THE STRUCTURAL, FUNCTIONAL, AND BEHAVIORAL PLASTICITY OF

SENSORIMOTOR INTEGRATION

By

ALEJANDRA BARRERA CURIEL

Bachelor of Science in Physical Education
Benemerita Universidad
Puebla, Puebla, Mexico
2011

Master of Science in Leisure Studies
Oklahoma State University
Stillwater, OK
2015

Master of Science in Management and Marketing
Universidad Popular Autónoma del Estado de Puebla
Puebla, Puebla, Mexico
2015

Submitted to the Faculty of the
Graduate College of the
Oklahoma State University
in partial fulfillment of
the requirements for
the Degree of
DOCTOR OF PHILOSOPHY
July, 2020

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INTEGRATION

Dissertation Approved:

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Dr. Jason DeFreitas, Chair

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Dr. Tim R. J. Passmore

_____

Dr. Nathaniel D. M. Jenkins

_____

Dr. Jerome Hausselle

ACKNOWLEDGEMENTS

During my defense, Dr. Passmore asked me, what did I learned during my PhD? I started thinking about neuromuscular changes, motor unit behavior, etc.; but then as I have had more time to analyze it, I came to the conclusion that the most important thing I learned was that to earn a degree, you need the support and love of those around you.

Este camino empieza con mi familia, la familia Barrera, quien con su ejemplo me enseñó a luchar por mis sueños; y la familia Curiel, quien con su bondad me enseñó a ser una mejor persona. La unión de ambas, Barrera – Curiel, me dio la mejor familia que pude haber soñado; mis dos pilares, Gorri y momi. Gorri, en quien siempre he tenido un superhéroe listo para rescatarme; y mi momi, quien me dio mis alas para volar. Mis hermanas, Parmen, quien desde pequeña me exigió y guio para dar lo mejor de mí, y Luluchas, quien con su ejemplo me enseña lo lejos que puedo llegar. Mi nueva familia, Rafa, quien me enseña que la felicidad está en disfrutar lo que tenemos; mis sobrinos, Fer y Pau, quienes con su sonrisa iluminan mis días; mi suegra, quien con cada visita nos llena de amor y alegría; mi cuñadits, quien me enseña a disfrutar el presente; y Vale, quien hoy como médico me enseña el valor de la responsabilidad. Todos y cada uno han sido elementales en este proceso, gracias por cada lección, palabra, consejo, y por creer en mí. Gracias a estos fuertes cimientos me animé a seguir este camino; tenía la certeza de que sin importar lo alto o lejos que volara, siempre iba y voy a contar con mi familia. Hoy más que nunca quisiera estar con ustedes, pero mi corazón los siente aquí a pesar de la distancia.

Después, durante la preparatoria, por primera vez me pregunte qué quería ser cuando fuera grande. Gracias a profesores, amigos, y mi tribu empecé un camino de autoconocimiento. Gracias mi hermosa tribu por hacerme sentir tan especial, a Jess, mi forever 360 pvt tq1mmbymr, a Ale, mi conciencia gramatical, a Chio, mi porción llena de magia, a Andie, mi compañera científica café con leche, a Gaby, mi búsqueda incansable de la perfección, a Rosy, mi parte humana en el mundo de la ciencia, a Dany, mi

luchadora constante, y a Brenda, mi paz mental. Llevamos ~20 años de amigas y vamos por una eternidad.

After high school, Oklahoma became part of my dream when 15 years ago, a very beautiful family received into their lives and hearts. To my American/Oklahoman/Mexican family, thanks for being there for me; here was where the dream of studying abroad became tangible because I knew I had a family to come to when I decided to leave my country. Conrado y Denise, siempre me han hecho sentir parte de la familia, han cuidado de mi como una hermana, hija, amiga, gracias por haber hecho cada transición a Oklahoma más fácil, gracias por ser mi familia.

La vida me sorprendió durante la universidad, por un momento me perdí, pero gracias al apoyo de profesores honestos y amigas que se convirtieron en familia, aprendí a dejar las cosas fluir. Gracias Chelo, por haber estado allí en uno de los momentos más difíciles de mi vida y apoyarme hasta que me volví a levantar; gracias profesor Gerardo por defenderme y hacerme saber que hay gente que luchará contra las injusticias; gracias profesor Benjamín, por enseñarme el tema de la propiocepción, y sembrar en mi la semilla de la investigación. Gracias vida y Dios por haber cambiado mi destino.

Finally, all of these steps led me to Oklahoma State University, where I found great Mexican and non-Mexican friends who made the weight of being away from family so much lighter, Brenda, my all smiles friend; Sergio, my grumpy on the outside sweet on the inside friend, Marla, my cheerleader, Ish, my fitness junky; Curtis, my open-minded comrade; Javi, my traveling pal; Tania, my dog loving friend; Chio, my sport's rival; Rebe, my team; Moni, my crazy friend; Zaira, my debate mate; Paty, my partner in crime; and Miguel, my kiddo friend.

