THESIS

EVALUATING CENTRAL MECHANISMS FOR AGE-RELATED FORCE CONTROL DEFICITS OF THE LEGS

Submitted by

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In partial fulfillment of the requirements

For the Degree of Master of Science

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Fall 2019

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ABSTRACT

EVALUATING CENTRAL MECHANISMS FOR AGE-RELATED FORCE CONTROL DEFICITS OF THE LEGS

Advancing age is accompanied by several motor control impairments, including increased movement and force variability. Specifically, older adults display more variable and less accurate submaximal forces than young adults, which have been associated with fall risk in the aged population. These motor control changes take place in muscles in both the upper and lower limbs, and the mechanisms of these alterations are multifactorial, including sources in the peripheral and central nervous systems. Furthermore, inhibitory signaling in the motor cortex is related to force variability in small hand muscles, as well as to coordination of the legs during walking. It is unknown, however, whether inhibition is associated with force variability in the legs. Therefore, the purpose of this study was to assess the relationship between motor cortex inhibition and force variability in the quadriceps muscles of young and old adults. We measured quadriceps force variability and accuracy during a 2-minute force matching task and inhibition via the cortical silent period in 14 young and 15 old adults. Older adults produced more variable and less accurate forces than the young adults, though these differences were not significant. Additionally, older adults displayed less inhibition in their right cortical hemisphere than young adults, as well as interhemispheric inhibitory differences. Specifically, the left hemisphere displayed more inhibition than the right hemisphere in old adults. Furthermore, young adults with more inhibition generally produced more variable and less accurate forces than young adults with less inhibition, while older adults with more inhibition displayed less variable and more accurate forces. The between- and within-group differences in inhibition may point to age-related decline in right hemispheric function. Moreover, between-group differences in inhibition and force variability associations indicate a shift in the inhibitory control of movement, which is a similar finding to previous work on inhibition and lower limb coordination.

ACKNOWLEDGEMENTS

I would like to primarily thank Dr. Fling for allowing me to join his lab and providing an incredible experience for me in the past year. His patience, continuous kindness, and trust in me has allowed me to grow as a scientist and person, and I am so appreciative of everything that he has done for me. I would also like to thank Clayton Swanson, Sutton Richmond, and Tyler Whittier for their support with questions about statistics, data analysis, and life decisions. Their friendship has encouraged and blessed me immensely, and I am so grateful for them. Thank you to the graduate students in the Department of Health and Exercise Science for being supportive classmates and dear friends. Additionally, I am grateful to the faculty and staff in Health and Exercise Science for their support, counsel, and for the opportunity to pursue and complete a Master's degree in such an amazing environment.

Finally, I would like to thank my family, without whose love and steadfast guidance I would not be in the place that I am now. I love you all dearly and pray that you know how much you mean to me. Thank you to Erica, Christian, and Marta for letting me get excited about things that you may not appreciate the way I do. Mom and Dad, thank you for loving me and helping me find my way with your patient support and advice.

Thank you to everyone I have encountered throughout this journey. You have all taught me, encouraged me, and made this some of the best times of my life.

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1. INTRODUCTION

The aging population in the developed world, particularly in the United States, is rapidly growing. By 2050, it is projected that there will be 89 million people over the age of 65 in the United States, which will account for nearly 23% of the population[1]. Advancing age is a risk factor for nearly every chronic disease in the developed world, including cardiovascular disease, cancer, and neurodegeneration[2]. Even in healthy individuals, aging is typically accompanied by several deleterious effects on motor performance which impact older adults' daily functioning and overall quality of life (QoL). These changes include the attenuated ability to coordinate movement, gait and balance impairments, slowed movement, and decreases in movement and force steadiness[3]. As individuals age, they become less able to steadily maintain submaximal force outputs, or their force variability increases. Several studies have produced this finding, indicating that when older adults are asked to produce submaximal forces, the variability around their average force output is higher than that of younger adults, even when normalized to maximal force[4–6]. These functional detriments culminate to increase fall risk and impair older adults' abilities to perform activities of daily living (ADLs), including bathing, dressing, and grocery shopping[7]. Lower limb muscles are impacted by these changes and can particularly influence QoL because of their role in postural stability and mobility. The quadriceps muscles, specifically, play a crucial role in posture and gait. Age-related strength losses in this muscle group have been associated with mobility deficits, including decreased gait speed[8], impaired balance[9], and difficulty rising from a seated position or managing stairs[10,11]. These mobility deficits have been associated with increased fall risk, and while quadriceps strength is important to maintain function, quadriceps force variability is also predictive of functional ability. For example, Carville and colleagues found that older adults with a fall history exhibited more variable quadriceps forces than their non-falling counterparts[12].

Increased force variability associated with age has been well-documented in aging literature, though the mechanisms of these alterations remain unclear. Furthermore, force accuracy deficits have also been documented in older adults and are associated with functional impairments in this population[13–15].

Because of the detrimental effects of increased force variability and accuracy on QoL, it is imperative to understand the neural mechanisms associated with force control and advanced age. The neuromuscular and neurophysiologic adaptations that precipitate increases in force variability are multifactorial, taking place at sites throughout the central and peripheral nervous systems (CNS and PNS, respectively), including the motor unit, spinal cord, and brain. Understanding how changes at these levels impact muscle force variability will provide a better understanding of the aging nervous and neuromuscular systems in an increasingly older society.

The motor unit (MU) is the functional unit of the neuromuscular system and the site at which electrical signals in the nervous system are converted to muscular force. A MU consists of a lower motor neuron and the muscle fibers that it innervates (Figure 1).

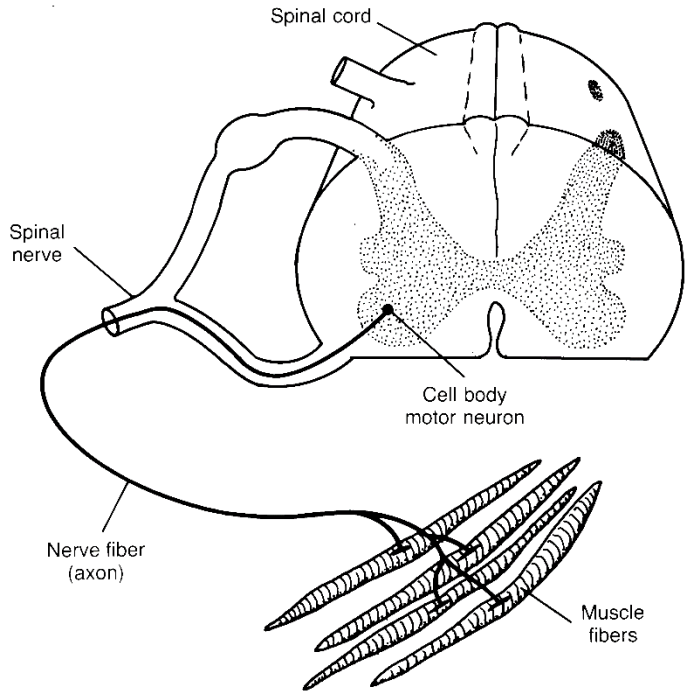

Figure 1. *Diagram of the motor unit, including a lower motor neuron and its associated muscle fibers.*

