared the manuscript.

2.2 Introduction

Agility helps us navigate complex and unpredictable environments; it reflects one's ability to quickly change their body position, relying on a combination of strength, endurance, balance, coordination, and reflexes (Morat et al., 2020). Even "normal" or typical aging induces complex neurophysiological changes that alter the neuromuscular system, including the central nervous system and skeletal muscle structures integral to agility (Hunter et al., 2016; McNeil & Rice, 2018; Wu et al., 2016). Age-related neuromuscular decline is associated with worse health outcomes (Buch et al., 2016; Cadore et al., 2019; Swiecicka et al., 2019). However, such decline may be delayed given that exercise programs incorporating agility training have improved balance (Lichtenstein et al., 2020; Liu-Ambrose et al., 2004; Tollar et al., 2019), reduced the risk of falls (Donath et al., 2016; Reed-Jones et al., 2012; Rodrigues et al., 2023), and enhanced

quality of life (Galan-Arroyo et al., 2022; Liu-Ambrose et al., 2005; Tollar et al., 2019), vitality (Bray et al., 2020; Labott & Donath, 2023), and brain health (Bray et al., 2023; Montero-Odasso et al., 2023). Measuring agility throughout the lifespan is challenging; typical sport-related agility field tests are inappropriate and preclude assessment of movement quality given that they focus on completion time (Coelho-Junior et al., 2018; Miyamoto et al., 2008; Pauole et al., 2000; Young et al., 2021). Currently, there is no gold standard agility measure suitable for aging adults.

Bipedal hopping, defined as an explosive, repetitive, horizontal jumping motion, is a measure of agility given that it comprises the necessary components (i.e., strength, endurance, balance, coordination, and reflexes). Several tools incorporate hopping or hopping elements to detect impairment, such as the Berg Balance Scale (Blum, 2008), Gross Motor Function Classification System (Palisano, 1997), and the Community Balance and Mobility Scale (Knorr et al., 2010). However, the tests are technically reserved for unique (clinical) populations, and each calculates hopping differently, making between-test comparisons challenging. Additionally, the tests primarily measure whether individuals can initiate and complete the hopping task independently. Exploring hopping spatiotemporal variables could provide further insight, potentially uncovering covert changes indicative of future impairment.

Several gait studies have demonstrated that analyzing spatiotemporal values via an electronic instrumented walkway provides additional insight over and above speed or completion time, especially for those experiencing subtle or prodromal neuromuscular changes. For example, among older adults at-risk of a dementia syndrome, Pieruccini-Faria et al. found stride time variability was positively associated with the risk of injurious falls (Pieruccini-Faria et al., 2020), and Montero-Odasso et al. demonstrated that dual-tasking altered gait variability more than speed (Montero-Odasso et al., 2020). Further, stride length, time, and variability uncover

gait abnormalities for multiple sclerosis patients despite low disability scores (Chen et al., 2020). Initial work from our group indicates that propulsive bipedal hopping completed on an electronic walkway detects subtle lower limb agility impairments in individuals living with multiple sclerosis (Kirkland et al., 2018; Kirkland et al., 2017; Kirkland et al., 2022). More specifically, people with multiple sclerosis showing "normal" neurological exams and unimpaired walking demonstrate covert agility declines uncovered through propulsive bipedal hopping (Kirkland et al., 2018; Kirkland et al., 2017). No previous work has explored if propulsive bipedal hopping on an instrumented walkway is useful in detecting subtle age-related agility deficits, nor the underlying neuromuscular changes that may be responsible for such deterioration.

Transcranial Magnetic Stimulation (TMS), a non-invasive brain stimulation technique, probes the functional integrity of the corticospinal tract (CST); the main motor pathway that controls trunk and limb movement (Chaves et al., 2021). TMS generates electrical currents over the motor cortex to induce motor-evoked potentials (MEPs) in targeted muscles measured via electromyography (Rossini et al., 2015). TMS is a useful tool for probing the integrity of human motor pathways as several age-related neuromuscular function studies have identified CST changes, such as decreased CST excitability, lower MEPs, and reduced voluntary muscle activation (Hassanlouei et al., 2017; Rozand et al., 2019; Swanson & Fling, 2020). Similarly, age-related decline at the muscular level is well documented. For example, altered muscle architecture via changes in fiber characteristics results in reduced muscle strength (Wu et al., 2016), and decreased neuromuscular junction efficiency disrupts the neuron-muscle connection to affect motor performance (Dobrowolny et al., 2021; Hunter et al., 2016). More broadly, muscle atrophy is a global health concern for all older adults (Keevil & Romero-Ortuno, 2015). Whether CST integrity or muscle strength predicts age-related differences in agility has not been

examined; however, exploring the underlying physiology of the covert clinical manifestations detected by propulsive bipedal hopping on an instrumented walkway could enhance our understanding and subsequently help create more effective intervention strategies.

To this end, we recruited a healthy group of non-athletic middle to older-aged (30+ years of age) adults to determine whether CST integrity (i.e., upstream nervous system) or muscle strength (i.e., downstream muscle) more strongly predicts propulsive bipedal hopping spatiotemporal properties. We hypothesized that both muscle strength and CST integrity would significantly contribute to agility.

2.2 Materials and Methods

2.2.1 Participants

After receiving Health Research Ethics Board approval (#2021.210), participants provided informed written consent to attend a 2-hour visit, where we collected demographics, strength, CST integrity, and propulsive bipedal hopping (more details below). Participants met the following inclusion criteria: (1) ≥ 30 years of age; (2) able to jump forward two times consecutively; (3) no pain, inflammation, or sprains in any region of the lower body; (4) able to walk indoors without an assistive gait device (e.g., cane, walker, etc.); (5) no prior surgeries on their back or lower body; (6) not a competitive athlete in a high-performance sport (e.g., marathon runner, triathlon athlete, etc.); (7) met all TMS safety requirements (Rossini et al., 2015); and (8) walking speed ≥120 cm/s, a safe minimum speed for community ambulation (Salbach et al., 2014).

2.2.2 Sample Size

We calculated the sample size using G*Power software, Version 3.1.9.4 (Aichach, Germany). According to a regression analysis with alpha set at 0.05, power at 0.80, a large effect size ($f^2 = .35$), and three predictors, we required a minimum of 20 participants. However, we increased this value (n=32) allowing for incomplete data and outliers.

2.2.3 Demographics

We collected participants' chronological age (years) and biological sex (i.e., sex assigned at birth). We measured height (centimeters; cm) and weight (kilograms; kg) and, by extension, body mass index (kg/m^2) using a Health-O-Meter Professional scale (McCook, IL, USA). Using a tape measure, we calculated leg length (cm) from the anterior superior iliac spine to the medial malleolus of the right leg (Bolz & Davies, 1984).

2.2.4 Quadriceps Strength

We quantified muscle strength using the quadriceps given its role in hopping. We measured quadriceps strength using a Manual Muscle Tester (Unit 01165, Lafayette Instrument, Lafayette, IN, USA). Participants sat on an elevated table with their arms placed across their chest and legs hanging over the table. The examiner positioned the Muscle Tester across the anterior tibia, ~5 cm superior to the lateral malleolus, using a strap looped through the dynamometer and secured to the table leg. As such, the participant's knee was flexed to ~90°. Participants performed a maximum voluntary contraction after being instructed to "extend at the knee as hard as possible for five seconds." Force outputs during contractions were measured in kg. The testing order was randomized, and the participant completed the protocol twice on each leg, with all four (i.e., two on the left side and two on the right side) scores averaged into a single

leg strength score. Previous work has demonstrated that this leg strength protocol possesses strong validity (Lesnak et al., 2019).

2.2.5 Measuring Corticospinal Tract Integrity Using Transcranial Magnetic Stimulation

Pinch strength (kg) was required to determine the participant's weaker hand for our TMS protocol. We used a pinch gauge (B&L Engineering, Santa Ana, CA, USA) and participants placed the gauge between their thumb and index finger (i.e., thumb on top and the index finger below) while sitting in an upright position with no back support, feet firmly on the ground, and elbow flexed to 90°. Participants performed a maximum voluntary contraction after being instructed to "pinch as hard as possible for five seconds." Participants completed the task twice on each side, with the average force (kg) calculated for each hand separately.

We started by cleaning and debriding the skin surface before attaching surface electromyography electrodes (Kendall 200 Covidien, Mansfield, MA) over the first dorsal interosseus muscle (active electrode), the proximal interphalangeal joint of the index finger (reference electrode), and the ulnar styloid process (ground electrode). The first dorsal interosseous muscle is prominently used to measure active motor threshold in healthy individuals (Houde et al., 2018; Rozand et al., 2019) and previous works indicate TMS variables derived from the upper limb are representative of overall CST integrity (Singh et al., 2014; Walsh et al., 2019). A built-in electromyography system used 2500V/V amplification and collected at a 3kHz sampling rate with a gain of 600V/V and a bandwidth of 16-550Hz. Electromyography data were analyzed using Signal Software, version 6.06 (Cambridge Electronic Design Ltd, Cambridge UK).

As per previous recommendations, we targeted the hemisphere corresponding to the weaker hand (i.e., lower pinch strength) as it provides stronger and more consistent predictors of

clinical outcomes (Chaves et al., 2021). With the participant in a seated position, we used Neuronavigation (Brainsight, Rogue Research Inc, Montreal, QC, Canada) to guide head and coil positioning. Using monophasic magnetic posterior-anterior pulses from a BiStim 200^2 stimulator (Magstim Co. Whitland, UK), we administered single-pulse TMS with the coil placed tangentially to the scalp and held at a 45° angle from the midline perpendicular to the central sulcus. We stimulated positions along the primary motor area at a supra-threshold intensity to determine the motor "hotspot" or the location with the greatest response as per MEP peak-to-peak amplitude measured in microvolts (μV) (Chaves et al., 2021).

After identifying the hotspot, we performed two TMS protocols. First, the active motor threshold protocol required the participant to hold 10% of their maximum voluntary contraction pinch, as determined via the pinch gauge test, during TMS stimulation. Active motor threshold represents the maximum stimulator output obtained in 5 out of 10 MEP responses ≥200μV. A higher active motor threshold indicates lower excitability and, therefore, reduced CST integrity. Second, we executed a recruitment curve (REC) protocol by stimulating participants six times each at six supra-threshold intensities (36 separate stimulations): 105%, 115%, 125%, 135%, 145%, and 155% of the active motor threshold. For each pulse, 1-second-long sweeps collected electromyography activity from 100 ms before the TMS pulse to 900 ms afterwards. We calculated the excitatory REC using the average MEP amplitudes during the 6 supra-threshold intensities (Chaves et al., 2019; Chaves et al., 2021). Similarly, we calculated the inhibitory REC by taking the average CSP at each supra-threshold intensity (Chaves et al., 2019; Chaves et al., 2021). The CSP represents the time (ms) between MEP onset (time of MEP exceeding ± 2SD from background electromyography activity) and returning electromyography activity (Rossini et al., 2015). We determined the area under the excitatory and inhibitory MEP RECs using the

trapezoid integration technique (Potter-Baker et al., 2016; Talelli et al., 2008). The excitatory MEP REC reflects voltage-gated ion channel and glutamatergic activity (Rossini et al., 2015; Ziemann et al., 2015), while the inhibitory MEP REC indexes the excitability of GABAergic corticospinal neurons (Rossini et al., 2015; Ziemann et al., 2015). In summary, our TMS variables of interest include the: 1) (excitatory) active motor threshold; 2) area under the curve for the excitatory REC; and 3) area under the curve for the inhibitory REC.