When I started the PhD, in our first meeting I met the other students that were pursuing the same goal; I still remember our eagerness to prove who we were. Soon these students became friends each one of them taught me something. Tyler, Mike, Cameron, and Masoud, I could not have asked for better partners in crime; Cameron, thank you for being patient with my 1000 questions a day; Mike, thank you for bringing all of us together and for all the comida; Tyler, thank you for always sharing materials that you had developed; Masoud, thank you for being my partner for group projects. In addition, thanks to the guidance of previous generations, they were patient and eager to teach me, Ryan and Mitch, thank you for giving me the confidence and support I needed at the beginning; and Garret, thank you for teaching me the ropes, if I got this position was thanks to you. Also, thank to those that made data collection possible, without your

support and encouragement the process would have been much more difficult, Jojo, my FEMALE partner in crime; Rob, with your fantastic questions that always challenged me; and Tyler, the quickest learner I have met. Furthermore, thank you to the faculty members that guided me through this process, Dr. Passmore, thank you for helping me start my journey at OSU and support me until the end; Dr. Price, thank you for making me feel special, for your constant support, and your friendship; Dr. Stock, thank you for teaching me how to use TMS; Dr. Jenkins, thank you for lending me all your toys; Dr. Hausselle, thank you for being part of this process; and foremost, thank you Dr. DeFreitas, you made this dream possible and you helped me achieved it. The first time I met you I was shaking, I was impressed by your CV and worried you would notice my lack or research experience. However, you focused on my determination and dedication and gave the opportunity of a lifetime. The PhD was a journey of constant challenges and doubts but you always had a kind word accompanied by great wisdom. Today, I leave a better scientist and person.

Finally, I want to thank my love, my accomplice, my best friend, my coworker, my person, Jesús. The PhD has been the biggest professional and personal challenge I have had to endure, specially this last year; through your patience, love, humor, and dedication, I was able to get to the finish line, which became very blurry due to the pandemic. People have described me as someone determined, but they do not know how much of my strength comes from our union; thank you, soulmate.

Therefore, to all of you and the ones I might have missed, I am forever thankful. Este camino no ha sido fácil, me detuve, regresé, quise bajar, pero su apoyo me ayudo a continuar, hoy llegue al Everest, no fue fácil, pero valió la pena. Creía que llegar al pico era lo más importante; sin embargo, veo que el camino fue lo mejor, cada risa, derrota, duda, alegría, tristeza, reto, me hicieron una mejor persona. Gracias por estar conmigo durante este magnífico camino vamos por el siguiente reto.

Name: ALEJANDRA BARRERA CURIEL

Date of Degree: JULY, 2020

Title of Study: THE STRUCTURAL, FUNCTIONAL, AND BEHAVIORAL

PLASTICITY OF SENSORIMOTOR INTEGRATION

Major Field: HEALTH AND HUMAN PERFORMANCE

Abstract: The general purpose of this dissertation was to analyze structural, functional, and behavioral changes of sensorimotor integration. Study 1 was designed to analyze the effects of altered stretch reflex sensitivity, via vibration, on motor unit behavior. We discovered that altering muscle spindle function resulted in altered MU behavior, with an increase in recruitment thresholds, decrease in firing rates, and reduced motor output; 9% reduction in maximal strength. Study 2's goal was to analyze structural and functional changes associated with aging, their relationships, and how they affect performance. Older adults had smaller CSA_{RF} (~5cm2), lower MQ_{RF} (~14 au), greater R_{MAG} (~10% MVC), less STR (~101Nm), slower RTD (~554 Nm/s), and poorer balance (~ 0.5 sway index) when compared to the younger. The middle-age group had smaller CSA_{RF} (~2 cm^2), less STR (~ 39 Nm), slower RTD (~ 415 Nm/s), and poorer performance (~0.29 sway index) when compared to the young group. When comparing the middle-age group to the older group, the older group had smaller CSA_{RF} (~3cm^2), less STR (~63 Nm) and poorer balance performance in the balance conditions EOSS and ECSS (~0.55 sway index). Variance in STR and RTD were explained by CSA_{RF} and R_{MAG} (STR: ~65%; RTD: ~13%). However, most of the variance in RTD was explained by MQ_{RF} (~32%). Regarding balance, R_{MAG} was the functional variable explaining most of the variance in EOSS (~30%) condition and CSA_{RF} explained most of the variance in ECSS (~99%). Study 3 was designed to identify the determinants behind the age-related changes in antagonist muscle coactivation. The study is still in progress; so far it seems that the variables related to greater coactivation are: cortical agonist-antagonist representation areas overlap, the location of the muscles center of gravity and cortical inhibition. Therefore, age alters many dimensions in the control of voluntary movement; in these studies, we showed the relationship between spindle function and motor unit behavior and output; then we saw discovered significant relationships between sensory variables and motor variables and how they affect performance. In conclusion, to understand the aging process, it is important to analyze plasticity of sensorimotor integration as a whole.