In older adults, motor neuron death leads to subsequent muscle fiber reinnervation by neighboring motor neurons, resulting in fewer and larger MUs. Larger MUs have reduced discharge rate, conduction

velocity, recruitment range, and voluntary activation[6]. In addition, noise, activation variability and firing rate variability increase in these large MUs with advancing age[6]. Historically, increased MU size was hypothesized to be the mechanism for increased force variability in old adults[16]. However, while increased MU size is associated with aging, it is not the primary driver of force variability in these individuals[17–19]. A substantial body of research indicates that increased firing rate variability, not MU size, is a better predictor of age-related force variability increases[5,18,20]. Sources of firing rate variability are intrinsic to the MU, as well as stemming from spinal and supraspinal origins[5,21]. There are several inputs to MUs that can influence their firing rates, both independent to, and common among, motor neurons. The common synaptic input originates from supraspinal sources, and recent research from Castronovo and colleagues has postulated that common synaptic input predicts MU discharge variability[21].

The common synaptic input (CSI) is the input signal from the CNS that influences a large pool of motor neurons. This low-frequency current is responsible for producing the neural drive to muscle and predicts the extent of muscle force production, as well as force variability. CSI consists of two components: common drive and common noise. Where common drive is the low-frequency signal responsible for force matching, common noise accounts for the higher-frequency fluctuations around the control signal that are related to variations in motor neuron firing rate and force production[22]. Negro and Farina discovered that the CSI is generally transmitted linearly from the motor cortex, such that an increase in firing rate at a cortical level equates to a similar increase at the level of the MU[23]. Furthermore, variability in this signal is predictive of force variability. For example, in a study of upper limb dexterity, Feeney et al. found that variability in the common synaptic input explained 35% of the increased force variability in both young and old adults[24]. Additionally, Negro et al. found in 2009 that the low-frequency input signal was responsible for 60-70% of the force variability during isometric contractions in an intrinsic finger muscle[25]. Another recently published report stated that variability in the common synaptic input, not individual MU characteristics, predicted age-related force variability in the

tibialis anterior muscles[26]. With the mounting evidence that age-related increases in force variability are centrally-based, evaluating cortical mechanisms for peripheral force control detriments is an important next step.

Although previous work has established the importance of CNS input on force control, more research is needed to elucidate the neurophysiological mechanisms of that relationship. Neuroimaging techniques provide opportunities to better understand the associations between age-related central and peripheral nervous system alterations and their effects on functional performance. Transcranial magnetic stimulation (TMS) is a noninvasive neuroimaging technique that induces a magnetic stimulation to the cortex, which can be used to indirectly measure cortical neurotransmitter concentrations and corticospinal excitability. In the context of this study, TMS is used concurrently with electromyography (EMG) in the periphery to assess excitatory and inhibitory cortical signaling. In the current study, a suprathreshold TMS stimulation over the primary motor cortex (M1) was used to elicit a motor evoked potential (MEP) in peripheral muscles during a submaximal contraction, which can be used to estimate excitatory neurotransmitter concentrations. The cortical silent period (cSP) in the EMG signal follows the MEP, providing an indirect measure of gamma amino-butyric acid (GABA), the primary inhibitory neurotransmitter within the nervous system.

Previous work has found that older adults display shorter silent periods than young adults, indicating attenuated inhibitory signaling capacity. This reduced inhibitory capacity has been associated with increased force variability in the upper limbs and impaired gait coordination[27,28]. On the contrary, an opposing relationship has been observed in young adults, where longer silent period duration has been associated with poorer force control[29]. The mechanisms of this dichotomous relationship are not well understood, but some have hypothesized that de-differentiation of cortical networks and increased excitatory signaling in older adults may be related to adverse motor function[27,30]. Therefore, adults who maintain cortical inhibition with age may have a functional advantage. The majority of research on force variability, particularly in regard to its relationship to cortical signaling, has been conducted in the upper

limbs[8,18,24,31,32]. While this research provides valuable information about upper extremity function and the aging process, the results do not necessarily translate to the legs. Therefore, it is important to evaluate these relationships in the lower limb for multiple reasons. This knowledge will expand our understanding of age-related neuromuscular adaptations. Consequently, the purpose of this study was to assess the relationship between lower extremity force output control and cortical inhibition in neurotypical young and older adults. We hypothesized that older adults would display more variable and less accurate knee extensor forces than young adults, and that older adults would display shorter cSPs (indicating less inhibition). Finally, we hypothesized that older adults with longer silent periods would demonstrate better force control, while young adults with longer silent periods would demonstrate poorer force control.

2. METHODS

2.1 Participants

Fourteen healthy young (YA) (six females, age 27 ± 9.8 years) and fifteen older adults (OA) (six females, age 72 ± 5.2 years) participated in this study. All participants were able to ambulate with no assistive device or supervision, had no recent fall history (in the prior 6 months) and were free of any neuromuscular, neurodegenerative, cognitive, orthopedic, or other diagnoses that could impact gait or are known contraindications for TMS. Participants were screened over-the-phone or in-person, and once eligibility was established, participants were scheduled for their TMS visit. This study was part of a larger project evaluating the relationships between TMS metrics and functional performance outcomes. The TMS visit took place on one day and will be described here. This study was performed in accordance with the Declaration of Helsinki and approved by the Colorado State University Institutional Review Board (#17-7053H). All participants provided written informed consent before participating.

2.2 Procedures

2.2.1 Force Steadiness and TMS Protocol

Participants were seated in an adjustable, upright chair with their legs off the ground and hip and knee joints at 90° angles. The distal shank of each leg was attached to a force transducer via a Velcro strap and adjustable bar (Figure 2). The bar was adjusted to account for each participant's leg length and seated foot width, ensuring that the force transducer was parallel to the floor. The dominant and non-dominant legs were both tested in the following approach, with random selection of the first leg tested. Participants were asked to produce several maximal voluntary contractions (MVCs) with their knee extensor muscles, and identification of maximal force was completed when force did not increase, and the two highest forces were within 10% of each other. Subsequently, 15% of MVC force was calculated for each participant and projected to a screen in front of the participants. The visual force feedback consisted of a target force bar, which the participants attempted to match during the TMS trials. Furthermore, to provide feedback on their accuracy, a vertical bar that grew or shrunk relative to the participant force was

also projected to the screen. Participants were instructed to maintain their force as steadily as possible for the duration of the trial, and their voluntary force output was recorded.