2.2.6 Propulsive Bipedal Hopping Agility Test

Before proceeding to the propulsive bipedal hopping agility test, we measured participants "comfortable" gait speed (cm/s) via an 18ft (length) by 3ft (width) ProtoKinetics Zeno Walkway (ProtoKinetics LLC, Havertown, PA) and ProtoKinetics Movement Analysis Software (PKMAS; ProtoKinetics LLC, Havertown, PA). Before executing a gait trial, participants received a demonstration from the assessor and the following instructions: "When I say 'GO,' please walk to the X at the other end of the mat at a comfortable pace. Once you reach the X, immediately turn around and walk back down the mat to the X at this end. You will do two lengths of the mat." As such, participants completed two lengths (i.e., up – back) with one turn as part of a single gait trial. All participants began and finished at the same end of the track and started, finished, and turned ~1 meter before/after the walkway end (i.e., the marked X) to avoid recording acceleration/deceleration phases. Two trials of walking were completed with approximately one minute of rest in between trials (Chen et al., 2020). Participants with gait speed <120 cm/s did not proceed to the agility test, however there were no participants excluded based on this criteria. This protocol was to ensure participants could safely progress to the agility test. Using the same walkway, participants performed propulsive bipedal hopping agility test via multiple forward displacement jumps with both feet synchronously (i.e., leaving and returning to

the ground together) (Kirkland et al., 2022). Following a demonstration by the examiner, participants were provided with instructions similar to the comfortable gait task, with the exception being to place their hands on their hips and "hop as fast and safely as possible." Due to the physical demands, participants performed only one trial. However, participants could restart if they made an error, such as landing on the sides of the walkway where only partial footfalls are recorded or failing to complete the proper hopping technique. Hopping variables extracted from the walkway included: 1) hop length (cm) or the distance from the heel contact of one hop to the heel contact of the following hop; and 2) hop variability as per the coefficient of variation for hop length or the difference of all hop lengths (Figure 2.1). To account for anthropometric differences, we adjusted hop length for leg length (Davies, 1988; Kirkland et al., 2022). We recorded all hopping tests with a Logitech C920 Carl Zeiss HD 1080p Webcam (Logitech, San Jose, Ca) to qualitatively confirm hopping accuracy.

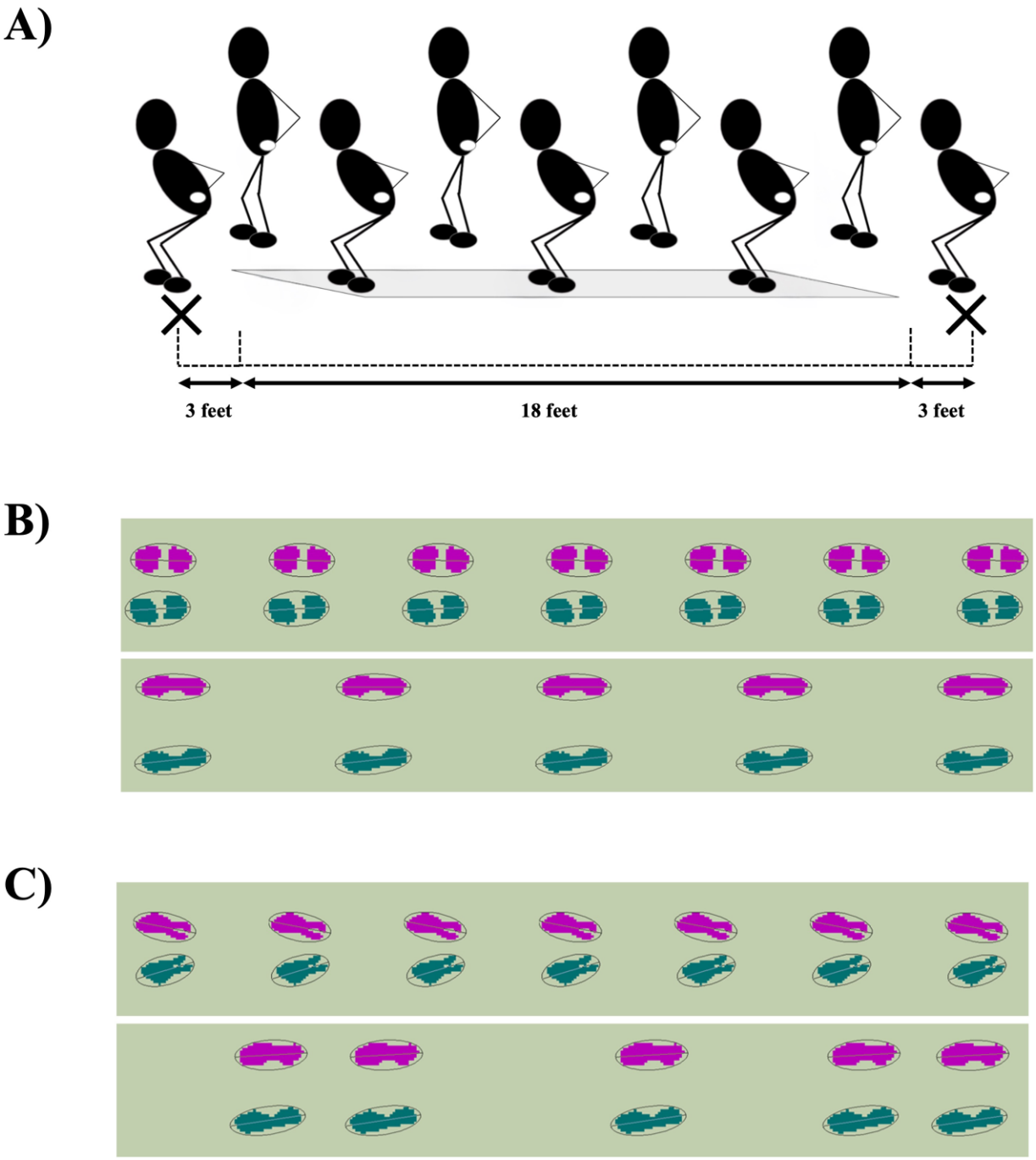

Figure 2.1 Propulsive Bipedal Hopping Protocol and Analysis

Panel A) Participant completing the bipedal propulsive hopping protocol. The total hopping distance is 48 feet ([18 feet [electronic mat] + 6 feet [to negate acceleration/deceleration] x 2 [turns of track]). **Panel B)** Example of participants with different hop lengths (top is shorter than the bottom). **Panel C)** Example of participants with different hop length variability (top is less variable or more consistent than the bottom). Original figure © Evan G MacKenzie.

2.2.7 Statistical Analysis

All statistical analyses were conducted in IBM SPSS Statistics, version 27 (IBM Corp, Armonk, NY), with a p-value < 0.05 indicating statistical significance. With the exception of sex, participant characteristics (i.e., age, height, weight, body mass index, and leg length) and outcomes (i.e., gait speed, quadriceps strength, CST integrity, and hopping variables) were reported as mean ± standard deviation.

First, we identified outliers as (raw) data points ±3 times the interquartile range in our variables of interest. We used Pearson correlations to clarify relationships between quadriceps strength, CST integrity (i.e., active motor threshold and area under the curve for excitatory/inhibitory REC) and bipedal hopping variables (i.e., hop length and hop length variability). Correlations between variables were considered weak at $r < 0.30$, moderate at $0.30 < r < 0.70$, and strong at $r > 0.70$. Only independent variables (i.e., quadriceps strength and CST integrity) demonstrating significant correlations with the dependent variables (i.e., hop length and hop length variability) proceeded to multivariate regression analyses.

Model 1 of our regression controlled for a single covariate, sex. We did not control for age as we expected it to impact the dependent variables given the age range of included participants. Model 2 included sex and a single independent variable (i.e., muscle strength or CST integrity); this approach was repeated for every independent variable that demonstrated a significant correlation with our dependent variables (i.e., hop length and hop length variability). All regressions satisfied the following assumptions: 1) Independence of observations via a Durbin-Watson statistic ranging from 1.5-2.5 (Draper & Smith, 1998); 2) Collective linearity of the independent variables or predictors, as well as homoscedasticity, via visual inspection of a scatterplot containing studentized residuals and (unstandardized) predictive values; 3) Linearity

of each independent variable or predictor via visual inspection of partial regression plots; 4) Absence of multicollinearity via a tolerance value >0.1 and variance inflation factor value <10 (Hair et al., 2014); 5) No unusual points, including outliers via studentized deleted residuals values >±3 and leverage points >0.2 or influential points via cook's distance >1 (Cook & Weisberg, 1982); and 6) Normality via visual inspection of the standardized residuals histogram and Q-Q plot.

2.3 Results

Our 32 participants (14 male, 18 female) were 55.75 ± 14.22 years of age, 168.35 ± 9.12 cm tall, weighed 74.80 ± 18.39 kg, and possessed a leg length of 87.33 ± 6.71 cm (Table 2.1). As expected, age was moderately correlated with hop length (r = -.671, p < .0001) and hop variability (r =.423, p =.016) (Figure 2.2). Hop length and hop variability were moderately correlated with quadriceps strength (Figure 2 Panel A: r =.581, p <.001; Figure 2 Panel B: r = -.384, p =.039) and active motor threshold (Figure 2 Panel C: r = -.364, p =.048; Figure 2 Panel D: r =.478, p =.007). We found no significant correlation between the excitatory or inhibitory RECs and hop length or hop length variability (p >.644); therefore, excitatory and inhibitory RECs did not proceed to the regression analysis.

Table 2.1 Participant characteristics

Characteristic	Mean ± SD	Range
***n*(female)**	32(18)	
Age (Years)	55.75 ± 14.22	31-84
Height (centimeters)	168.35 ± 9.12	155.50-187.60
Weight (kilograms)	74.80 ± 18.39	49.10-138.40
Body Mass Index	26.12 ± 4.67	19.97-41.78
Leg Length (centimeters)	87.33 ± 6.71	74.00-102.00
Gait Speed (centimeters/second)	171.62 ± 20.78	132.05-216.12
Quadriceps Strength (kilograms)	34.37 ± 9.18[a]	20.68-61.85
Hop length (centimeters)	85.51 ± 30.68	24.73-155.04
Hop Length Variability	9.56 ± 5.42	1.64-23.65
Active Motor Threshold (%MSO)	33.03 ± 9.35[b]	20-56
Excitatory REC AUC	51,724.48 ± 16,959.65[b]	24,995-87,970
Inhibitory REC AUC	5,243.23 ± 1,229.38[b]	2,896-7,447

Note. SD = standard deviation; % MSO = percentage of maximum stimulator output; REC = recruitment curve; AUC = area under the curve. [a]n = 29; [b]n=30.