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CHAPTER I

INTRODUCTION

Movement control is organized through the coordination of muscle pairs mediated by

central and peripheral mechanisms [1-4]. During movement, descending, efferent drive from

supraspinal mechanisms[1,5] and afferent feedback[2,3,6-8] are translated by complex spinal M

However, motor control is affected by the neuromuscular reorganization that the system

undergoes with aging[6,7]. In order to understand this neuromuscular reorganization,

Papegaaij and collaborators[7] provided three main dimensions to categorize and relate

age-related changes. The three categories are, structural, referring to neuromuscular

changes; functional, modifications in how the neuromuscular structures operate; and

behavioral, which denote changes in performance. Regarding behavioral changes, older

adults show poorer postural control [6,10,11], less coordination[12], and slower and weaker

movements[13-15]. The underlying structural and functional mechanisms behind the lower

performance include, loss of muscle mass and quality[16-20]; degradation of the

somatosensory system[6,21,22]; reduction in myelinated and unmyelinated fiber density[23]; shrinkage of cortical gray and white matter volume[24,25], decrease proprioceptive sensitivity[26], slower conduction velocity in peripheral nerves[27], change in muscle activation patterns[7,28-30], decreased spinal and cortical inhibition [31,32], among others. Furthermore, different studies have shown how one domain affects the others[6,7]; still the bigger picture is not very clear. For example, recent studies have shown that muscle spindles provide 8 – 30% of the excitation to the motorneuron pool[8,33-37]. However, these structures undergo morphological, biochemical, and function degradation with aging[6,15,21]. Altered spindle function, related to aging, could lead to less excitation to the motoneuron pool, preventing higher threshold motor units from activating[8]; thus it is possible that muscle spindle atrophy leads to muscle atrophy which affects other variables such as strength [13,14] and postural control [6,10]. Another example, is the functional adaptation where older adults use a disproportionate heightened coactivation during voluntary movements [7,29,30,38]. Underlying mechanisms related to this phenomenon include, less reciprocal inhibition[39], decreased presynaptic inhibition[31], and decreased spindle sensitivity[28]. Furthermore, increased antagonist coactivation has been associated with poorer performance [29,30]. To our knowledge the studies analyzing the relationship between age-related changes, are limited to one or two dimensions[21,40-43] or involve a review of other studies[6,7,28,38]. Since aging affects several domains of movement control, it is important to incorporate the three domains within the same protocol to further our understanding of aging.

Therefore, the general purpose of this dissertation was to analyze structural, functional, and behavioral changes of sensorimotor integration.

CHAPTER II

THE EFFECTS OF VIBRATION-INDUCED ALTERED STRETCH REFLEX SENSITIVITY

ON MAXIMAL UNIT FIRING PROPERTIES

2. Barrera-Curiel, A., Colquhoun, R.J., Hernandez-Sarabia, J.A. & DeFreitas, J.M.
(2019). The effects of vibration-induced altered stretch reflex sensitivity on maximal unit
firing properties. *J Neurophysiol., 121*: 2215 – 2221.

2.1. Introduction

Motor unit activation is controlled through the integration of descending, efferent drive

and afferent feedback, which provides a reflex assistance to supraspinal input (Macefield

et al. 1993). Collectively, these two mechanisms provide excitation and inhibition

(respectively) to motoneurons. Thus, changes in both central (i.e. descending drive)

and/or peripheral (i.e. afferent feedback) mechanisms could result in altered excitability

of the motoneuron pool.

Tendon or muscle vibration can alter the efficacy of the homonymous Ia afferent-alpha-

motoneuron pathway (Burke et al. 1976; Burke & Schiller, 1976; Desmedt & Godaux,

3

1978). Vibration has been shown to have both facilitatory and suppressive effects on muscle spindle activity, with either resulting in an altered motor output. It is believed that the effect of vibration on motor output depends on the duration of vibration. Prolonged vibration applied for 30 seconds or longer has been shown to significantly depress muscle spindle's activity, resulting in lower group Ia mean discharge rates (Ribot-Ciscar et al. 1998), reduced reflex magnitude, and increased (i.e. slower) reflex latency (Pope & DeFreitas, 2015). As a result, decreased spindle function has shown to lead to a significant decrease in maximal strength of 7 - 30% (Bongiovanni & Hagbarth, 1990; Macefield et al. 1993; Kouzaki et al. 2000; Jackson & Turner, 2003; Shinohara, 2005; Ushiyama et al. 2005; Herda et al. 2009). On the other hand, brief vibration, defined here as 2 to 25 seconds of vibration, has resulted in additional excitation to the motoneuron pool and ultimately enhanced force production (Bongiovanni & Hagbarth, 1990; Grande & Cafarelli, 2003). However, the facilitatory effect of brief vibration is not consistently shown. For example, Pope and DeFreitas (2015) showed that while brief vibration did increase the magnitude of the patellar tendon reflex (i.e. tendon taps), the increase was not statistically significant. Furthermore, the reflex latency actually became significantly slower. However, this study only shows the effects of vibration on an involuntary spinal reflex, and may not be representative of the effects altered spindle activity would have on voluntary motor control. In addition, the effects of spindle activity facilitation appear to be dependent on the intensity and duration of the voluntary contraction. For instance, an enhancement of force production after brief vibration has been apparent only during weak contractions (Grande & Cafarelli, 2003), but this facilitatory effect disappeared as force

level increased (Spiliopoulou et al. 2012). There is also an exception during fatiguing contractions, where brief vibration applied during a maximal contraction regained its facilitatory effect, seen by an increment in force level and electromyographic (EMG) activity (Bongiovanni & Hagbarth, 1990a).