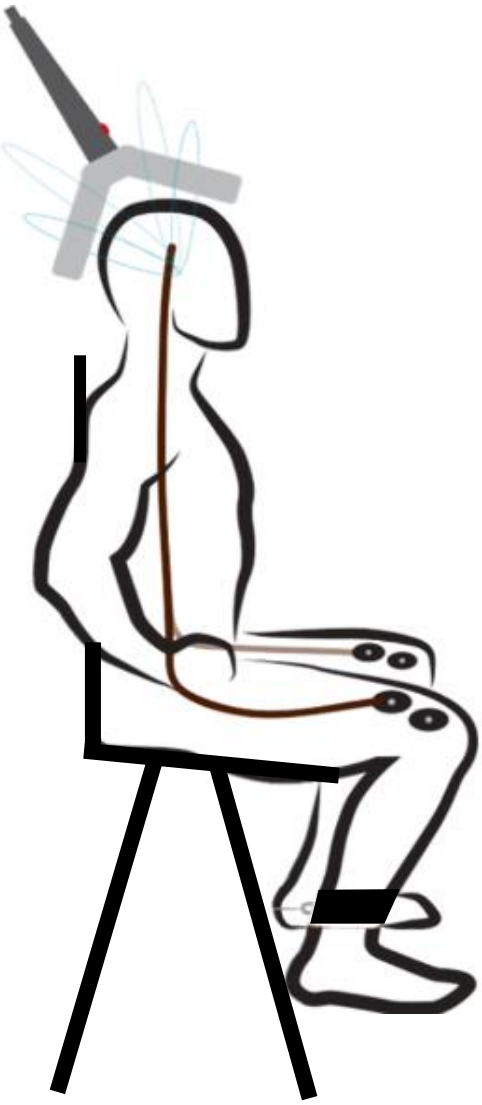

Figure 2. *The TMS and force recording set-up. Participants remained seated in the TMS chair, with their distal shank strapped to the force transducer. EMG electrodes were secured to the vastus medialis oblique muscle to record knee extensor muscle activity throughout the trial.*

While participants were seated in the TMS chair, motor evoked potentials (MEPs) were elicited in the vastus medialis oblique (VMO) muscle of the respective legs using a MagPro ×100 stimulator

(MagVenture, Farum, Denmark) with a 2 × 95 mm angled butterfly coil (120-degree, Cool D-B80). The center of the head (Cz) was determined and marked by measuring from nasion to inion sagittally and from tragus to tragus coronally[33]. After establishing Cz, the location of the M1 was estimated by measuring 2cm laterally and 5.5cm anteriorly, and marks were made in this location as a reference for coil placement. The coil was placed against the scalp at approximately 45° from the mid-sagittal line, roughly perpendicular to the central sulcus allowing for optimal TMS current direction. The cortical "hot spot" for the VMO was established as the location on the scalp where the TMS stimulation resulted in a maximal EMG response from active the VMO. The resting motor threshold (RMT) was then determined in both cortical hemispheres and defined as the minimum stimulus intensity to evoke a response of at least 50μV in five out of ten trials. Electrical muscle activity from the VMO was recorded using bipolar EMG electrodes (Ag-AgCl, 8mm diameter, 20mm distance between electrodes, MVAP Medical Supplies, Inc.), sampled at 1500 Hz and transmitted to a laboratory computer. The cSP was elicited and recorded for both hemispheres and respective legs (Figure 3), and the testing order (right vs. left hemisphere and respective leg) was randomized across participants. The participants maintained an isometric contraction of the quadriceps muscles at 15% of their MVC force throughout the duration of the trial, which lasted two minutes. Throughout this time, the participant received a stimulation at 120% of RMT every 7-10 seconds. This resulted in an average of 12 stimulations per hemisphere[27].

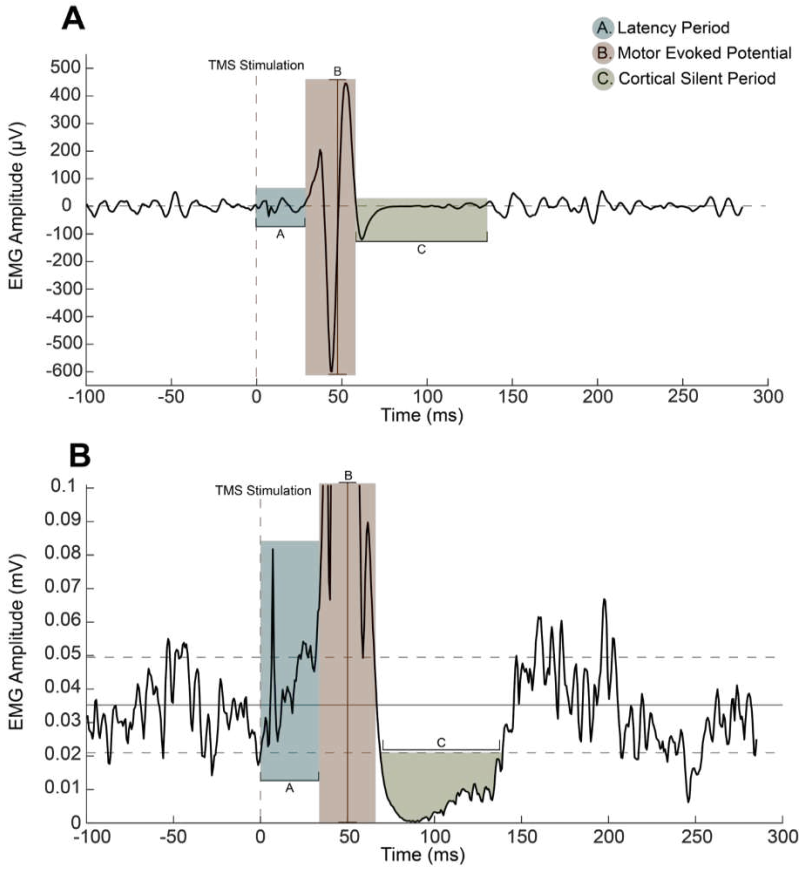

Figure 3. *A) EMG trace of one TMS stimulation from a representative participant. B) Filtered and rectified EMG trace from the mean of all TMS stimulations. The cSP is indicated by the time at which the EMG signal drops 1.5 standard deviations below the total trial EMG mean.*

3. DATA ANALYSIS

3.1 Force Variability and Accuracy Analysis

Force data were imported into a custom MATLAB script and analyzed for force variability and accuracy. For force variability and accuracy measures, the 150ms prior to and 1300ms post-stimulation were removed from the data in order to avoid measuring the force fluctuations as a result of the TMS stimulations. Following stimulation removal, the coefficient of variation (CoV) and root mean square error (RMSE) of each participant's force was calculated in MATLAB and exported as the measure of force variability and accuracy, respectively.