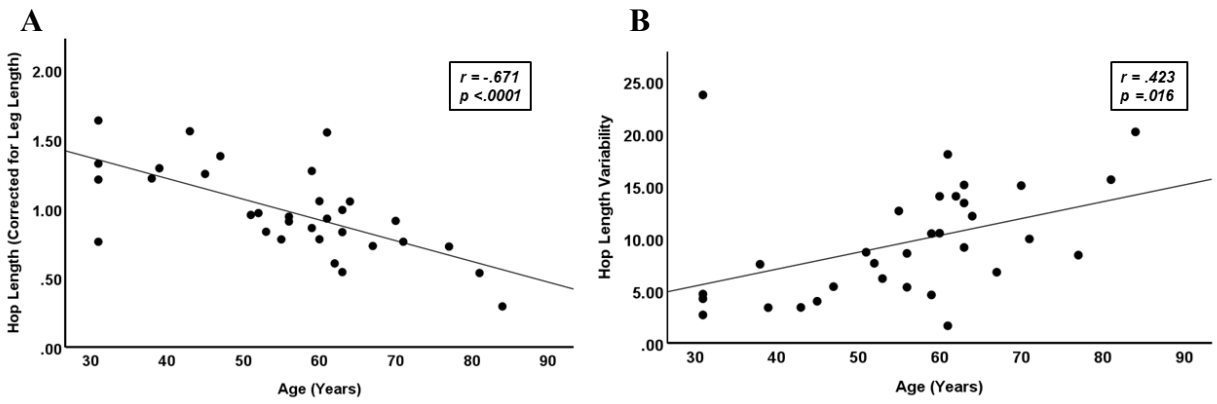

Figure 2.2 Scatterplots of propulsive bipedal hopping variables and age

Age (years) is significantly correlated with hop length (Panel A) and hop length variability (Panel B).

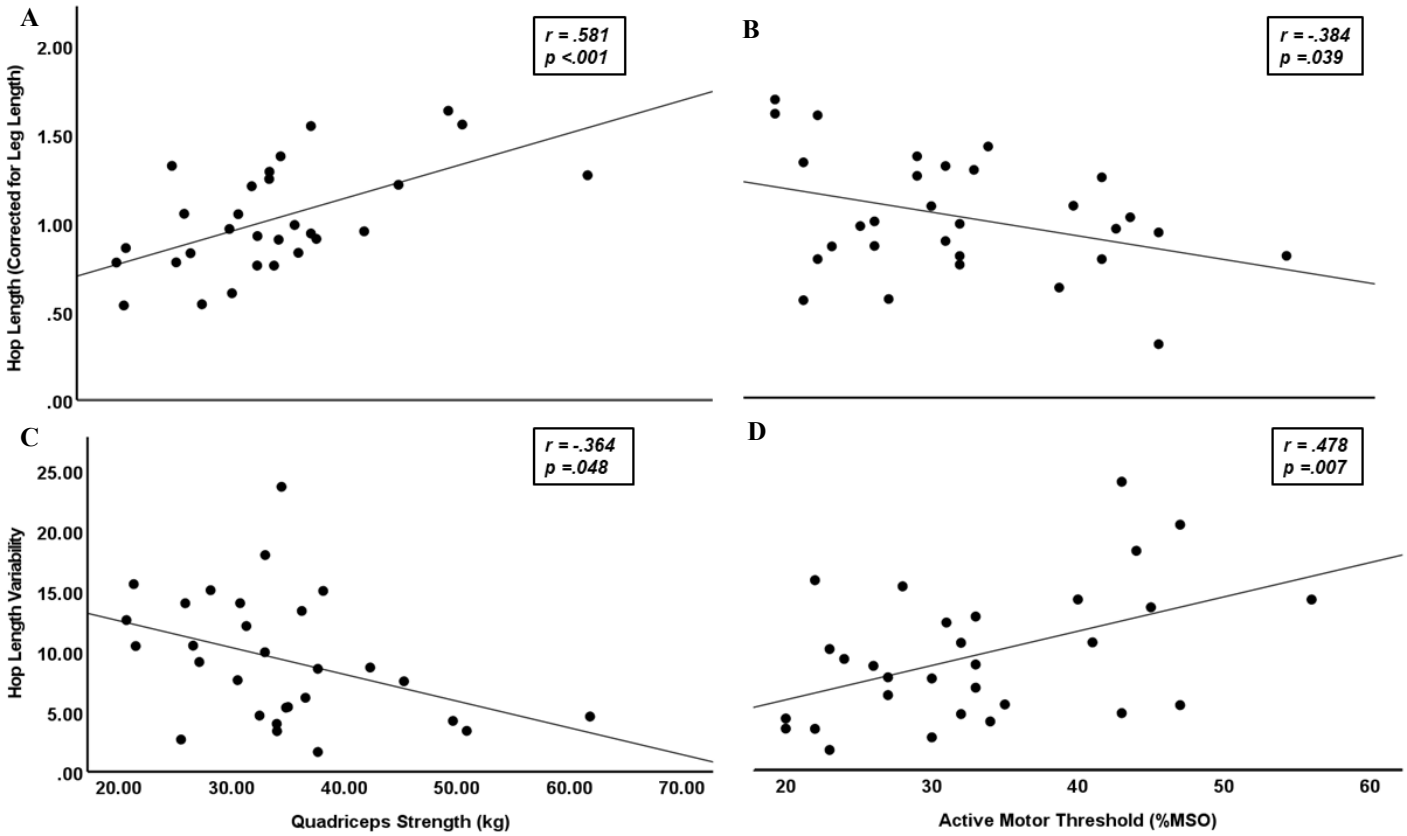

Figure 2.3 Scatterplots of propulsive bipedal hopping variables, quadriceps strength, and Active Motor Threshold

Quadriceps strength (kg = kilograms) is significantly correlated with hop length (Panel A) and hop length variability (Panel B). Similarly, active motor threshold (%MSO = percentage of maximum stimulator output) is significantly correlated with hop length (Panel C) and hop length variability (Panel D). For hop length variability, higher values indicate more variability in hopping distance.

2.3.1 Quadriceps Strength Predicts Hop Length while Active Motor Threshold Predicts Hop Variability

After controlling for biological sex, quadriceps strength significantly explained 31.1% of hop length (R^2 =.345, p =.002; Table 2). Therefore, hop length increased by one centimeter for every 0.311 kg increase in quadriceps strength. Active motor threshold did not significantly explain hop length (R^2 =.143, p =.075; Table 3).

After controlling for sex, quadriceps strength did not significantly explain hop variability (R^2 =.148, p =.069; Table 2). However, active motor threshold significantly explained 19.6% of hop length variability (R^2 =.239, p =.014; Table 3). Therefore, hop length variability increased by one unit for every 0.196% maximum stimulator output increase in the active motor threshold.

Table 2.2 Quadriceps strength but not active motor threshold predicts hop length

Model	Variables	β	R	R^2	Adjusted R^2	R^2 Change	F Change	Sig. F Change
1	**Sex**	.866	.185	.034	-.002	.034	.953	.338
2	**Sex and Quadriceps Strength**[a]	.408	.587	.345	.294	.311	12.331	.002
1	**Sex**	.821	.184	.034	-.001	.034	.980	.331
2	**Sex and Active Motor Threshold**[b]	1.281	.378	.143	.080	.109	3.441	.075

Note. Linear regression model. Dependent Variable: Hop length (measured in centimeters). Independent Variables: Sex, Quadriceps Strength (measured in kilograms), and Active Motor Threshold (AMT) (measured in percentage of maximum stimulator output). *B* = Unstandardized beta. [a]n=29; [b]n=30.

Table 2.3 Active motor threshold but not quadriceps strength predicts hop length variability

Model	Variables	β	R	R^2	Adjusted R^2	R^2 Change	F Change	Sig. F Change
1	**Sex**	11.924	.173	.030	-.006	.030	.832	.370
2	**Sex and Quadriceps Strength**[a]	16.974	.384	.148	.082	.118	3.597	.069
1	**Sex**	12.643	.206	.042	.008	.042	1.239	.275
2	**Sex and Active Motor Threshold**[b]	2.157	.488	.239	.182	.196	6.956	.014

Note. Linear regression model. Dependent Variable: Hop length variability (measured as the coefficient of variation). Independent Variables: Sex, Quadriceps Strength (measured in kilograms), and Active Motor Threshold (measured in percentage of maximum stimulator output). *B* = Unstandardized beta. [a]n=29; [b]n=30.

2.4 Discussion

We undertook this study to determine whether performance on an agility task was influenced by muscle strength or CST integrity. We report three main findings. First, older age was associated with shorter hop length and greater hop length variability supporting the use of the propulsive bipedal hopping agility test to detect age-related changes in agility. Additionally, biological sex was not predictive of agility in the model. Secondly, quadriceps strength predicted hop length, but CST excitability did not. Finally, lower CST excitability (higher active motor threshold), but not quadriceps strength, predicted greater hop variability, an indicator of incoordination and inconsistency in agility.

2.4.1 Measuring age-related changes in agility using a propulsive bipedal hopping test

The propulsive bipedal hopping agility task is a novel complex and intricate assessment of human movement. Previous work in individuals diagnosed with multiple sclerosis (but without sensorimotor disability) found bipedal hopping performance was similar to that of older adults in terms of muscle strength (hop length), power (hop length and hop velocity), and inter-limb coordination (symmetry) (Kirkland et al., 2018; Kirkland et al., 2017; Kirkland et al., 2022). Specifically, older adults (> 70 years old) demonstrated significantly poorer muscle strength and power (decreased hop length) and coordination (center of pressure path efficiency percentage, integral pressure variability, hop length variability, hop time variability, and stance percentage variability) in comparison to people with multiple sclerosis and healthy adults (18-69 years old) (Kirkland et al., 2017).

Commonly used agility tasks are limited for older adults as many protocols emphasize temporal outcome measures such as speed and time, excluding quality of movement (Coelho-Junior et al., 2018; Miyamoto et al., 2008; Pauole et al., 2000; Young et al., 2021). For example,

the timed up and go test is hindered as an agility measure as it only records the time using a stopwatch and does not assess the participants quality of the movement to complete the task. Another measure, the ten step test, measures agility by participants stepping on a 10 cm step alternating their foot each time as quickly as possible for 10 rounds (Miyamoto et al., 2008). As with the timed up and go test, the ten-step test is measured using a stopwatch and involves minimal coordination to place the foot on top of the step. Finally, the agility challenge for the elderly is a more dynamic agility test involving stop-and-go, change of direction, and spatial orientation segments (Lichtenstein et al., 2019). While this task is an improvement over prior tests regarding task difficulty, it only uses temporal measures of agility. Although we currently use a laboratory-based instrumented walkway and its associated software to extract hopping spatiotemporal variables, portable applications offer promise to capture the same precise data simply and in real-world environments (Gallardo-Fuentes et al., 2016; Whiteley et al., 2023). Furthermore, machine learning applied to continuous pressure data from the walkway may reveal novel variables not extracted using conventional approaches (Hu et al., 2022a, 2022b). Future work should examine longitudinal changes in agility and whether extracted variables are associated with more obvious changes in agility such as falls or confidence in activities of daily living.