Previous studies have also investigated the influence of vibration on motor unit (MU) firing rates (FR) during submaximal contractions, showing an initial increase in FRs following brief vibration (Grande & Cafarelli, 2003) and subsequent decrease after prolonged vibration (Bongiovanni et al. 1990). However, these studies were performed at a low, submaximal force levels (Grande & Cafarelli, 2003; Mosier et al. 2017) or had long lasting, fatiguing contractions (e.g. 1 min. long in Bongiovanni & Hagbarth, 1990b). However, the effects of altered spindle function on motor unit behavior during maximal efforts remains unknown.

Due to technological limitations, analyzing firing behavior for more than a few MUs at a time was not possible in previous investigations. Nowadays, the surface electromyography (sEMG) decomposition technique developed by De Luca and collaborators (2006) allows the analysis of motor unit action potential trains during high-intensity contractions with greater motor unit yields when compared with indwelling recordings (De Luca & Hostage, 2010). This technology could provide a deeper insight into maximal motor unit behavior following altered muscle spindle activity.

Considering these previous findings, the purpose of this study is to analyze the effects of altered stretch reflex sensitivity, via brief and prolonged vibration, on motor unit firing

rates and recruitment thresholds during maximal contractions. We hypothesized that brief vibration, which stimulates the muscle spindles, would increase excitation to the motoneuron pool, thereby increasing motor unit firing rates. Conversely, we also hypothesized that prolonged vibration, which depresses the group Ia afferent pathway, would decrease the tonic excitation to the motoneuron pool, thereby decreasing motor unit firing rates.

2.2. Methods

2.2.1 Participants

Fourteen females and ten males (age: 25 ± 6 years), volunteered for this study. Prior to testing, each participant was informed about the experimental procedures, risks and their ability to withdraw at any moment and participants gave their written consent prior to any testing. To be included in this study, participants had to be completely free of any musculoskeletal injury or any diagnosed neurological disorder. This investigation was conducted in accordance with the Declaration of Helsinki and approved by the University's Institutional Review Board.

2.2.2 Experimental Design

We examined the effects of altered stretch reflex sensitivity on maximal motor unit firing properties. The sensitivity of the quadriceps stretch reflex was systematically manipulated by applying vibration to the muscle. A crossover design was utilized in which each subject performed each condition in the same order. Therefore, each

participant performed 1–3 maximal ramp contractions of the knee extensors (the number

of contractions depended on the participant's ability to follow the trajectory accurately)

under 3 separate conditions: 1) control; 2) brief vibration, applied during the contraction;

and 3) prolonged vibration, applied for ~20 min prior to the contraction. Multi-channel

EMG was recorded from the vastus lateralis (VL) during each contraction and

decomposed into its constituent motor unit action potential trains. A flow chart of the

protocol is shown in Figure 1. This study is part of a larger project, and the efficacy of

this exact protocol in altering stretch reflex properties was shown in a previous

publication from this project (Pope & DeFreitas, 2015).
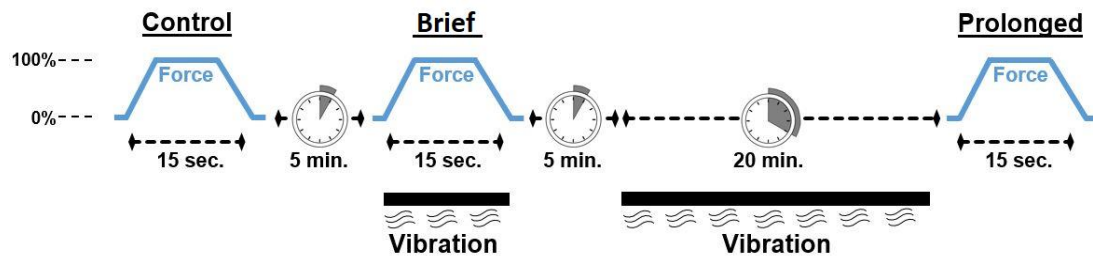
Figure 1. Time line for experimental protocol. Three different conditions: control; brief vibration, applied during the contraction; and prolonged vibration, applied for ~20 min prior to the contraction.

2.2.3 Application of Localized Vibration

As described in previously (Pope and DeFreitas, 2015), sinusoidal vibration was applied

to the distal quadriceps group superior to the patella using a percussion hammer

(Foredom Percussion Hammer, Bethel, CT, USA) with an amplitude of 1.5 mm set at our

hammer's maximal frequency (~ 66-70 Hz). A frequency between 70 and 100 Hz has

been shown to preferentially activate Ia afferents (Roll et al. 1989). Additionally, an

amplitude of 1.5 mm has shown to be effective for both types of vibration protocols,

facilitation (Burke et al. 1976; Burke & Schiller, 1976; Grande & Cafarelli, 2003) and

depression (Bongiovanni et al. 1990; Richardson et al. 2006). For the brief condition, the

vibration of the quadriceps began at the onset of the ramp contraction. For the prolonged

condition, the vibration was applied for ~20 min after completion of the brief condition

maximal voluntary contractions (MVCs) and reapplied for 1-3 min in-between each of

the 3 post-vibration ramp contractions to maintain depressed spindle activity (Ribot et al.

1998; Ruiter et al. 2002). These brief and prolonged protocols were designed with the

intent of facilitating and depressing the sensitivity of the stretch reflex, respectively.