3.2 cSP Analysis

To record cSP, participants maintained 15% MVC force in each leg while the contralateral cortical hemisphere was stimulated. This procedure was repeated in both hemispheres, where the stimulated hemisphere elicited a twitch in the contralateral VMO that was recorded via EMG. EMG signals from the cSP trials were filtered and rectified offline using AcqKnowledge software (Biopac Inc., Santa Barbara, CA). This data was imported into a custom MATLAB (MathWorks, Nantick, MA) script to identify and calculate individual cSP durations following established approaches[28,34]. The EMG signal was extracted from 100 ms prior to each stimulation to 350 ms post-stimulation. The cSP duration was defined as the duration of time that the EMG signal dropped below 1.5 standard deviations of the pre-stimulus mean and ended when the EMG signal returned to within 1.5 standard deviations of the pre-stimulus EMG mean for five consecutive data points.

3.3 Statistical Analysis

All statistical analysis was performed in JMP statistical software (JMP®, Version *13.0.0*. SAS Institute Inc., Cary, NC, 1989-2019.) with the alpha level set to .05. During data collection, we were unable to locate the hot spot for two participants (one YA and one OA). During data processing, one YA did not have quantifiable TMS measures. Therefore, their data was excluded from further analysis. An

exploratory outlier test revealed one force variability outlier and one cSP outlier in the OA group, and those data points were excluded from further analysis. Shapiro-Wilks tests revealed that the data were normally distributed. Intergroup differences in demographic information were assess using independent *t-tests*. We used a 2 x 2 ANOVA to assess between-group (young and old) and leg (right and left) differences in force variability and accuracy. Furthermore, another 2 x 2 ANOVA was used to assess between-group and hemisphere differences in cSP duration. Linear regression analyses were used to identify relationships between leg force control metrics and hemisphere-specific cSP durations.

4. RESULTS

4.1 Participant Characteristics

Participant characteristics are represented in Table 1. The OA were significantly older than the YA (mean age difference = 48 years, $p < 0.001$). The OA had significantly higher BMI than the young adults ($p = 0.009$), though their height and weight were not significantly different ($p = 0.86$ and 0.08, respectively). Finally, the YA reported higher activity intensities than the OA ($p = 0.04$). There were no other significant differences between the YA and OA groups.

Table 1

Demographic, anthropometric, and activity characteristics. Results are reported as mean (SD). p values are representative of main effects of age between groups, with statistically significant differences in bold.

Characteristics	Young adults (n = 14)	Older adults (n = 15)	*p* value
Age (years)	24.36 (3.59)	72.27 (5.76)	**< 0.001**
Female participants (n, % female)	6, 42.86%	6, 40.00%	
Height (cm)	172.72 (8.10)	172.05 (11.06)	0.855
Body mass (kg)	69.03 (13.77)	79.27 (16.17)	0.078
BMI (kg/m^2)	22.98 (3.03)	26.61 (3.85)	**0.009**
Dominant leg (n, % right)	11, 78.57%	15, 100%	
Right leg length (cm)	88.30 (5.10)	92.20 (5.66)	0.159
Left leg length (cm)	88.04 (5.30)	92.16 (5.87)	0.058
Activity frequency (days)	4.57 (1.41)	4.23 (1.95)	0.600
Activity duration (min)	65.36 (18.76)	57.00 (33.16)	0.415
Activity intensity (RPE)	14.36 (1.74)	12.07 (3.69)	**0.044**

4.2 Force Measures

Participant performance in force measures are reported in Table 2. A repeated measures ANOVA (RMANOVA) revealed a significant main effect of group for MVC forces, where YA performed greater MVC forces than OA in both the right and left legs (Figure 4A, mean force difference = 271.07 N, $p < 0.001$). OA displayed a trending main effect of age on normalized RMSE values, where they were less accurate than YA in both legs (Figure 4B, mean normalized force accuracy difference = 0.359, $p = 0.087$). Furthermore, although OA displayed more variable force production than YA, these differences were not statistically significant (Figure 4C).

Table 2

Age group performance on force measures. Results are reported as mean (SD).

	Young adults	Older adults	*p* - value
Right Leg MVC (N)	663.84 (207.24)	401.12 (177.59)	**< 0.001**
Left Leg MVC (N)	656.07 (234.87)	376.65 (164.59)	**< 0.001**
Right Leg Accuracy (RMSE)	0.68 (0.20)	0.79 (0.28)	0.29
Left Leg Accuracy (RMSE)	0.69 (0.27)	0.87 (0.43)	0.18
Right Leg Variability (CoV)	4.09 (1.18)	6.36 (3.91)	0.769
Left Leg Variability (CoV)	4.16 (1.38)	5.39 (2.62)	0.137

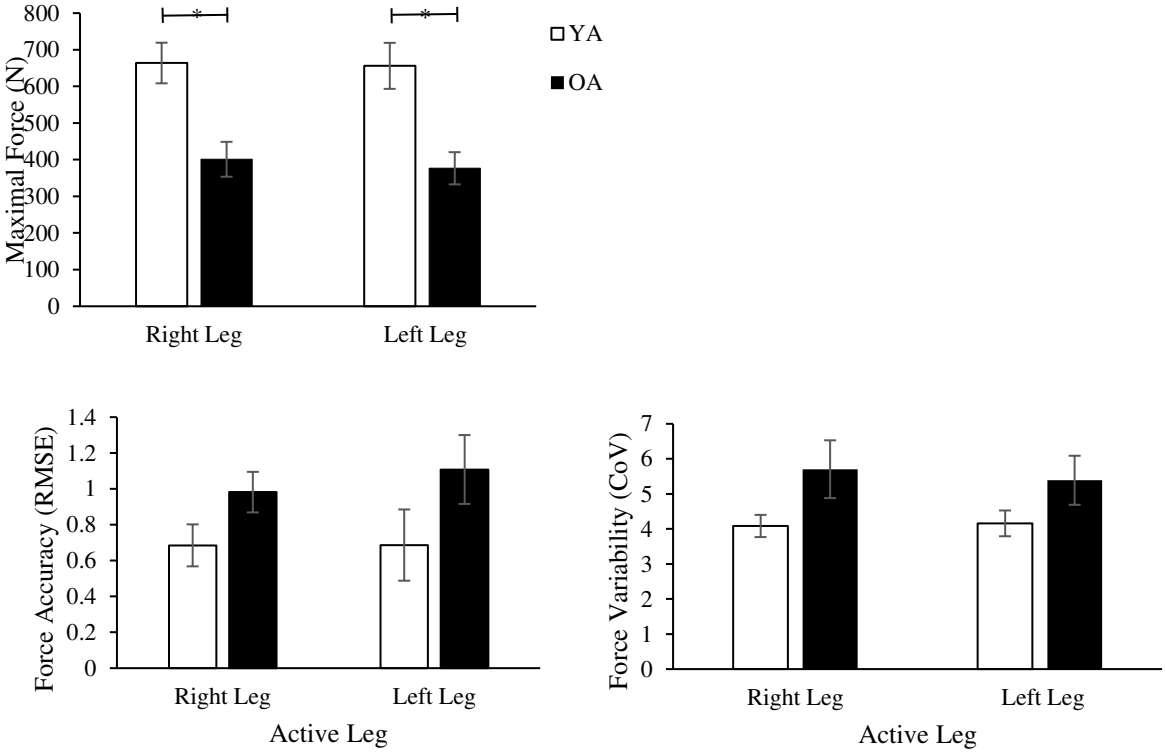

Figure 4. *Age differences between force measures. A) Differences between maximal contraction force in YA and OA.* *p < *0.001. B) Force accuracy differences between YA and OA (*p = 0*.087). C) Force variability differences between YA and OA (*p = *0.045). Error bars reflect standard error.*

4.3 Cortical Inhibition

A RMANOVA revealed both between- and within- participant differences in cSP duration for the YA and OA. YA displayed significantly longer cSPs than OA in the RH (Figure 5), and there was a significant group by hemisphere interaction in the OA, where the left hemisphere cSP was significantly longer than the right hemisphere cSP in the old group. Furthermore, OA demonstrated longer cSPs in the left hemisphere than YA, though this difference was not significant ($p = 0.210$, Figure 5).