2.4.2 Quadricep strength is an indicator of hop length while the corticospinal tract is linked to hop variability

Agility tasks require greater strength, power, and inter-limb coordination than walking, balancing, obstacle negotiation, and dual-task walking, which are frequently used measures in assessing movement (Barry et al., 2014; Conradsson et al., 2018; Miyamoto et al., 2008). In the current study, our results show hop length and hop variability are predicted by muscle strength and CST integrity, respectively. Hop length may represent contributions specifically from the

muscular system while hop variability could be nervous system induced. Alterations in lower limb muscle properties are prevalent in post-anterior cruciate ligament surgery. He et al. assessed quadricep and hamstring muscle function during a single-leg hop test in 30 individuals after anterior cruciate ligament reconstruction. They reported smaller hop length and height was associated with reduced muscle strength and peak torque in both quadricep and hamstring muscles along with delayed quadricep activation onset in the involved limb (He et al., 2022). In a similar study from Kotsifaki et al., hop length was decreased along with a lower reactive strength index, greater hamstring muscle contribution, but lower soleus contributions in the involved limb (Kotsifaki et al., 2022). Research shows muscle strength reduces with age due to Type I and Type II muscle fiber atrophy (McNeil & Rice, 2018; Power et al., 2013), motor unit loss and reduced motoneuron discharge rates from nervous system maladaptation (Hunter et al., 2016; Orssatto et al., 2022), and neuromuscular junction efficiency (Dobrowolny et al., 2021). However, age-related changes in the CST involve adaptations of the tract and cortical regions, such as reduced interhemispheric inhibition (later onset and shorter ipsilateral silent period), leading to deficits in interhemispheric communication and decreased muscle representation along the motor cortex (Coppi et al., 2014). Generally, studies report that the active motor threshold increases (decreased corticospinal excitability) with age (Bhandari et al., 2016; Rozand et al., 2019). Although no studies have linked agility to age-related changes in the central nervous system, other outcomes, such as gait and postural control, elucidate age-related alterations in the way cortical brain regions communicate. For instance, among older adults, standing requires greater activation of corticospinal pathways compared to younger adult cohort (Baudry et al., 2014). The CST reveals age-related deficits in the neuromuscular system, providing insight to specific mechanisms that underlie age-related reduced balance and postural control (Baudry,

2016; Baudry et al., 2015; Baudry et al., 2014; Hassanlouei et al., 2017). For instance, one study determined the corticospinal pathway becomes more activated and responsible for controlling leg muscle activity compared to spinal pathways in older adults compared to younger and middle-aged adults (Baudry, 2016). Future studies should investigate the contributions of muscle strength and the CST for specific biomechanical phases of propulsive bipedal hopping.

2.4.3 Study Limitations

Our study has several limitations. Our data is cross-sectional and therefore cannot account for age-related declines in muscle strength and CST integrity over time. Future research should measure the relationship between agility and the CST across the lifespan longitudinally, exploring early onset neuromuscular aging and risk of falls. Additionally, lifestyle factors such as physical activity were not included in our analysis and could contribute to the relationship between agility and the CST.

2.5 Conclusions

In the current study, we examined associations between agility and active motor threshold in a sample of healthy non-athletes with no walking impairments. We found a strong correlation between age and our hopping variables (hop length and hop variability). Hop length was a strong predictor of hop length while hop variability was predicted by alterations in the CST when accounting for sex. This study provides evidence that lower limb agility is a robust indicator of age-related adaptations in CST in healthy non-athletic individuals and a potential tool capable of revealing subtle age-related changes in neuromuscular functioning.

2.6 Grants

Funding: M.P. received funding from The Canadian Institutes for Health Research [Grant #s: 169649, 173526], Newfoundland and Labrador Research and Development Corporation

[Grant #: 5404.1699.104], and Canada Foundation for Innovation [Grant #: 33621]. M.P. is currently receiving funding from the Canada Research Chairs Program [Grant #: 230457].

2.7 Disclosures

The authors declare no conflicts of interest.

2.8 Disclaimers

No government agency work.

Chapter 3: Discussion

3.1 Overview of Key Findings

The purpose of this study was to investigate whether muscular strength or CST integrity measured using TMS were age-related contributors to agility using the propulsive bipedal hopping test. Based on previous findings, we measured hop length (lower limb strength) and hop variability (lower limb coordination) as our propulsive bipedal hopping variables. We analyzed TMS-derived variables active motor threshold (maximum stimulator output), and excitatory and inhibitory recruitment curves (area under the curve using MEP and CSP, respectively) as proxies of CST integrity. We hypothesized that both muscular strength and CST integrity would be predictors of agility (hop length and hop length variability). Interestingly, only active motor threshold correlated with our hopping variables. Additionally, active motor threshold predicted hop length variability, but not hop length. In interpreting our results, we propose that the propulsive bipedal hopping test involves unique and specific neuromuscular contributions that depend on the hopping variable measured. Gross motor output (i.e., hop length) was largely determined by muscular capacity (i.e., quadriceps strength) while more complex and intricate hopping variables that required greater amounts of coordination and balance (i.e., hop length variability) demanded more CST involvement (active motor threshold). This study was accompanied by limitations and challenges, which are discussed in the following section.

3.2 Limitations and Challenges

There are some limitations that could have influenced our results. Primarily, our sample was homogenous with the majority of participants being Caucasian, English speaking Canadians, which limits the generalizability of our results on a global scale. Our sample contained healthy, non-athlete participants with no previous lower limb injuries. However, we could not account for

those with underlying conditions such as arthritis or osteoporosis that may affect agility performance on the propulsive bipedal hopping test. Additionally, our exclusion criteria may have inadequately represented our older participant demographic as we could not include those with an existing mobility impairment, which is prevalent in older adults (Musich et al., 2018). Recent findings suggest that muscle power (maximal strength over a period of time) rather than muscle strength is a stronger outcome measure of functional lower limb decline with age (Reid & Fielding, 2012). Comparing muscle power of the quadriceps rather than strength to performance on propulsive bipedal hopping may reveal unique neuromuscular alterations that occur in older adults. When completing the propulsive bipedal hopping protocol, only one trial of hopping was performed for each participant, and those who made mistakes during the trial were allowed to repeat the test. Therefore, participants making more mistakes on the propulsive bipedal hopping test may be suffering more decline which becomes masked from our findings. Our hopping measure did not account for completion time, which could be an important variable to consider for differences in agility with age. Lastly, we did not include participant involvement in exercise in the current study, which may have been a confounding factor in hopping performance.

3.3 Future Directions

Future studies should use propulsive bipedal hopping and TMS to measure longitudinal changes of the CST and human movement in relation to an aging population. Additionally, other variables measured in propulsive bipedal hopping (e.g., hop width, hop speed, asymmetry) should be explored to determine its contribution to changes in muscle strength and CST integrity. These variables may reveal unique contributions to CST integrity that the active motor threshold could not identify (e.g., excitatory and inhibitory REC). Although single-pulse TMS is capable

of probing the entire CST, including the brain and spinal cord(Chaves et al., 2020), future work should measure the influence of the spinal cord separately and its effect on agility performance. While quadriceps strength is a prominent muscle group involved in hopping (Kirkland et al., 2017), it may also be important to examine the influences of other muscle groups involved in propulsive bipedal hopping (e.g., soleus, gastrocnemius, rectus femoris, gluteus maximus). Lifestyle factors such as physical activity should be investigated for a potential role in agility and the CST. Advancing the clinical application of hopping as an assessment tool is needed and could provide a new avenue for performance measurement of age-related decline in agility, thus revealing individuals who may be more prone to neuromuscular decline later in life. While this study was exploratory in nature, future research should aim to examine the reliability, validity, and clinically meaningful change for propulsive bipedal hopping and TMS measures in older adults. Identifying precise markers of decline in agility and the CST are crucial to evaluate and implement their use as outcome measures to predict lower limb functioning across the lifespan. Additional research is required to understand the exact mechanisms and contributions of propulsive bipedal hopping with age-related agility and neuromuscular functioning decline.

References

Abasiyanik, Z., Ozdogar, A. T., Sagici, O., Kahraman, T., Baba, C., Ertekin, O., & Ozakbas, S. (2020). Explanatory factors of balance confidence in persons with multiple sclerosis: Beyond the physical functions. *Mult Scler Relat Disord*, *43*, 102239. https://doi.org/10.1016/j.msard.2020.102239

Alawi, M., Lee, P. F., Deng, Z. D., Goh, Y. K., & Croarkin, P. E. (2023). Modelling the differential effects of age on transcranial magnetic stimulation induced electric fields. *J Neural Eng*, *20*(2). https://doi.org/10.1088/1741-2552/ac9a76

Allen, D., Ribero, L., Arshad, Q., & Seemungal, B. M. (2016). Age-Related Vestibular Loss: Current Understanding and Future Research Directions. *Front Neurol*, *7*, 231. https://doi.org/10.3389/fneur.2016.00231

Archer, Q., Brenya, J., Chavaria, K., Friest, A., Ahmad, N., Zorns, S.,…Keenan, J. P. (2024). The Sol Braiding Method for Handling Thick Hair During Transcranial Magnetic Stimulation: An Address for Potential Bias in Brain Stimulation. *J Vis Exp*(210). https://doi.org/10.3791/66001

Balasubramanian, C. K. (2015). The community balance and mobility scale alleviates the ceiling effects observed in the currently used gait and balance assessments for the community-dwelling older adults. *J Geriatr Phys Ther*, *38*(2), 78-89. https://doi.org/10.1519/JPT.0000000000000024

Barry, E., Galvin, R., Keogh, C., Horgan, F., & Fahey, T. (2014). Is the Timed Up and Go test a useful predictor of risk of falls in community dwelling older adults: a systematic review and meta- analysis. *BMC Geriatrics*, *14*(14). https://doi.org/10.1186/1471-2318-14-14

Bashir, S., Perez, J. M., Horvath, J. C., Pena-Gomez, C., Vernet, M., Capia, A.,…Pascual-Leone, A. (2014). Differential effects of motor cortical excitability and plasticity in young and old individuals: a Transcranial Magnetic Stimulation (TMS) study. *Front Aging Neurosci*, *6*, 111. https://doi.org/10.3389/fnagi.2014.00111

Baudry, S. (2016). Aging Changes the Contribution of Spinal and Corticospina Pathways to Control Balance. *American College of Sports Medicine*, *44*(3), 6. https://doi.org/10.1249/JES.0000000000000080

Baudry, S., Collignon, S., & Duchateau, J. (2015). Influence of age and posture on spinal and corticospinal excitability. *Experimental Gerontology*, *69*, 8. https://doi.org/10.1016/j.exger.2015.06.006

Baudry, S., Penzer, F., & Duchateau, J. (2014). Input-output characteristics of soleus homonymous Ia afferents and corticospinal pathways during upright standing differ between young and elderly adults. *Acta Physiol (Oxf)*, *210*(3), 667-677. https://doi.org/10.1111/apha.12233

Bernard, J. A., & Seidler, R. D. (2012). Evidence for motor cortex dedifferentiation in older adults. *Neurobiology of Aging*, *33*(9), 10. https://doi.org/10.1016/j.neurobiolaging.2011.06.021