However, it should be noted that our previous work showed that brief and prolonged

vibration had similar effects on reflex latency, resulting in a significant increased reflex

latency. (Pope and DeFreitas, 2015). In order to avoid any carryover effects, brief

vibration was applied first and during the contraction, because its effects dissipate as soon

as the stimulus is removed (Grande & Cafarelli, 2003; Roll, Vedel, & Ribot, 1989 &

Bongiovanni & Hagbarth, 1990a). On the other hand, the duration of prolonged vibration

effects has not been clearly defined. Forty seconds (Ribot et al. 1998) to more than 180

minutes (Ruiter et al. 2002) have been necessary for baseline measurements, such as Ia

mean discharge rates and voluntary strength, to return to its resting values. Consequently,

prolonged vibration was applied secondly and before the contraction (Ribot-Ciscar et al.

1998; Kouzaki et al. 2000; Herda, et al. 2009; Richardson, 2006). In addition, it has been

shown that prolonged sitting itself does not have any effect on knee extension MVC or

EMG of the quadriceps (Kouzaki et al. 2000).

2.2.4 Motor Unit Recordings

Motor unit action potentials were recorded using a specialized five-pin surface array sensor (Delsys, Inc., Natick, MA), which was placed over the VL muscle and secured with hypoallergenic surgical tape at approximately two-thirds the distance between the center of the muscle belly toward the distal tendon (Zaheer et al. 2012). A reference electrode (Dermatrode; American Imex, Irvine, CA) was placed on the spinous process of the C7 vertebrae (Zaheer et al. 2012). This 5-pin array sensor produces 4 separate EMG channels and the motor unit action potential trains were extracted by applying the Precision Decomposition III algorithm to the 4 channels, as described by De Luca et al. (2006) and improved upon by Nawab et al. (2010). Prior to the sensor placement, skin was properly prepared by shaving the area, gently abrading, and cleansing it with isopropyl alcohol. After electrode placement, subjects performed 3 unilateral isometric maximal knee extensions using the dominant leg, in which participants were seated in an upright position and restrained in a commercial dynamometer (Biodex System 4, Biodex Medical Systems, Shirley, NY, USA), with a knee angle of 120° and a hip angle of ~110°. Participants were instructed to push as hard as possible for 3 – 4 seconds; the highest force value measured during a 1000 ms epoch from the 3 extensions was designated as the subject's MVC. These MVC's were used to normalize the live torque feedback provided during the maximal ramp contractions while motor units' firings instances were recorded. Before testing, participants practiced tracing submaximal ramps to familiarize and assure proper adherence. This familiarization also served as a warm-up prior to the maximal contractions.

2.2.5 Maximal Ramp Contractions

Participants performed 1 – 3 maximal ramp contractions which were normalized to each
participant's MVC. The normalized template was displayed on a monitor overlayed with
live torque feedback. These contractions lasted 15 seconds in total; the ramp increased
and decreased at a rate of + 20 and -20% MVC/s, respectively, with a 5 second plateau at
100% MVC in between. The participants were instructed to trace the template line for the
ramps up and down, but to contract as hard as possible during the maximal hold. An
example of a tracing for each condition can be seen in Figure 2. A 50-point moving
average window (with a single datum point shift) was applied to smooth the signal and
the highest window of torque (Nm) was considered the maximal voluntary strength for
that condition.
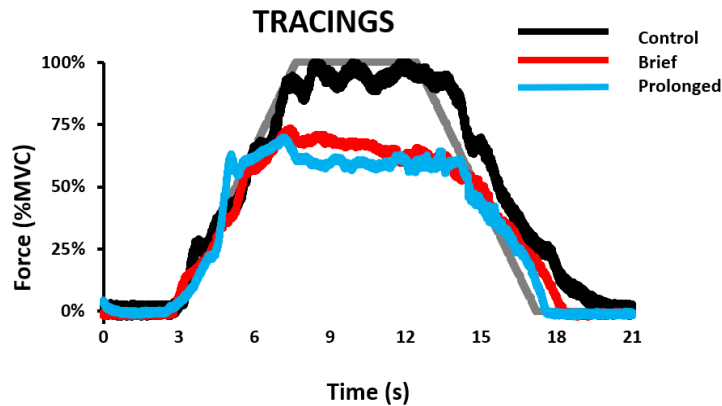
Figure 2. Example of a representative torque tracing for each condition. A normalized
template (gray line) was displayed on a monitor overlayed with live torque feedback.
Participants were instructed to trace the template line for the ramps up and down, but to
contract as hard as possible during the maximal hold. Control condition = black line; brief
vibration = red line; and prolonged vibration = blue line

2.2.6 MU Exclusion Criteria and Analysis

The accuracy of each individual MU was assessed using the Decompose-Synthesize-

Decompose-Compare test (De Luca & Contessa, 2012). Only MU's that demonstrated at

least 90.0% accuracy were used for further analysis. The firing characteristics of the

accurate MU's were analyzed using custom-written software (LabVIEW; National

Instruments, Austin, TX, USA); this software was used to calculate the following

properties for each identified MU; 1) Maximal Firing Rate (FR_{MAX}; pulses per second),

assessed as the highest point on a smoothed mean firing rate curve (smoothing was

performed with a 1-s Hanning window); and 2) Recruitment Threshold (RT), expressed

as the absolute torque level (Nm) at which the MU began discharging, and 3) MU AP_{SIZE}

(mV), measured as peak-to-peak amplitude of the action potential (AP) waveform

templates (a template is the average shape of the AP across the contraction). To be able to

compare within conditions, absolute recruitment thresholds were chosen due to the

possible changes in maximal strength after brief (Grande & Cafarelli, 2003; Bongiovanni

& Hagbarth, 1990) and prolonged vibration (Bongiovanni et al. 1990; Kouzaki et al.