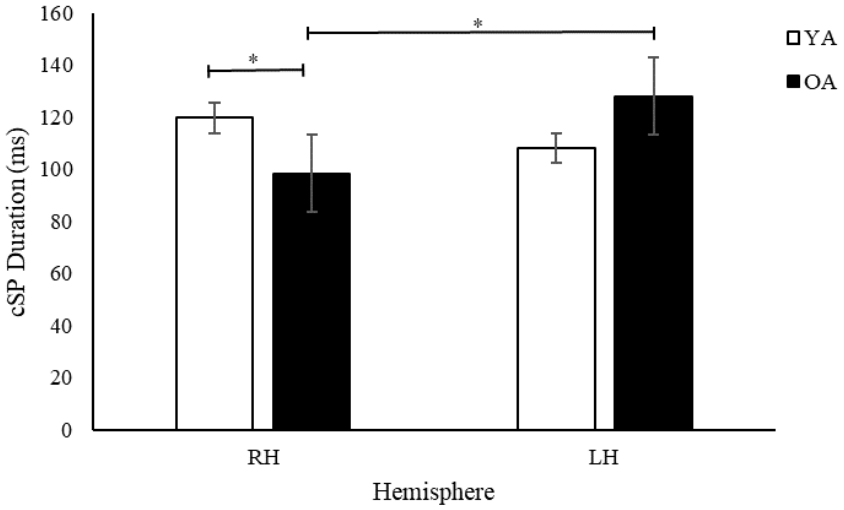

***Figure 5**. Between- and within-group differences in cSP duration between YA and OA. *p < 0.05. Error bars reflect standard error.*

4.4 Inhibition and Force Relationships

4.4.1 Force Variability and Cortical Inhibition

The only significant association existed between left hemisphere cSP duration and right leg force variability in the YA, whereas cSP duration increased, so did force variability in those individuals. However, though there were no other significant relationships between cSP duration and force variability, we observed a similar trend, where in the OA, as cSP duration increased, force variability improved, indicated by a decrease in force CoV (Figure 6).

4.4.2 Force Accuracy and Cortical Inhibition

Linear regressions between cortical inhibition and force accuracy and variability measures revealed weak associations between inhibitory signaling and force measures. Table 3 contains r-values for linear regressions between cSP duration and force measures between YA and OA. Specifically, in OA, longer cortical silent periods demonstrated a negative correlation to force RMSE, where older adults with

more inhibition displayed better ability to match their target force. In the YA, however, we observed the opposite trend, where longer silent periods were associated with slightly poorer force accuracy (Figure 7).

Table 3

R-values for correlations between cSP duration (hemisphere) and leg accuracy and variability. * denotes statistically significant correlations.

Hemisphere	Group	RL Accuracy	LL Accuracy	RL Variability	LL Variability
Right Hemisphere	Young	0.069	0.005	0.39	0.21
	Old	0.103	0.32	0.005	0.31
Left Hemisphere	Young	**0.51***	0.33	**0.60***	0.49
	Old	0.44	0.44	0.40	0.45

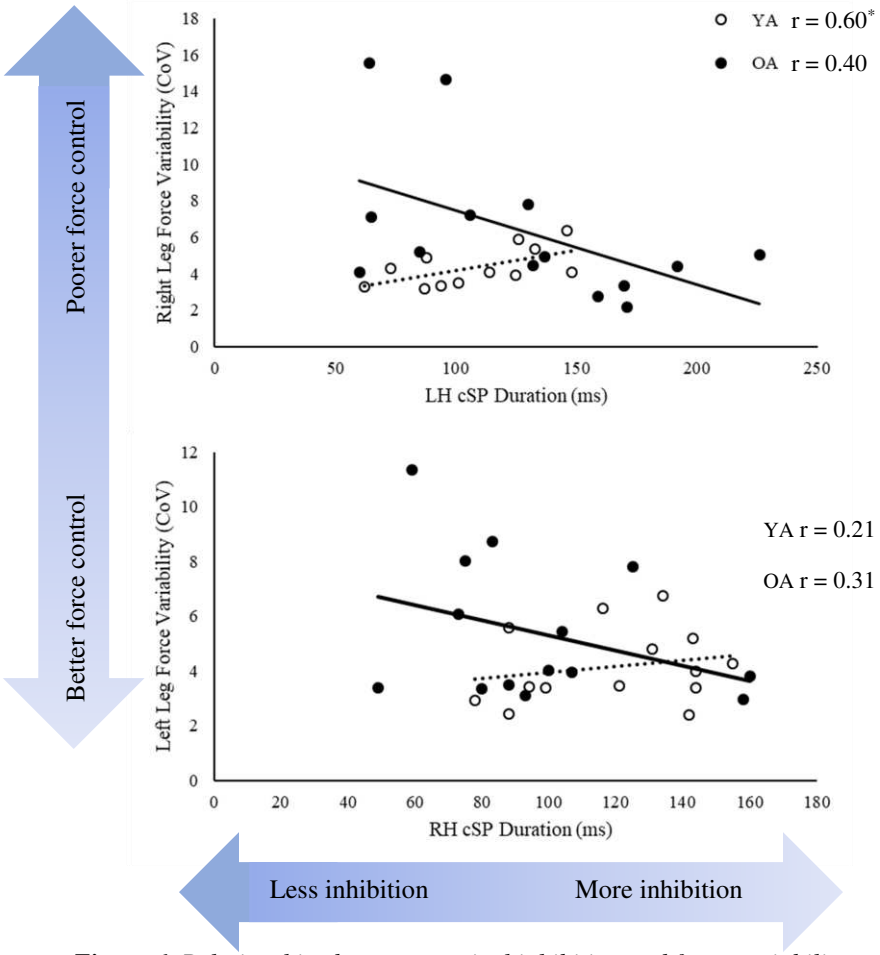

Figure 6. *Relationships between cortical inhibition and force variability measures in YA and OA. A) Relationship between left hemisphere inhibition and right leg variability. B) Relationship between right hemisphere inhibition and left leg force variability.*