Bernard, J. A., & Seidler, R. D. (2014). Moving forward: age effects on the cerebellum underlie cognitive and motor declines. *Neurosci Biobehav Rev*, *42*, 193-207. https://doi.org/10.1016/j.neubiorev.2014.02.011

Bhandari, A., Radhu, N., Farzan, F., Mulsant, B. H., Rajji, T. K., Daskalakis, Z. J., & Blumberger, D. M. (2016). A meta-analysis of the effects of aging on motor cortex

neurophysiology assessed by transcranial magnetic stimulation. *Clin Neurophysiol*, *127*(8), 2834-2845. https://doi.org/10.1016/j.clinph.2016.05.363

Blum, L., Korner-Bitensky, N. (2008). Usefulness of the Berg Balance Scale in Stroke Rehabilitation: A Systematic Review. *Physical Therapy*, *88*(5), 8. https://doi.org/10.2522/ptj.20070205

Bolz, S., & Davies, G. J. (1984). Leg Length Differences and Correlation with Total Leg Strength. *The Journal of Orthopaedics and Sports Physical Therapy*, *6*(2), 7. https://doi.org/10.2519/jospt.1984.6.2.123

Bray, N. W., Jones, G. J., Rush, K. L., Jones, C. A., & Jakobi, J. M. (2020). Multi-Component Exercise with High-Intensity, Free-Weight, Functional Resistance Training in Pre-Frail Females: A Quasi-Experimental, Pilot Study. *J Frailty Aging*, *9*(2), 111-117. https://doi.org/10.14283/jfa.2020.13

Bray, N. W., Pieruccini-Faria, F., Witt, S. T., Bartha, R., Doherty, T. J., Nagamatsu, L. S.,…Montero-Odasso, M. (2023). Combining exercise with cognitive training and vitamin D(3) to improve functional brain connectivity (FBC) in older adults with mild cognitive impairment (MCI). Results from the SYNERGIC trial. *Geroscience*, *45*(3), 1967-1985. https://doi.org/10.1007/s11357-023-00805-6

Brown, K. E., Neva, J. L., Ledwell, N. M., & Boyd, L. A. (2014). Use of transcranial magnetic stimulation in the treatment of selected movement disorders. *Degenerative Neurological and Neuromuscular Disease*, *4*, 133-151. https://doi.org/10.2147/DNND.S70079

Buch, A., Carmeli, E., Boker, L. K., Marcus, Y., Shefer, G., Kis, O.,…Stern, N. (2016). Muscle function and fat content in relation to sarcopenia, obesity and frailty of old age--An overview. *Exp Gerontol*, *76*, 25-32. https://doi.org/10.1016/j.exger.2016.01.008

Cabral, D. F., Bigliassi, M., Cattaneo, G., Rundek, T., Pascual-Leone, A., Cahalin, L. P., & Gomes-Osman, J. (2022). Exploring the interplay between mechanisms of neuroplasticity and cardiovascular health in aging adults: A multiple linear regression analysis study. *Auton Neurosci*, *242*, 103023. https://doi.org/10.1016/j.autneu.2022.103023

Cadore, E. L., Saez de Asteasu, M. L., & Izquierdo, M. (2019). Multicomponent exercise and the hallmarks of frailty: Considerations on cognitive impairment and acute hospitalization. *Exp Gerontol*, *122*, 10-14. https://doi.org/10.1016/j.exger.2019.04.007

Castillo de Lima, V., Castano, L. A. A., Sampaio, R. A. C., Sampaio, P. Y. S., Teixeira, C. V. L., & Uchida, M. C. (2023). Effect of agility ladder training with a cognitive task (dual task) on physical and cognitive functions: a randomized study. *Front Public Health*, *11*, 1159343. https://doi.org/10.3389/fpubh.2023.1159343

Chaves, A. R., Devasahayam, A. J., Kelly, L. P., Pretty, R. W., & Ploughman, M. (2020). Exercise-Induced Brain Excitability Changes in Progressive Multiple Sclerosis: A Pilot Study. *J Neurol Phys Ther*, *44*(2), 132-144. https://doi.org/10.1097/NPT.0000000000000308

Chaves, A. R., Kelly, L. P., Moore, C. S., Stefanelli, M., & Ploughman, M. (2019). Prolonged cortical silent period is related to poor fitness and fatigue, but not tumor necrosis factor, in Multiple Sclerosis. *Clin Neurophysiol*, *130*(4), 474-483. https://doi.org/10.1016/j.clinph.2018.12.015

Chaves, A. R., Snow, N. J., Alcock, L. R., & Ploughman, M. (2021). Probing the Brain-Body Connection Using Transcranial Magnetic Stimulation (TMS): Validating a Promising Tool to Provide Biomarkers of Neuroplasticity and Central Nervous System Function. *Brain sciences*, *11*(3), 384. https://doi.org/https://doi.org/10.3390/brainsci11030384

Chen, A., Kirkland, M. C., Wadden, K. P., Wallack, E. M., & Ploughman, M. (2020). Reliability of gait and dual-task measures in multiple sclerosis. *Gait Posture*, *78*, 19-25. https://doi.org/10.1016/j.gaitpost.2020.03.004

Chen, Z., Bian, C., Liao, K., Bishop, C., & Li, Y. (2021). Validity and Reliability of a Phone App and Stopwatch for the Measurement of 505 Change of Direction Performance: A Test-Retest Study Design. *Front Physiol*, *12*, 743800. https://doi.org/10.3389/fphys.2021.743800

Clark, B. C., Taylor, J. L., Hong, S. L., Law, T. D., & Russ, D. W. (2015). Weaker Seniors Exhibit Motor Cortex Hypoexcitability and Impairments in Voluntary Activation. *J Gerontol A Biol Sci Med Sci*, *70*(9), 1112-1119. https://doi.org/10.1093/gerona/glv030

Coelho-Junior, H. J., Rodrigues, B., Goncalves, I. O., Asano, R. Y., Uchida, M. C., & Marzetti, E. (2018). The physical capabilities underlying timed "Up and Go" test are time-dependent in community-dwelling older women. *Exp Gerontol*, *104*, 138-146. https://doi.org/10.1016/j.exger.2018.01.025

Conradsson, D., Paquette, C., & Franzen, E. (2018). Medio-lateral stability during walking turns in older adults. *PloS One*, *13*(6). https://doi.org/10.1371/journal.pone.0198455

Cook, R. D., & Weisberg, S. (1982). *Residuals and Influence in Regression*. Chapman and Hall.

Coppi, E., Houdayer, E., Chieffo, R., Spagnolo, F., Inuggi, A., Straffi, L.,…Leocani, L. (2014). Age-related changes in motor cortical representation and interhemispheric interactions: a transcranial magnetic stimulation study. *Front Aging Neurosci*, *6*, 209. https://doi.org/10.3389/fnagi.2014.00209

Davies, B. N., Greenwood,E.J., Jones, S.R. (1988). Gender difference in the relationship of performance in the handgrip and standing long jump tests to lean limb volume in young adults. *European Journal of Applied Physiology*, *58*, 6. https://doi.org/10.1007/BF00417269.

Davies, G. J., McCarty, E., Provencher, M., & Manske, R. C. (2017). ACL Return to Sport Guidelines and Criteria. *Curr Rev Musculoskelet Med*, *10*(3), 307-314. https://doi.org/10.1007/s12178-017-9420-9

Deng, Y., & Sato, N. (2024). Global frailty screening tools: Review and application of frailty screening tools from 2001 to 2023. *Intractable Rare Dis Res*, *13*(1), 1-11. https://doi.org/10.5582/irdr.2023.01113

Dobrowolny, G., Barbiera, A., Sica, G., & Scicchitano, B. M. (2021). Age-Related Alterations at Neuromuscular Junction: Role of Oxidative Stress and Epigenetic Modifications. *Cells*, *10*(6). https://doi.org/10.3390/cells10061307

Donath, L., van Dieen, J., & Faude, O. (2016). Exercise-Based Fall Prevention in the Elderly: What About Agility? *Sports Med*, *46*(2), 143-149. https://doi.org/10.1007/s40279-015-0389-5

Draper, N. R., & Smith, H. (1998). *Applied Regression Analysis* (Third ed.). John Wiley & Sons.

Elam, C., Aagaard, P., Slinde, F., Svantesson, U., Hulthén, L., Magnusson, P. S., & Bunketorp-Käll, L. (2021). The effects of ageing on functional capacity and stretch-shortening cycle muscle power. *The Journal if Physical Therapy Sciences*, *33*, 11. https://doi.org/10.1589/jpts.33.250

Fujiyama, H., Hinder, M. R., Schmidt, M. W., Garry, M. I., & Summers, J. J. (2012). Age-related differences in corticospinal excitability and inhibition during coordination of upper and lower limbs. *Neurobiology of Aging*, *33*(7), 14. https://doi.org/10.1016/j.neurobiolaging.2011.12.019

Galan-Arroyo, C., Pereira-Payo, D., Hernandez-Mocholi, M. A., Merellano-Navarro, E., Perez-Gomez, J., Rojo-Ramos, J., & Adsuar, J. C. (2022). Association between Agility, Health-Related Quality of Life, Depression, and Anthropometric Variables in Physically Active Older Adult Women with Depression. *Healthcare (Basel)*, *10*(1). https://doi.org/10.3390/healthcare10010100

Gallardo-Fuentes, F., Gallardo-Fuentes, J., Ramirez-Campillo, R., Balsalobre-Fernandez, C., Martinez, C., Caniuqueo, A.,…Izquierdo, M. (2016). Intersession and Intrasession Reliability and Validity of the My Jump App for Measuring Different Jump Actions in Trained Male and Female Athletes. *J Strength Cond Res*, *30*(7), 2049-2056. https://doi.org/10.1519/JSC.0000000000001304

Gilmour, H., & Ramage-Morin, P. L. (2021). Association of frailty and pre-frailty with increased risk of mortality among older Canadians. *Health Reports*, *32*(4), 12. https://doi.org/10.25318/82-003-x202100400002-eng

Gordon, E. M., Chauvin, R. J., Van, A. N., Rajesh, A., Nielsen, A., Newbold, D. J.,…Dosenbach, N. U. F. (2023). A somato-cognitive action network alternates with effector regions in motor cortex. *Nature*, *617*(7960), 351-359. https://doi.org/10.1038/s41586-023-05964-2

Gowland, C., Stratford, P., Ward, M., Moreland, J., Torresin, W., Van Hullenaar, S.,…Plews, N. (1993). Measuring physical impairment and disability with the Chedoke-McMaster Stroke Assessment. *Stroke*, *24*(1), 58-63. https://www.ncbi.nlm.nih.gov/pubmed/8418551

Greenberger, H. B., & Paterno, M. V. (1995). Relationship of knee extensor strength and hopping test performance in the assessment of lower extremity function. *Journal of Orthopaedic & Sports Physical Therapy*, *22*(5), 5. https://doi.org/10.2519/jospt.1995.22.5.202

Grèzes, J., & Decety, J. (2001). Functional anatomy of execution, mental simulation, observation, and verb generation of actions: A meta-analysis. *Human brain mapping*, *12*(1), 19. https://doi.org/https://doi.org/10.1002/1097-0193(200101)12:1<1::AID-HBM10>3.0.CO;2-V

Hair, J. F., Black, W. C., Babin, B. J., & Anderson, R. E. (2014). *Multivariate data analysis* (7th ed.). Pearson Education Limited.