2000; Herda, et al. 2009; Richardson et al. 2006). Since 4 AP waveforms are provided

from the 4 original EMG channels for each MU, the channel with the largest peak to peak

amplitude was considered as the most representative of that motor unit's true shape and

used for AP_{SIZE} analysis. Under the presumption that vibration would have no effect on

the amplitude of the action potentials, AP_{SIZE} was used as an independent variable to

examine potential changes in FR_{MAX} and RT. To establish a sufficient relationship for

MU RT vs. AP_{SIZE}, a RT range > 15% of MVC was required (per contraction) for each participant to be included in any analysis.

2.2.7 Statistical Analysis

RT vs. AP_{SIZE} and FR_{MAX} vs. AP_{SIZE} slope and y-intercept values were calculated for each subject and each condition with linear regression. Outliers were removed when the standardized score was higher than ± 2.5 standard deviations. Separate one-way repeated measures ANOVAs [control vs. brief vs. prolonged] were performed to assess the effects of vibration on the calculated regression coefficients for the aforementioned relationships. Two-way repeated measures ANOVAs [condition (control vs. brief vs. prolonged) × gender (female vs. male)] were used to test possible differences in voluntary maximal strength (Nm). When necessary post-hoc analyses with Bonferroni corrections were ran. An alpha-level of $p < 0.05$ was set a-priori to determine statistical significance. Cohen's d effect sizes were performed for the brief and prolonged conditions for the regression coefficients. All analyses were performed using SPSS software (version 21, IBM, Inc., Chicago, IL, USA).

2.3. Results

2.3.1 Effects of Vibration on Maximal Voluntary Strength

There were no 2-way interactions between conditions and gender ($p = 0.47$) for maximal strength. However, there was a main effect for condition ($p < 0.001$) and gender ($p = 0.003$). Post hoc analyses indicated an approximate 9% reduction in maximal voluntary

strength after both protocols (brief: -8.64%; prolonged -9.08%; compared to control, p

<0.001) (see Fig.3-A). Figure 3-B shows the individual responses to both vibration

conditions.
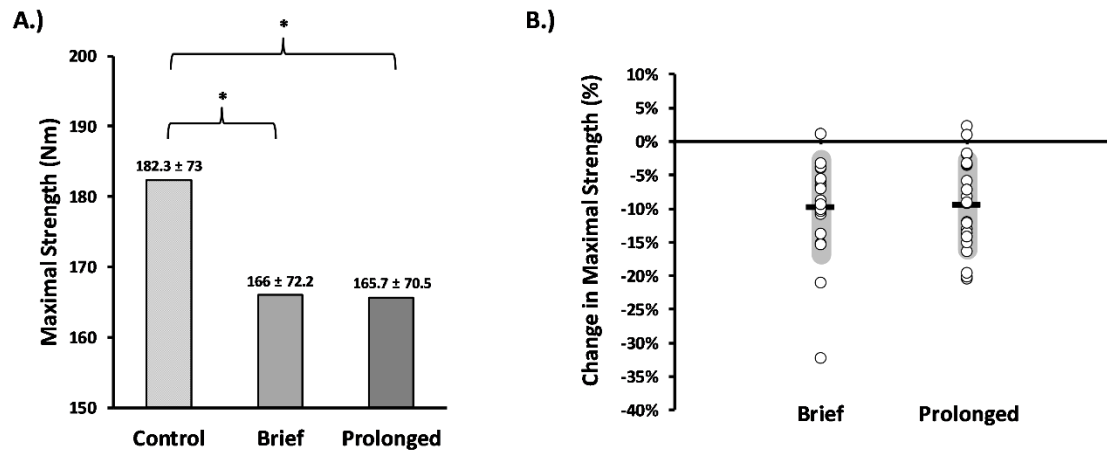
Figure 3. A.) Group means in maximal voluntary knee extension strength (Nm) for each condition. B.) Changes in maximal voluntary strength for each individual subject for the two conditions (relative to the control condition) (n = 24). * = Significant difference between conditions (p < 0.01)

2.3.2 MU Exclusion Analysis

Of the original 24 participants, 10 did not meet the established MU criteria (i.e., a RT

range <15% of MVC for either control, brief or prolonged conditions) or were identified

as outliers and were eliminated from all MU analyses. From the remaining 14 participants

(8 females and 6 males), 1318 MUs were detected (average per contraction = 34 MUs;

total control = 422 MUs; brief = 447 MUs; prolonged = 449 MUs).