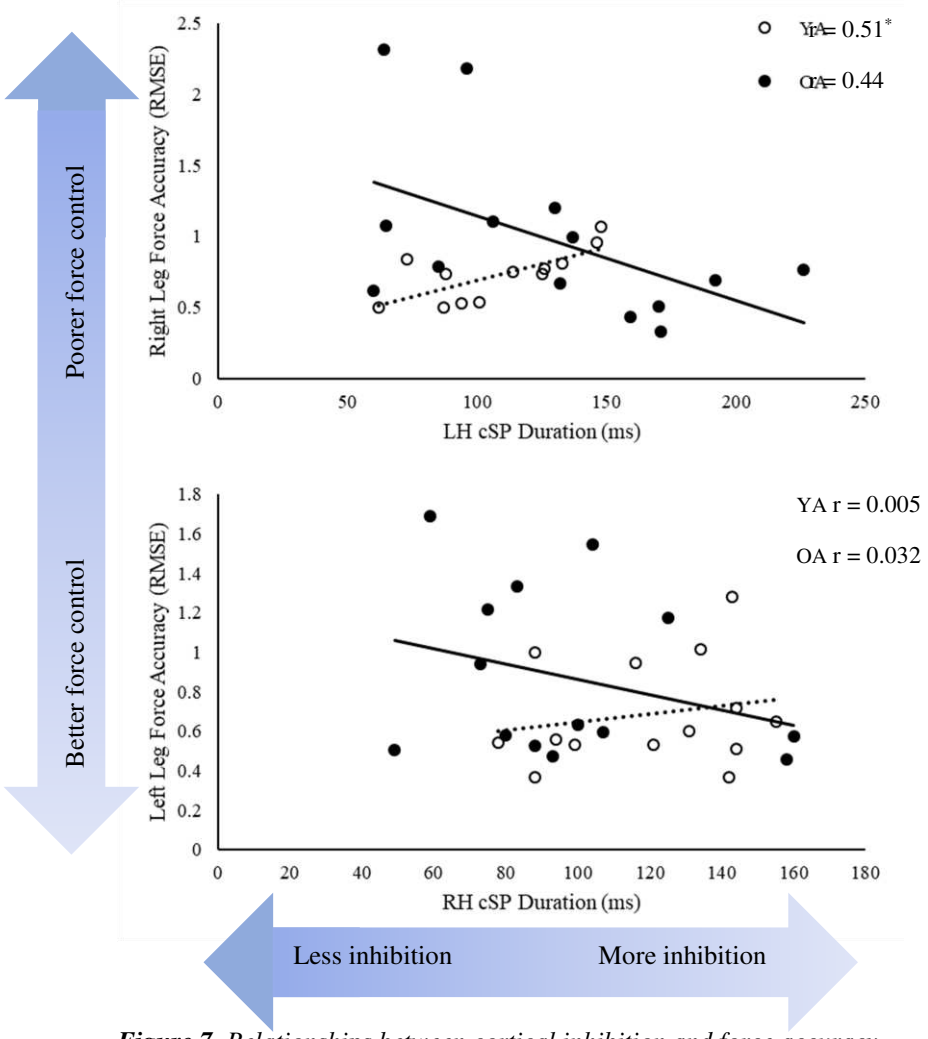

Figure 7. *Relationships between cortical inhibition and force accuracy measures in YA and OA. A) Relationship between left hemisphere inhibition and right leg accuracy. B) Relationship between right hemisphere inhibition and left leg force accuracy.*

5. DISCUSSION

The purpose of this study was to evaluate associations between cortical inhibition and force variability and accuracy in young and older adults. We hypothesized that OA would perform more poorly in the force control task than YA, in both force accuracy and force variability measures. Furthermore, we hypothesized that OA would display shorter cSPs (less inhibition) than YA and that OA with more inhibition would achieve better force control performances than their counterparts with less inhibition. Finally, we hypothesized that YA with more inhibition would demonstrate poorer force control, as previous reports have shown for the upper limbs[27,28]. To our knowledge, this is the first study to evaluate relationships between cortical inhibition and force control in the knee extensors of young and older adults.

Older adults performed more poorly at the force matching task than their younger counterparts in both legs, though this difference was not significant. Furthermore, in the right leg, older adults did display significantly more force variability than YA, though this difference was not observed in the left leg. Older adults displayed less inhibition in the right hemisphere as compared to YA, demonstrating decreased levels of $GABA_B$ activity on that side of the brain. Moreover, there was a significant difference in inhibitory signaling between the right and left hemispheres of the older adults, in that more inhibition was present in the left as opposed to the right hemisphere in this group. Linear regressions between cSP duration and force accuracy and variability measures in the young and older adults revealed one significant relationship in the YA, where YA with more inhibition in the right hemisphere displayed poorer force variability control in the left leg. There were no other significant associations, though there was a trend that older adults with more inhibition displayed better force control, while YA with more inhibition demonstrated poorer force control.

5.1 Force Measures

5.1.1 Maximal Force Production

The OA displayed significantly lower maximal forces than the YA, which is in accordance with previous reports[14,35–38]. We demonstrate significantly lower maximal voluntary force in the quadriceps muscles of OA as compared to YA, with a mean difference of nearly 40% between the YA and OA groups. Previous research has established similar force discrepancies between YA and OA in the knee extensors. For example, Tracy and Enoka found a 33% difference in maximal knee extensor force between YA and OA, and Christou and Carlton observed a 38% difference[36,38]. Therefore, the observed difference in this study is consistent with other healthy aging research. The mechanisms for force decreases in the OA population are likely varied and include declines in muscle cross-sectional area and muscle fiber quality[6]. Specifically, these aged muscle fibers display lower protein synthesis as compared to those in YA, lower specific tension (force per unit area), and impaired calcium turnover rates[6]. Seminal work in neuromuscular aging has reported that much of the loss of muscle force is associated with age-related muscle atrophy, as well as detriments in muscle contractile properties [39–41]. The preferential loss of type II muscle fibers in age-related sarcopenia also impacts force production capacity in these individuals. Type II fibers are important for maximal force production, so their decline impairs older adults' abilities to produce large forces, especially when producing that force quickly[42].