Hands, B., Licari, M., & Piek, J. (2015). A review of five tests to identify motor coordination difficulties in young adults. *Res Dev Disabil*, *41-42*, 40-51. https://doi.org/10.1016/j.ridd.2015.05.009

Haslband, U., Ito, N., Tanji, J., & Freund, H. J. (1993). The role of premotor cortex and the supplementary motor area in the temporal control of movement in man. *Brain: a journal of neurology*, *116*(1), 23. https://doi.org/https://doi.org/10.1093/brain/116.1.243

Hassanlouei, H., Sundberg, C. W., Smith, A. E., Kuplic, A., & Hunter, S. K. (2017). Physical activity modulates corticospinal excitability of the lower limb in young and old adults. *J Appl Physiol (1985)*, *123*(2), 364-374. https://doi.org/10.1152/japplphysiol.01078.2016

He, X., Qiu, J., Cao, M., Ho, Y. C., Leong, H. T., Fu, S. C.,…Yung, P. S. (2022). Effects of Deficits in the Neuromuscular and Mechanical Properties of the Quadriceps and Hamstrings on Single-Leg Hop Performance and Dynamic Knee Stability in Patients After Anterior Cruciate Ligament Reconstruction. *Orthop J Sports Med*, *10*(1), 23259671211063893. https://doi.org/10.1177/23259671211063893

Hernandez-Ochoa, E. O., & Schneider, M. F. (2018). Voltage sensing mechanism in skeletal muscle excitation-contraction coupling: coming of age or midlife crisis? *Skelet Muscle*, *8*(1), 22. https://doi.org/10.1186/s13395-018-0167-9

Herzog, W., Powers, K., Johnston, K., & Duvall, M. (2015). A new paradigm for muscle contraction. *Front Physiol*, *6*, 174. https://doi.org/10.3389/fphys.2015.00174

Hoffren-Mikkola, M., Ishikawa, M., Rantalainen, T., Avela, J., & Komi, P. V. (2015). Neuromuscular mechanics and hopping training in elderly. *Eur J Appl Physiol*, *115*(5), 863-877. https://doi.org/10.1007/s00421-014-3065-9

Hoffrén, M., Ishikawa, M., Avela, J., & Komi, P. V. (2012). Age-related fascicle-tendon interaction in repetitive hopping. *Eur J Appl Physiol*, *112*(12), 4035-4043. https://doi.org/10.1007/s00421-012-2393-x

Hoffren, M., Ishikawa, M., Rantalainen, T., Avela, J., & Komi, P. V. (2011). Age-related muscle activation profiles and joint stiffness regulation in repetitive hopping. *J Electromyogr Kinesiol*, *21*(3), 483-491. https://doi.org/10.1016/j.jelekin.2011.01.009

Houde, F., Laroche, S., Thivierge, V., Martel, M., Harvey, M. P., Daigle, F.,…Leonard, G. (2018). Transcranial Magnetic Stimulation Measures in the Elderly: Reliability, Smallest Detectable Change and the Potential Influence of Lifestyle Habits. *Front Aging Neurosci*, *10*, 379. https://doi.org/10.3389/fnagi.2018.00379

Howe, J. A., Inness, E. L., Venturini, A., Williams, J. I., & Verrier, M. C. (2006). The Community Balance and Mobility Scale a balance measure for individuals with traumatic brain injury. *Clinical Rehabilitation*, *20*, 11. https://doi.org/10.1177/0269215506072183

Hu, W., Combden, O., Jiang, X., Buragadda, S., Newell, C. J., Williams, M. C.,…Ploughman, M. (2022a). Machine learning classification of multiple sclerosis patients based on raw data from an instrumented walkway. *Biomed Eng Online*, *21*(1), 21. https://doi.org/10.1186/s12938-022-00992-x

Hu, W., Combden, O., Jiang, X., Buragadda, S., Newell, C. J., Williams, M. C.,…Ploughman, M. (2022b). Machine learning corroborates subjective ratings of walking and balance difficulty in multiple sclerosis. *Front Artif Intell*, *5*, 952312. https://doi.org/10.3389/frai.2022.952312

Hunter, S. K., Pereira, H. M., & Keenan, K. G. (2016). The aging neuromuscular system and motor performance. *J Appl Physiol (1985)*, *121*(4), 982-995. https://doi.org/10.1152/japplphysiol.00475.2016

Hupfeld, K. E., McGregor, H. R., Hass, C. J., Pasternak, O., & Seidler, R. D. (2022). Sensory system-specific associations between brain structure and balance. *Neurobiol Aging*, *119*, 102-116. https://doi.org/10.1016/j.neurobiolaging.2022.07.013

Iyer, P. C., & Madhavan, S. (2019). Characterization of stimulus response curves obtained with transcranial magnetic stimulation from bilateral tibialis anterior muscles post stroke. *Neurosci Lett*, *713*, 134530. https://doi.org/10.1016/j.neulet.2019.134530

James, S. L., Lucchesi, L. R., Bisignano, C., Castle, C. D., Dingels, Z. V., Fox, J. T.,…Murray, C. J. L. (2020). The global burden of falls: global, regional and national estimates of morbidity and mortality from the Global Burden of Disease Study 2017. *Inj Prev*, *26*(Supp 1), i3-i11. https://doi.org/10.1136/injuryprev-2019-043286

Jang, S. H., & Seo, J. P. (2015). Aging of corticospinal tract fibers according to the cerebral origin in the human brain: a diffusion tensor imaging study. *Neurosci Lett*, *585*, 77-81. https://doi.org/10.1016/j.neulet.2014.11.030

Keevil, V. L., Osuafor, C. N., Mackett, A. J., & Biram, R. (2020). Frailty Assessment in Clinical Practice: Opportunity in the Midst of a Pandemic. *Geriatrics (Basel)*, *5*(4). https://doi.org/10.3390/geriatrics5040092

Keevil, V. L., & Romero-Ortuno, R. (2015). Ageing well: a review of sarcopenia and frailty. *Proc Nutr Soc*, *74*(4), 337-347. https://doi.org/10.1017/S0029665115002037

Kirkland, M. C., Chen, A., Downer, M. B., Holloway, B. J., Wallack, E. M., Lockyer, E. J.,…Ploughman, M. (2018). Bipedal hopping timed to a metronome to detect impairments in anticipatory motor control in people with mild multiple sclerosis. *Clin Biomech (Bristol, Avon)*, *55*, 45-52. https://doi.org/10.1016/j.clinbiomech.2018.04.009

Kirkland, M. C., Downer, M. B., Holloway, B. J., Wallack, E. M., Lockyer, E. J., Buckle, N. C. M.,…Ploughman, M. (2017). Bipedal Hopping Reveals Evidence of Advanced Neuromuscular Aging Among People With Mild Multiple Sclerosis. *J Mot Behav*, *49*(5), 505-513. https://doi.org/10.1080/00222895.2016.1241750

Kirkland, M. C., Wadden, K. P., & Ploughman, M. (2020). Bipedal hopping as a new measure to detect subtle sensorimotor impairment in people with multiple sclerosis. *Disability and Rehabilitation*, 1-12.

Kirkland, M. C., Wadden, K. P., & Ploughman, M. (2022). Bipedal hopping as a new measure to detect subtle sensorimotor impairment in people with multiple sclerosis. *Disabil Rehabil*, *44*(8), 1544-1555. https://doi.org/10.1080/09638288.2020.1820585

Knorr, S., Brouwer, B., & Garland, S. J. (2010). Validity of the Community Balance and Mobility Scale in community-dwelling persons after stroke. *Arch Phys Med Rehabil*, *91*(6), 890-896. https://doi.org/10.1016/j.apmr.2010.02.010

Kojima, G. (2019). Increased healthcare costs associated with frailty among community-dwelling older people: A systematic review and meta-analysis. *Arch Gerontol Geriatr*, *84*, 103898. https://doi.org/10.1016/j.archger.2019.06.003

Kotsifaki, A., Van Rossom, S., Whiteley, R., Korakakis, V., Bahr, R., Sideris, V., & Jonkers, I. (2022). Single leg vertical jump performance identifies knee function deficits at return to sport after ACL reconstruction in male athletes. *British Journal of Sports Medicine*, *56*(9), 10. https://doi.org/10.1136/bjsports-2021-104692

Kuhnow, J., Hoben, M., Weeks, L. E., Barber, B., & Estabrooks, C. A. (2022). Factors Associated with Falls in Canadian Long Term Care Homes: a Retrospective Cohort Study. *Can Geriatr J*, *25*(4), 328-335. https://doi.org/10.5770/cgj.25.623

Labott, B. K., & Donath, L. (2023). Agility performance in healthy older adults is associated with handgrip strength and force development: results from a 1-year randomized controlled trial. *Eur Geriatr Med*, *14*(3), 547-555. https://doi.org/10.1007/s41999-023-00789-8

Laforce, R., Jr., & Doyon, J. (2001). Distinct contribution of the striatum and cerebellum to motor learning. *Brain Cogn*, *45*(2), 189-211. https://doi.org/10.1006/brcg.2000.1237

Lanciego, J. L., Luquin, N., & Obeso, J. A. (2012). Functional neuroanatomy of the basal ganglia. *Cold Spring Harb Perspect Med*, *2*(12), a009621. https://doi.org/10.1101/cshperspect.a009621

Lee, S. (2021). Falls associated with indoor and outdoor environmental hazards among community-dwelling older adults between men and women. *BMC Geriatr*, *21*(1), 547. https://doi.org/10.1186/s12877-021-02499-x

Lesnak, J., Anderson, D., Farmer, B., Katsavelis, D., & Grindstaff, T. L. (2019). Validity of Hand-Held Dynamometry in Measuring Quadriceps Strength and Rate of Torque

Development. *International Journal of Sports Physical Therapy*, *14*(2), 180-187. https://doi.org/10.26603/ijspt20190180

Levin, O., Fujiyama, H., Boisgontier, M. P., Swinnen, S. P., & Summers, J. J. (2014). Aging and motor inhibition: a converging perspective provided by brain stimulation and imaging approaches. *Neurosci Biobehav Rev*, *43*, 100-117. https://doi.org/10.1016/j.neubiorev.2014.04.001

Lichtenstein, E., Faude, O., Zubler, A., Roth, R., Zahner, L., Rossler, R.,…Donath, L. (2019). Validity and Reliability of a Novel Integrative Motor Performance Testing Course for Seniors: The "Agility Challenge for the Elderly (ACE)". *Front Physiol*, *10*, 44. https://doi.org/10.3389/fphys.2019.00044

Lichtenstein, E., Morat, M., Roth, R., Donath, L., & Faude, O. (2020). Agility-based exercise training compared to traditional strength and balance training in older adults: a pilot randomized trial. *PeerJ*, *8*, e8781. https://doi.org/10.7717/peerj.8781

Lin, H. W., & Bhattacharyya, N. (2012). Balance disorders in the elderly: epidemiology and functional impact. *Laryngoscope*, *122*(8), 1858-1861. https://doi.org/10.1002/lary.23376