2.3.3 Effects of Vibration on Maximal Motor Unit Firing Properties

Vibration had a large effect on FR_{MAX} slopes and y-intercepts after brief (Cohen's d = -1.52; 2.08; respectively) and prolonged vibration (-1.49; 1.31), as shown by a shift in the FR_{MAX} vs. AP_{SIZE} relationships. One-way ANOVAs revealed a significant change in slopes (p = 0.02) and y – intercepts (p = 0.042). Post hoc analyses showed greater y - intercept values for the brief condition (32.89 ± 5.35) when compared to the control (29.42 ± 2.7) (p = 0.039). On the other hand, vibration had a small to moderate, non-significant (p-values > 0.05) effect on RT slopes and y-intercepts after brief (Cohen's d = 0.49; -0.76) and prolonged (0.38; -0.77) vibration. Figure 4 shows the individual and group mean regression results to vibration.
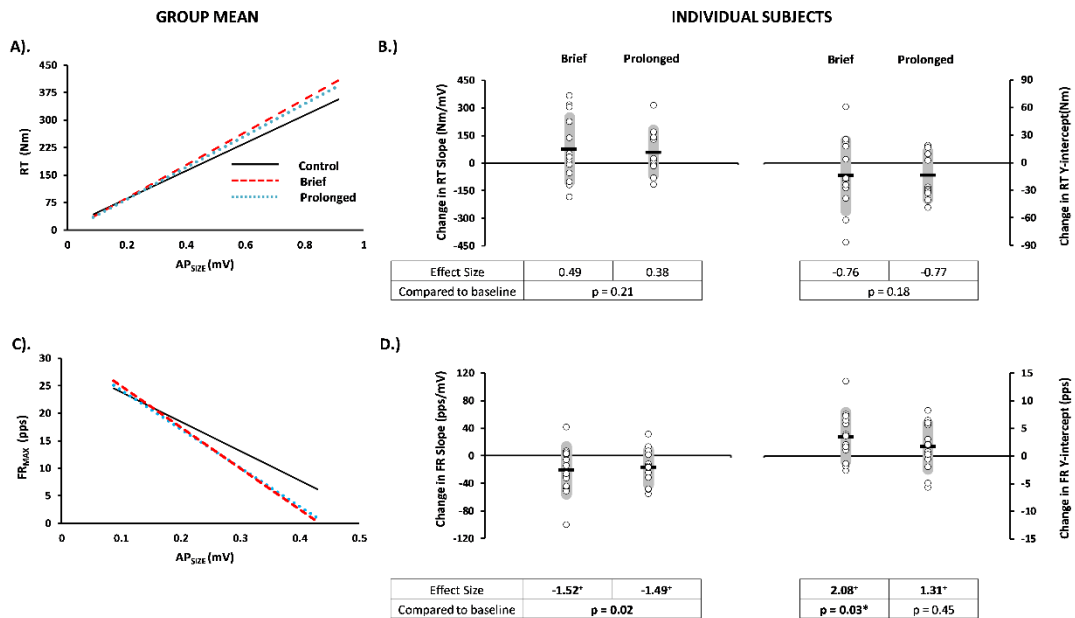
Figure 4. Regression was performed on each individual subject's motor unit data. The two dependent variables were maximal motor unit firing rates (FR_{MAX}) and absolute recruitment thresholds (RT), and action potential size (AP_{SIZE}) was used as the independent variable. **Plots A and C:** Group means were calculated from the slopes and intercept coefficients of each

individual subject's regressions. These regression lines are the group mean for each condition. **Plots B and D:** The changes in the individual subject regression coefficients from brief and prolonged vibration (relative to the control condition) (n = 14). * = Significantly lower than the control condition (p < 0.05). [+] = Large effect size.

2.4. Discussion

The primary finding from this study was vibration's detrimental effect on motor unit firing properties, independent of the vibration condition (brief or prolonged). This decrease in motor unit output was likely the cause behind an approximate 9% reduction in maximal voluntary strength.

2.4.1 Effects of Brief Vibration during a Maximal Contraction

Based on previous studies, we had hypothesized that 15 seconds of vibration would result in a facilitatory effect (Bosco et al. 2001). Surprisingly, we saw the opposite effect, where maximal strength was reduced and MU behavior results were similar to the prolonged vibration condition. There are two possible mechanisms that can explain this phenomenon; one has to do with Golgi tendon organs (GTO) and the other with the duration of our vibration protocol. Fallon and Macefield (2007) showed that when vibration is applied during a contraction the discharge frequency of Group Ib afferents increases. Group Ib afferents synapse with inhibitory interneurons, which could have resulted in increased inhibition to the homonymous motoneuron pool. The vibration applied in this protocol was during the contraction, which, therefore, could have activated GTOs. On the other hand, regarding the duration of our vibration protocol, to our knowledge the exact moment when muscle spindle facilitation starts to be depressed is

unknown. The closest study we found is Bongiovanni and Hagbarth's study (1990a) who saw a facilitatory effect at the beginning of a 20 seconds vibration protocol, but the initial increase was followed by a rapid decline. However, the exact duration for the facilitatory effect is not reported. It appears that after only a few seconds the facilitatory effect of vibration on motor output reverts. For instance, 2 seconds of vibration showed an increase in force (Grande & Cafarelli, 2003); 3 – 4 seconds showed no difference (Bongiovanni & Hagbarth, 1990); and our protocol which lasted 15 seconds, showed a decrease in maximal strength. Consequently, it is also possible that our protocol was too long. Hence, these are two possible mechanisms that could explain the strength loss. However, further analyses are required to understand each one.