5.1.2 Force Accuracy

Force accuracy was not different between the YA and OA in this study. Research on force accuracy in the aging population is limited, though there is evidence that OA perform more poorly than YA at force matching activities[13–15,43–46]. However, the majority of research on force accuracy has been completed in intrinsic hand muscles or small muscles of the upper limb. For example, Christou and colleagues conducted a study in which participants performed isometric contractions with the first dorsal interosseus muscle, matching a force that was 25% of their MVC. Furthermore, this study and other

similar studies differed from the current project in that these authors were evaluating end-point force accuracy as compared to force-matching accuracy in general over the course of a continuous muscle force production task. Specifically, the participants in these studies were required to reach the target force within 150ms, and their end-point accuracy was defined as the error from the target force and target time[45]. Lodha et al. performed a similar end-point accuracy study evaluating accuracy of the dorsiflexor muscles and overground walking in stroke survivors compared to neurotypical OA[44]. In a training study by Hortobagyi and colleagues, young and old participants performed isometric, concentric, and eccentric knee extensor force-matching activities. In the isometric task, a 25N target force was projected to a monitor in front of the participants, and participants were instructed to match the target force as steadily as possible. The authors did not note the duration for which the participants must match the force. Furthermore, these authors used the 25N force for all participants, regardless of age or MVC force. They found that OA performed a force matching task with less accuracy than YA and that this error was improved after a resistance training protocol but did not achieve the accuracy values reached by the YA[14].

These prior studies have observed differences between YA and OA in force accuracy, but it is important to note the differences not only in the muscle groups studied but in the specific force matching tasks and study paradigms. Most research in this area has evaluated upper limb force accuracy, particularly in the FDI muscle, and much of the lower limb research has been completed in the plantar- and dorsiflexor muscles of the leg[43,44]. Differences in the size of the muscles studied could also influence force accuracy outcomes. For example, Poston and colleagues (2007) found that in an end-point accuracy test, young participants displayed poorer force accuracy with the second palmar interosseus muscle (a small adductor of the first finger) than with the first dorsal interosseus muscle (a comparatively larger hand muscle)[46]. They argue that muscle size may be predictive of the muscle's capacity to produce accurate forces, with larger muscles being more accurate than smaller muscles[46]. These findings may partially explain the lack of difference between YA and OA for force accuracy in this study, as the inherent qualities of the larger quadriceps muscles may promote more accurate force matching in OA.

5.1.3 Force Variability

There were no significant force variability differences between the YA and OA. Though OA displayed more variable knee extensor forces than YA in both legs, these differences were not statistically significant. While it is generally understood that force variability increases as a function of age, some work in larger muscles groups has shown no differences in force variability between young and old adults[19]. For example, in the elbow flexor muscles, Graves et al. found no differences in force variability between young and old adults[47]. Furthermore, Holmes et al. demonstrated no differences in force steadiness in the plantar- and dorsiflexors muscles during a co-contraction task in young and old adults[48]. However, in smaller muscles groups (i.e. intrinsic hand muscles), force variability reliably increases with advancing age[4,15,43].

Similar to force accuracy, force variability may decrease as a function of increasing muscle size. A 2004 study by Hamilton et al. revealed that motor output variability improved with increasing muscle size by evaluating torque CoV for several different upper limb muscles[49]. If the age-related increases in force variability primarily occur at low force levels, muscles that produce comparably large forces may not demonstrate similar impairments to these age-related neuromuscular adaptations[5]. Muscles like the first dorsal interosseus muscle (a first finger abductor) that are capable of producing relatively low forces could be more susceptible to age-related changes in control[19].

5.2 Age-Related Inhibitory Differences

Significant between- and within- group interactions reveal important potential effects of age on corticospinal neurophysiology. YA displayed significantly longer cSPs in the right hemisphere than old adults, demonstrating more GABA-ergic activity than OA in that hemisphere (Figure 4). Additionally, within the OA group, more inhibition was present in the left hemisphere than in the right (Figure 4). Preceding work has found similar between-group differences for inhibition, though the results on this finding are inconsistent. For example, Fujiyama and colleagues found that OA displayed less inhibition in

both hemispheres when performing a bimanual motor task[50]. Furthermore, work from Bashir et al. revealed that OA displayed significantly less inhibition in both hemispheres as compared to YA during a repetitive TMS trial[51].

Much aging research in the cognitive field has found inhibitory dysfunction in older adults, which has been previously reviewed[52]. One such study indicated that, in a "Go/NoGo" task where participants were asked to respond to relevant stimuli but ignore irrelevant stimuli, inhibitory signaling was diminished in the older participants as compared to middle-aged and young participants. Furthermore, this study revealed that older adults had more diffuse activation throughout motor planning and cognitive cortical areas during the task[53]. Other work has also shown widespread activation in OA to perform decision-making and motor tasks[31,50,54]. Recent functional connectivity research from Cassady et al. (2019) indicated that the sensorimotor network in OA was less segregated than that in YA, as well as that OA had lower concentrations of GABA. OA in this study also performed more poorly at a battery of tasks assessing sensorimotor functioning. Through a mediation analysis, they illustrated that performance on the functional tasks was associated with GABA concentrations and mediated by sensorimotor network segregation[31]. They posit that the increased activation in accessory brain areas during motor tasks may be mediated by a loss of inhibitory functioning. Our study revealed lower GABA-ergic activity in older adults' right hemisphere, which may influence functional outcomes for those individuals.

These inhibitory differences could fit into two different neural aging models: the right hemi-aging hypothesis or the hemispheric asymmetry reduction in old adults (HAROLD) model[55]. The right hemi-aging model states that cortical functions controlled by the right hemisphere are more affected by the effects of aging than those associated with the left hemisphere[55]. This is evidenced by studies that reveal that functions controlled by the right hemisphere are impaired to a greater extent than those for which both hemispheres or the left hemisphere are responsible[56,57]. Research in this field has found that on intelligence tests, OA display better performance on the verbal component of these tests compared to the spatial component, each of which are representative of left and right hemispheric functions,

respectively[55]. The apparently impaired inhibition in the right hemisphere of our older adult participants may be evidence for this theory; the diminished inhibitory function on that side of the brain could be implicated in the deficits associated with the right hemisphere in aging. Furthermore, the significant interhemispheric differences in the OA group may be a compensatory mechanism for the deficits in the right hemisphere. Much work has found that individuals become more strongly handed with age, and with the importance of inhibition for motor control, more inhibitory signaling in the dominant (left) hemisphere likely supports this[58,59].

The HAROLD aging model proposes that frontal lobe functions are less lateralized in OA than YA. Within this theory, two different mechanisms have been suggested. The first is that the diminished lateralization is compensatory, that additional areas of the brain contribute to function because the areas activated in YA are impaired in OA. The other hypothesis is that dedifferentiation occurs, or functional brain areas become less segregated, and is the cause for impaired function in OA. The 2019 study from Cassady and colleagues provides support for the second theory in that impaired sensorimotor function was associated with GABA concentrations and mediated by a lack of functional network segregation[31]. However, a PET study by Cabeza et al. (2001) found that OA with more activation in both hemispheres performed better in a functional test than OA with similar activation patterns to YA, supporting the compensation theory for HAROLD[60]. In the current study, increased inhibition in the left hemisphere as compared to the right may also provide support for the HAROLD model, in that the increased left hemispheric inhibition may reflect asymmetrical reductions in this group.