Liu-Ambrose, T., Khan, K. M., Eng, J. J., Lord, S. R., & McKay, H. A. (2004). Balance confidence improves with resistance or agility training. Increase is not correlated with objective changes in fall risk and physical abilities. *Gerontology*, *50*(6), 373-382. https://doi.org/10.1159/000080175

Liu-Ambrose, T. Y., Khan, K. M., Eng, J. J., Lord, S. R., Lentle, B., & McKay, H. A. (2005). Both resistance and agility training reduce back pain and improve health-related quality of life in older women with low bone mass. *Osteoporos Int*, *16*(11), 1321-1329. https://doi.org/10.1007/s00198-005-1842-3

Matamala, J. M., Nunez, C., Lera, L., Verdugo, R. J., Sanchez, H., Albala, C., & Castillo, J. L. (2013). Motor evoked potentials by transcranial magnetic stimulation in healthy elderly people. *Somatosens Mot Res*, *30*(4), 201-205. https://doi.org/10.3109/08990220.2013.796922

McGregor, K. M., Carpenter, H., Kleim, E., Sudhyadhom, A., White, K. D., Butler, A. J.,…Crosson, B. (2012). Motor map reliability and aging: a TMS/fMRI study. *Exp Brain Res*, *219*(1), 97-106. https://doi.org/10.1007/s00221-012-3070-3

McNeil, C. J., & Rice, C. L. (2018). Neuromuscular adaptations to healthy aging. *Appl Physiol Nutr Metab*, *43*(11), 1158-1165. https://doi.org/10.1139/apnm-2018-0327

Middleton, A., Fritz, S. L., & Lusardi, M. (2015). Walking speed: the functional vital sign. *J Aging Phys Act*, *23*(2), 314-322. https://doi.org/10.1123/japa.2013-0236

Miyamoto, K., Takebayashi, H., Takimoto, K., Miyamoto, S., Morioka, S., & Yagi, F. (2008). A new simple performance test focused on agility in elderly people: The Ten Step Test. *Gerontology*, *54*(6), 365-372. https://doi.org/10.1159/000146787

Montero-Odasso, M., Speechley, M., Muir-Hunter, S. W., Pieruccini-Faria, F., Sarquis-Adamson, Y., Hachinski, V.,…Cognition, N. (2020). Dual decline in gait speed and cognition is associated with future dementia: evidence for a phenotype. *Age Ageing*, *49*(6), 995-1002. https://doi.org/10.1093/ageing/afaa106

Montero-Odasso, M., Zou, G., Speechley, M., Almeida, Q. J., Liu-Ambrose, T., Middleton, L. E.,…Cognition, N. (2023). Effects of Exercise Alone or Combined With Cognitive Training and Vitamin D Supplementation to Improve Cognition in Adults With Mild Cognitive Impairment: A Randomized Clinical Trial. *JAMA Netw Open*, *6*(7), e2324465. https://doi.org/10.1001/jamanetworkopen.2023.24465

Monti, R. J., Roy, R. R., & Edgerton, V. R. (2001). Role of motor unit structure in defining function. *Muscle Nerve*, *24*(7), 848-866. https://doi.org/10.1002/mus.1083
Morat, M., Faude, O., Hanssen, H., Ludyga, S., Zacher, J., Eibl, A.,…Donath, L. (2020). Agility Training to Integratively Promote Neuromuscular, Cognitive, Cardiovascular and Psychosocial Function in Healthy Older Adults: A Study Protocol of a One-Year Randomized-Controlled Trial. *Int J Environ Res Public Health*, *17*(6). https://doi.org/10.3390/ijerph17061853
Musich, S., Wang, S. S., Ruiz, J., Hawkins, K., & Wicker, E. (2018). The impact of mobility limitations on health outcomes among older adults. *Geriatr Nurs*, *39*(2), 162-169. https://doi.org/10.1016/j.gerinurse.2017.08.002
Myer, G. D., Schmitt, L. C., Brent, J. L., Ford, K. R., Barber Foss, K. D., Scherer, B. J.,…Hewett, T. E. (2011). Utilization of modified NFL combine testing to identify functional deficits in athletes following ACL reconstruction. *J Orthop Sports Phys Ther*, *41*(6), 377-387. https://doi.org/10.2519/jospt.2011.3547
Narayanan, S., & Thirumalai, V. (2019). Contributions of the Cerebellum for Predictive and Instructional Control of Movement. *Curr Opin Physiol*, *8*, 146-151. https://doi.org/10.1016/j.cophys.2019.01.011
Narici, M. V., & Maganaris, C. N. (2006). Adaptability of elderly human muscles and tendons to increased loading. *Journal of Anatomy*, *208*(4), 11. https://doi.org/10.1111/j.1469-7580.2006.00548.x
Nilwik, R., Snijders, T., Leenders, M., Groen, B. B., van Kranenburg, J., Verdijk, L. B., & van Loon, L. J. (2013). The decline in skeletal muscle mass with aging is mainly attributed to a reduction in type II muscle fiber size. *Exp Gerontol*, *48*(5), 492-498. https://doi.org/10.1016/j.exger.2013.02.012
Ofori-Asenso, R., Chin, K. L., Mazidi, M., Zomer, E., Ilomaki, J., Zullo, A. R.,…Liew, D. (2019). Global Incidence of Frailty and Prefrailty Among Community-Dwelling Older Adults: A Systematic Review and Meta-analysis. *JAMA Netw Open*, *2*(8), e198398. https://doi.org/10.1001/jamanetworkopen.2019.8398
Opie, G. M., Hand, B. J., & Semmler, J. G. (2020). Age-related changes in late synaptic inputs to corticospinal neurons and their functional significance: A paired-pulse TMS study. *Brain Stimulation*, *13*(1), 239-246. <Go to ISI>://WOS:000499654900027
Orssatto, L. B. R., Borg, D. N., Pendrith, L., Blazevich, A. J., Shield, A. J., & Trajano, G. S. (2022). Do motoneuron discharge rates slow with aging? A systematic review and meta-analysis. *Mech Ageing Dev*, *203*, 111647. https://doi.org/10.1016/j.mad.2022.111647
Osnabruegge, M., Kanig, C., Schwitzgebel, F., Litschel, K., Seiberl, W., Mack, W.,…Schoisswohl, S. (2023). On the reliability of motor evoked potentials in hand muscles of healthy adults: a systematic review. *Front Hum Neurosci*, *17*, 1237712. https://doi.org/10.3389/fnhum.2023.1237712
Palisano, R., Rosenbaum, P., Walter, S., Russell, D., Wood, E., Galuppi, B. (1997). Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Developmental medicine and child neurology*, *39*(4), 9. https://doi.org/10.1111/j.1469-8749.1997.tb07414.x.
Paquette, C., & Fung, J. (2011). Old age affects gaze and postural coordination. *Gait Posture*, *33*(2), 227-232. https://doi.org/10.1016/j.gaitpost.2010.11.010
Pascual-Leone, A., Freitas, C., Oberman, L., Horvath, J. C., Halko, M., Eldaief, M.,…Rotenberg, A. (2011). Characterizing brain cortical plasticity and network dynamics across the age-

span in health and disease with TMS-EEG and TMS-fMRI. *Brain Topogr*, *24*(3-4), 302-315. https://doi.org/10.1007/s10548-011-0196-8

Pauole, K., Madole, K., Garhammer, J., Lacourse, M., & Rozenek, R. (2000). Reliability and Validity of the T-test as a Measure of Agility, leg Power, and Leg Speed in college-Aged Men and Women. *Journal of strength and Conditioning Research*, *14*(4), 8.

Pieruccini-Faria, F., Sarquis-Adamson, Y., Anton-Rodrigo, I., Nogueron-Garcia, A., Bray, N. W., Camicioli, R.,…Montero-Odasso, M. (2020). Mapping Associations Between Gait Decline and Fall Risk in Mild Cognitive Impairment. *J Am Geriatr Soc*, *68*(3), 576-584. https://doi.org/10.1111/jgs.16265

Plotkin, D. L., Roberts, M. D., Haun, C. T., & Schoenfeld, B. J. (2021). Muscle Fiber Type Transitions with Exercise Training: Shifting Perspectives. *Sports (Basel)*, *9*(9). https://doi.org/10.3390/sports9090127

Potter-Baker, K. A., Varnerin, N. M., Cunningham, D. A., Roelle, S. M., Sankarasubramanian, V., Bonnett, C. E.,…Plow, E. B. (2016). Influence of Corticospinal Tracts from Higher Order Motor Cortices on Recruitment Curve Properties in Stroke. *Front Neurosci*, *10*, 79. https://doi.org/10.3389/fnins.2016.00079

Power, G. A., Dalton, B. H., & Rice, C. L. (2013). Human neuromuscular structure and function in old age: A brief review. *J Sport Health Sci*, *2*(4), 215-226. https://doi.org/10.1016/j.jshs.2013.07.001

Redfern, M. S., Yardley, L., & Bronstein, A. M. (2001). Visual influences on balance. *Anxiety Disorders*, *15*(1-2), 14. https://doi.org/https://doi.org/10.1016/s0887-6185(00)00043-8

Reed-Jones, R. J., Dorgo, S., Hitchings, M. K., & Bader, J. O. (2012). Vision and agility training in community dwelling older adults: incorporating visual training into programs for fall prevention. *Gait Posture*, *35*(4), 585-589. https://doi.org/10.1016/j.gaitpost.2011.11.029

Reid, K. F., & Fielding, R. A. (2012). Skeletal muscle power: a critical determinant of physical functioning in older adults. *Exerc Sport Sci Rev*, *40*(1), 4-12. https://doi.org/10.1097/JES.0b013e31823b5f13

Rodrigues, F., Monteiro, A. M., Forte, P., & Morouco, P. (2023). Effects of Muscle Strength, Agility, and Fear of Falling on Risk of Falling in Older Adults. *Int J Environ Res Public Health*, *20*(6). https://doi.org/10.3390/ijerph20064945

Rolenz, E., & Reneker, J. C. (2016). Validity of the 8-Foot Up and Go, Timed Up and Go, and Activities-Specific Balance Confidence Scale in older adults with and without cognitive impairment. *J Rehabil Res Dev*, *53*(4), 511-518. https://doi.org/10.1682/JRRD.2015.03.0042

Rossini, P. M., Burke, D., Chen, R., Cohen, L. G., Daskalakis, Z., Di Iorio, R.,…Ziemann, U. (2015). Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. *Clin Neurophysiol*, *126*(6), 1071-1107. https://doi.org/10.1016/j.clinph.2015.02.001

Rozand, V., Senefeld, J. W., Sundberg, C. W., Smith, A. E., & Hunter, S. K. (2019). Differential effects of aging and physical activity on corticospinal excitability of upper and lower limb muscles. *J Neurophysiol*, *122*(1), 241-250. https://doi.org/10.1152/jn.00077.2019

Russell, D. J., Rosenbaum, P. L., Cadman, D. T., Gowland, C., Hardy, S., & Jarvis, S. (1989). The gross motor function measure: a means to evaluate the effects of physical therapy. *Dev Med Child Neurol*, *31*(3), 341-352. https://doi.org/10.1111/j.1469-8749.1989.tb04003.x

Rygiel, K. A., Picard, M., & Turnbull, D. M. (2016). The ageing neuromuscular system and sarcopenia: a mitochondrial perspective. *J Physiol*, *594*(16), 4499-4512. https://doi.org/10.1113/JP271212

Salat, D. H., Tuch, D. S., Greve, D. N., van der Kouwe, A. J., Hevelone, N. D., Zaleta, A. K.,…Dale, A. M. (2005). Age-related alterations in white matter microstructure measured by diffusion tensor imaging. *Neurobiol Aging*, *26*(8), 1215-1227. https://doi.org/10.1016/j.neurobiolaging.2004.09.017

Salbach, N. M., O'Brien, K., Brooks, D., Irvin, E., Martino, R., Takhar, P.,…Howe, J. A. (2014). Speed and distance requirements for community ambulation: a systematic review. *Arch Phys Med Rehabil*, *95*(1), 117-128 e111. https://doi.org/10.1016/j.apmr.2013.06.017

Sanchez-Trigo, H., Zange, J., Sies, W., Böcker, J., Sañudo, B., & Rittweger, J. (2022). Effects of Aging and Fitness on Hopping Biomechanics. *International Journal of Environmental Research and Public Health*, *19*(13696), 11. https://doi.org/10.3390/ijerph192013696

Seidler, R. D., Bernard, J. A., Burutolu, T. B., Fling, B. W., Gordon, M. T., Gwin, J. T.,…Lipps, D. B. (2010). Motor control and aging: links to age-related brain structural, functional, and biochemical effects. *Neurosci Biobehav Rev*, *34*(5), 721-733. https://doi.org/10.1016/j.neubiorev.2009.10.005

Sheets, D. J., & Gallagher, E. M. (2013). Aging in Canada: state of the art and science. *Gerontologist*, *53*(1), 1-8. https://doi.org/10.1093/geront/gns150

Sheppard, J. M., & Young, W. B. (2006). Agility literature review: classifications, training and testing. *J Sports Sci*, *24*(9), 919-932. https://doi.org/10.1080/02640410500457109

Shibuya, K., Park, S. B., Geevasinga, N., Huynh, W., Simon, N. G., Menon, P.,…Kiernan, M. C. (2016). Threshold tracking transcranial magnetic stimulation: Effects of age and gender on motor cortical function. *Clinical Neurophysiology*, *127*, 7. https://doi.org/10.1016/j.clinph.2016.03.009

Singh, A. M., Duncan, R. E., Neva, J. L., & Staines, W. R. (2014). Aerobic exercise modulates intracortical inhibition and facilitation in a nonexercised upper limb muscle. *BMC Sports Science, Medicine & Rehabilitation*, *6*(23). https://doi.org/10.1038/s41598-019-55858-5

Smith, J. (2014). *Vertical Foundations: The physiology, biomechanics, and technique of explosive vertical jumping*. Just Fly Sports.

Sollmann, N., Tanigawa, N., Bulubas, L., Sabih, J., Zimmer, C., Ringel, F.,…Krieg, S. M. (2017). Clinical Factors Underlying the Inter-individual Variability of the Resting Motor Threshold in Navigated Transcranial Magnetic Stimulation Motor Mapping. *Brain Topogr*, *30*(1), 98-121. https://doi.org/10.1007/s10548-016-0536-9

Steindl, R., Kunz, K., Schrott-Fischer, A., & Scholtz, A. W. (2006). Effect of age and sex on maturation of sensory systems and balance control. *Dev Med Child Neurol*, *48*(6), 477-482. https://doi.org/10.1017/S0012162206001022

Straight, C. R., Ades, P. A., Toth, M. J., & Miller, M. S. (2018). Age-related reduction in single muscle fiber calcium sensitivity is associated with decreased muscle power in men and women. *Exp Gerontol*, *102*, 84-92. https://doi.org/10.1016/j.exger.2017.12.007

Sundberg, C. W., Kuplic, A., Hassanlouei, H., & Hunter, S. K. (2018). Mechanisms for the age-related increase in fatigability of the knee extensors in old and very old adults. *J Appl Physiol (1985)*, *125*(1), 146-158. https://doi.org/10.1152/japplphysiol.01141.2017

Swanson, C. W., & Fling, B. W. (2020). Associations between Turning Characteristics and Corticospinal Inhibition in Young and Older Adults. *Neuroscience*, *425*, 59-67. https://doi.org/10.1016/j.neuroscience.2019.10.051

Swiecicka, A., Piasecki, M., Stashuk, D. W., Ireland, A., Jones, D. A., Rutter, M. K., & McPhee, J. S. (2019). Frailty phenotype and frailty index are associated with distinct neuromuscular electrophysiological characteristics in men. *Exp Physiol*, *104*(8), 1154-1161. https://doi.org/10.1113/EP087579

Talelli, P., Ewas, A., Waddingham, W., Rothwell, J. C., & Ward, N. S. (2008). Neural correlates of age-related changes in cortical neurophysiology. . *NeuroImage*, *40*(4), 1772–1781. https://doi.org/https://doi.org/10.1016/j.neuroimage.2008.01.039

Tang, X., Huang, P., Li, Y., Lan, J., Yang, Z., Xu, M.,…Xu, N. (2019). Age-Related Changes in the Plasticity of Neural Networks Assessed by Transcranial Magnetic Stimulation With Electromyography: A Systematic Review and Meta-Analysis. *Front Cell Neurosci*, *13*, 469. https://doi.org/10.3389/fncel.2019.00469

Teka, W. W., Hamade, K. C., Barnett, W. H., Kim, T., Markin, S. N., Rybak, I. A., & Molkov, Y. I. (2017). From the motor cortex to the movement and back again. *PLoS One*, *12*(6), e0179288. https://doi.org/10.1371/journal.pone.0179288

Tinetti, M. E., & Kumar, C. (2010). The patient who falls: "It's always a trade-off". *JAMA*, *303*(3), 258-266. https://doi.org/10.1001/jama.2009.2024

Tollar, J., Nagy, F., Moizs, M., Toth, B. E., Sanders, L. M. J., & Hortobagyi, T. (2019). Diverse Exercises Similarly Reduce Older Adults' Mobility Limitations. *Med Sci Sports Exerc*, *51*(9), 1809-1816. https://doi.org/10.1249/MSS.0000000000002001

United Nations. (2015). United Nations, Department of Economic and Social Affairs, Population Division, World Fertility Report 2013: Fertility at the Extremes. *Population and development review*, *41*(3), 555. https://doi.org/10.1111/j.1728-4457.2015.00081.x

Vaishya, R., & Vaish, A. (2020). Falls in Older Adults are Serious. *Indian J Orthop*, *54*(1), 69-74. https://doi.org/10.1007/s43465-019-00037-x

Van Hoornweder, S., Geraerts, M., Verstraelen, S., Nuyts, M., Caulfield, K. A., & Meesen, R. (2024). Differences in scalp-to-cortex tissues across age groups, sexes and brain regions: Implications for neuroimaging and brain stimulation techniques. *Neurobiol Aging*, *138*, 45-62. https://doi.org/10.1016/j.neurobiolaging.2024.02.011

Walsh, J. A., Stapley, P. J., Shemmell, J. B. H., Lepers, R., & McAndrew, D. J. (2019). Global Corticospinal Excitability as Assessed in A Non-Exercised Upper Limb Muscle Compared Between Concentric and Eccentric Modes of Leg Cycling. *Sci Rep*, *9*(1), 19212. https://doi.org/10.1038/s41598-019-55858-5

Ward, R. E., Quach, L., Welch, S. A., Leveille, S. G., Leritz, E., & Bean, J. F. (2019). Interrelated Neuromuscular and Clinical Risk Factors That Contribute to Falls. *J Gerontol A Biol Sci Med Sci*, *74*(9), 1526-1532. https://doi.org/10.1093/gerona/glz030

Whiteley, I., Sideris, V., Kotsifaki, R., King, E., & Whiteley, R. (2023). The MyJump App is a Valid Method of Assessing and Classifying Limb Symmetry During Recovery from Anterior Cruciate Ligament Reconstruction. *Int J Sports Phys Ther*, *18*(5), 1156-1165. https://doi.org/10.26603/001c.88005

Wu, R., Delahunt, E., Ditroilo, M., Lowery, M., & De Vito, G. (2016). Effects of age and sex on neuromuscular-mechanical determinants of muscle strength. *Age (Dordr)*, *38*(3), 57. https://doi.org/10.1007/s11357-016-9921-2

Xue, Q. L. (2011). The frailty syndrome: definition and natural history. *Clin Geriatr Med*, *27*(1), 1-15. https://doi.org/10.1016/j.cger.2010.08.009

Young, W., Rayner, R., & Talpey, S. (2021). It's Time to Change Direction on Agility Research: a Call to Action. *Sports Med Open*, *7*(1), 12. https://doi.org/10.1186/s40798-021-00304-y

Zandvoort, C. S., Daffertshofer, A., & Dominici, N. (2022). Cortical contributions to locomotor primitives in toddlers and adults. *iScience*, *25*(10), 105229. https://doi.org/10.1016/j.isci.2022.105229

Zhang, Y., Gu, Z., Xu, Y., He, M., Gerber, B. S., Wang, Z.,…Peng, C. (2024). Global scientific trends in healthy aging in the early 21st century: A data-driven scientometric and visualized analysis. *Heliyon*, *10*(1), e23405. https://doi.org/10.1016/j.heliyon.2023.e23405

Ziemann, U., Reis, J., Schwenkreis, P., Rosanova, M., Strafella, A., Badawy, R., & Muller-Dahlhaus, F. (2015). TMS and drugs revisited 2014. *Clin Neurophysiol*, *126*(10), 1847-1868. https://doi.org/10.1016/j.clinph.2014.08.028

Appendices

HREB - Approval of Ethics Renewal 20222114
administrator@hrea.ca
Sent: Wednesday, November 27, 2024 12:57 PM
To: Bray Nick Walter(Key Contact) [nwb267@mun.ca]
Cc: Ploughman, Michelle; Hreaadministrator

Researcher Portal File #: 20222114

Dear Dr. Michelle Ploughman:

This e-mail serves as notification that your ethics renewal for study HREB # 2021.210 – Mapping the Neurophysiology of Neuromuscular Aging – has been **approved**. Please log in to the Researcher Portal to view the approved event.

Ethics approval for this project has been granted for a period of twelve months effective from 10 Dec 2024 to 10 Dec 2025.

Please note, it is the responsibility of the Principal Investigator (PI) to ensure that the Ethics Renewal form is submitted prior to the renewal date each year. Though the Research Ethics Office makes every effort to remind the PI of this responsibility, the PI may not receive a reminder. The Ethics Renewal form can be found on the Researcher Portal as an "Event".

The ethics renewal will be reported to the Health Research Ethics Board at their meeting dated 12 Dec 2024.

Thank you,

Research Ethics Office
Health Research Ethics Authority
760 Topsail Road
Mount Pearl, NL A1N 3J5
(e) info@hrea.ca
(t) 709-864-8871
(f) 709-864-8870
(w) www.hrea.ca