5.3 Relationships between inhibition and force control

The only significant correlation between inhibitory function and force control performance in this study was the moderate association between left hemisphere inhibitory signals and right leg variability of YA ($r = 0.6$, $p = 0.04$). Though no other significant relationships were found, an age-related trend appeared, where better force control (lower force CoV and RMSE) was associated with more inhibition in the OA, and the opposite relationship was apparent in the YA. Previous work in our lab found that

differences in inhibitory signals in YA and OA were related to differences in bilateral walking coordination. Specifically, that study indicated that OA with more inhibition displayed better bilateral coordination than their counterparts with less inhibition, and YA with more inhibition displayed poorer coordination[61]. Another similar study found that in the upper limb, OA with more inhibition performed better at a motor control task, but YA with more inhibition performed the task more poorly[29]. Both these previous studies, however, were evaluating force control in different contexts than that of this study: bilateral walking coordination and upper limb control.

Cortical inhibition is imperative in the control of the upper limb to avoid mirror movements during bimanual tasks. The hemispheres must work together to manage excitatory and inhibitory signals and ensure that activities of daily living, which often require the hands to work independently of each other, are completed successfully. Furthermore, in whole-body coordination, precise control of individual body parts in time and space is crucial for successfully maneuvering the complex physical environment that daily life entails. The results of the current study indicate that the mechanisms that regulate upper limb and whole-body coordination are likely different than those that are responsible for controlling muscle-level force variability in the legs.

In regard to the control of quadriceps muscle force variability, several mechanisms likely contribute to age-associated increases in force variability, including changes to the motor unit (MU), common synaptic input (CSI) and cortical neurotransmitters in addition to GABA. Individual and population MU properties can influence motor control through several mechanisms. For example, in a simulation and experimental study by Taylor and colleagues (2003), the authors cite three ways in which MUs contribute to force variability: organization of the MU pool, recruitment and firing rate properties of the MUs, and the pattern through which the MU pool is activated. In muscles with fewer MUs, the contribution of individual MUs to overall muscle force control is greater. Therefore, discharge rate variability of individual MUs within that muscle will influence force variability[20]. This may be an additional mechanism for Hamilton's finding that smaller muscles display more force variability than

their larger counterparts[49]. The large number of MUs in the quadriceps muscles may assist in dampening the effects of individual MU twitch force variabilities on overall force variability, accounting for the lack of significant force variability differences in the current study. Furthermore, muscle force is regulated by changing the number of MUs recruited and the firing rate of active MUs. As more MUs are recruited to increase muscle force, the pattern in which they are recruited and firing rate variability will affect the variability of the muscle force[20]. Finally, the way in which the pool of MUs is activated and regulated with influence force output. This is largely influenced by the CSI to the MU pool.

Motor neurons receive many types of inputs from throughout the nervous system, both independent to individual neurons and common among the motor neuron pool. In order for motor neurons to appropriately regulate force production, there must be a common signal reaching a large proportion of the motor neurons. If individual motor neurons were producing output coming from all different sources of input, they would not be able to adequately activate motor units to produce muscular force. The CSI is the low-frequency input that is common among the motor neuron pool that provides the signal necessary for effective neural drive to muscle and can be detected as the signal that is common among motor neuron *outputs*, as it is maintained by the neurons[22]. The effects of individual inputs to motor neurons are largely cancelled out due to the process by which motor neurons average the various inputs and produce an effective output. Castronovo and colleagues (2018), in a study evaluating force variability differences between YA and OA, found that the increased motor output variability in OA was largely predicted by increased strength and variability of the CSI[26]. The CSI is considered to originate in the cortex, but it may not be closely linked to corticospinal inhibition and may regulate force control through other avenues. Specifically, interactions between several types of neurotransmitters and brain structures likely influence the CSI signal and determine its variability.

This study evaluated the relationship between $GABA_B$, as assessed by TMS using the cSP, to evaluate force control relationships. While measuring approximate GABA levels may be a valuable potential target for observing changes in force steadiness, it may also be an approach that is too simplistic

to measure the complex age-related changes in force control. We observed significant interhemispheric differences in inhibition in the OA group, but this change is likely also accompanied by changes in other neurotransmitter activity, including glutamate, dopamine, and cholinergic function[62]. While GABA concentrations did not appear to strongly influence force control outcomes in this study, they may have played a more nuanced role than we hypothesized. Imaging techniques like magnetic resonance spectroscopy allow for more accurate quantification of cortical neurotransmitter concentrations, and by enabling scientists to evaluate relationships between neurotransmitter concentrations (i.e.: through ratios of excitatory to inhibitory neurotransmitters), they may be able to elucidate the complex relationships between cortical neurophysiology and force control in aging[53,63,64]. Future studies should quantify relationships between inhibition and excitation to determine whether those affect force control outcomes in OA.

6. LIMITATIONS

This study provided insight into age-related changes in neurophysiology and functional outcomes in OA. However, it is limited in several ways. First, the small sample size could have prevented some of the force control and relationship findings from reaching statistical significance. Secondly, the active OA in this study likely do not reflect the spectrum of function in the aged population. The healthy, active OA that we recruited for this study may have been too healthy to see differences between groups. Furthermore, this study was not powered to detect sex or leg dominance differences in the participants. Additionally, while inhibitory signaling is a crucial regulator of force control, the type of evaluation we performed may have been too narrow to provide a full picture of the complex regulation of force control in aging. Future multimodal approach studies should measure $GABA_A$, as well as other types of neurotransmitters and nervous system structures and function to determine the various contributors to motor control. Finally, while significant relationships were not observed in the quadriceps muscles, those results do not necessarily translate to other muscles of the lower limb, and further research should evaluate the influence of cortical inhibition on force variability in the knee flexors and dorsi- and plantarflexor muscles.

7. CONCLUSION

Force variability and accuracy output is impaired with age and adversely impacts QoL in older adults. Furthermore, force control and overall coordination have previously been shown to be related to cortical inhibition in OA[27,54,61]. Though differences in force accuracy were not significant, OA in this study generally displayed less accurate forces than YA. Additionally, in the right leg, OA exhibited significantly more variable knee extensor forces than their YA counterparts, but no other significant differences were found in force variability between the YA and OA groups. The lack of significance may be related to the large muscle group studied in this project, or it may be due to the small sample size of the study.

There were significant differences in right hemisphere inhibition between the young and old adults, revealing a potential right hemisphere-related effect of aging in the OA. This supports the right-hemi aging model that has been previously discussed[55]. Furthermore, within OA, the left hemisphere displayed more inhibition than the right, indicating a possible effect of handedness in these individuals and preferential use the of left hemisphere over the right for force control. This may also be related to age-related to cortical de-differentiation in OA. In regard to the relationships between cortical inhibition and force control, weak associations existed between cortical inhibition and force control in these individuals, revealing that cortical inhibition, as assessed by TMS and the cSP, may not be influencing force variability in old adults. Future work should evaluate the complex aging system and understand that force variability is likely influenced by several mechanisms working in concert rather than one particular component of the neurophysiological or neuromuscular system.

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