2.4.2 Effects of Vibration on Maximal Voluntary Strength

Our results showed a decrease in maximal strength of 8.64% after brief vibration and 9.08% after prolonged vibration. As previously mentioned, the results for the brief condition may be explained by changes in afferent feedback from muscle spindles and/or GTOs. On the other hand, prolonged vibration has been shown to decrease Group Ia mean discharge rates (Ribot-Ciscar et al. 1998), reduced reflex magnitude, and increased (i.e. slower) reflex latency (Pope & DeFreitas, 2015). The mechanisms behind the reduction in Group Ia afferent activity due to vibration can be presynaptic inhibition (PSI) (Hultborn et al. 1987) and/or transmitter depletion (Curtis & Eccles, 1960) and/or increased threshold of Group Ia excitatory pathway to gamma-loop (Hayward et al. 1986). The muscle spindle activity reduction has been shown to negatively affect

maximal voluntary strength by 8% - 30% (Bongiovanni & Hagbarth, 1990; Macefield et al. 1993; Kouzaki et al. 2000; Jackson & Turner, 2003; Shinohara, 2005; Ushiyama et al. 2005; Herda et al. 2009). Therefore, the results from our prolonged vibration condition are in agreement with previous studies.

2.4.3 Effects of Vibration on Motor Unit Maximal Properties

Our rigorous MU inclusion criteria reduced our sample size of participants considerably. This loss of statistical power could explain why small to moderate increases in RT were not statistically significant. The changes seen in y-intercepts could be a product of the change in slopes. Pedhauzer (1997) recommends that y-intercepts should only be tested if no significant changes were seen in slopes. Therefore, due to the effect of vibration on the slopes, y-intercepts will not be further discussed. Figure 4 shows how changes to the slope coefficients of our primary two relationships (FR_{MAX} vs. AP_{SIZE}, and RT vs. AP_{SIZE}) were consistent not only on the group means (between conditions), but also at the individual subject level.

There was a small increment in RTs slopes and a steeper decline in FR_{MAX} seen after vibration. These results could indicate that MUs were being recruited later and achieved lower FRs, when vibration was applied. FRs are a function of RTs and excitation level, where there exists a hierarchical inverse relationship of RTs and FRs; meaning that later recruited MUs have lower FRs than the earlier recruited ones (De Luca & Hostage 2010; De Luca & Contessa, 2011). Therefore, it seems that when less net excitation is sent to the motoneuron pool, FRs decrease (De Luca & Erim, 1994). Contessa et al. (2016)

showed that an increase in excitation can result in a decrease in RTs and an increase in FRs. Our results follow the same principles of the hierarchal inverse relationship between RTs and FRs, only evidenced by movement in the opposite direction.

The reduction in FRs during maximal contractions is consistent with previous studies using prolonged vibration (Bongiovanni et al, 1990) or muscle deafferentation (Macefield et al. 1993). It seems that due to the lack of muscle spindle support, MUs cannot achieve greater FRs. Specifically; it appears that higher threshold MUs are the most affected with a significant decrease in FRs when Group Ia afferent feedback was removed (Macefield et al. 1993).

2.4.4 Proposed Model of the Underlying Mechanisms

Figure 5 shows a plausible explanation that ties all of our findings together. We have revised and modified the Hydraulic Model of Common Drive (Fig. 4 in De Luca & Erim, 1994) as a basis to explain the changes seen in this study. In short, the water pouring from the faucet into the beaker represents input excitation to the motor unit pool, the faucet at the bottom represents inhibition, and the level of water in the beaker would be the total net excitation. The spouts on the side represent the recruitment threshold (i.e. the MU will not activate until the net excitation reaches the level of the spout), and the distance the water projects from the spout would be the firing rate. Our primary modification to the model is the addition of multiple sources of excitation; the primary source would be descending drive, representing at least 2/3 of the total excitation. The secondary source would be excitation from Group Ia afferents, which may be as high as

1/3 of the excitation to the motoneuron pool (Macefield et al. 1993). We then include 5 observed or plausible changes due to the application of vibration. 1.) Vibration has been shown to decrease muscle spindle activity (Ribot-Ciscar et al. 1998; Pope & DeFreitas, 2015), possibly through presynaptic inhibition (Hultborn et al. 1987). 2.) As a result, the net excitation to the motoneuron pool was likely reduced (Macefield et al. 1993). 3.) A small increment in RTs was seen, possibly meaning that the same MU was being recruited later. 4.) In the brief condition, GTOs could have been activated during vibration (Fallon & Macefield, 2007), causing autogenic inhibition and thus decreasing the net excitation of the motoneuron pool. 5.) This later recruitment combined with the reduced excitation to the motoneuron pool would explain the reduction in FR_{MAX}. The firing rate of a motor unit is a function of how much additional excitation there is beyond the activation threshold of the neuron (until the motoneuron is saturated). Adding to the plausibility of this model is the fact that the slopes shown in Fig. 4C show that it is the larger, higher-threshold MUs that are most affected. Since these are the MUs whose firing rates are not saturated during maximal contractions, they are the units that would be susceptible to any changes in the net excitation to the pool. Therefore, it is probable that when there is less net excitation to the MU pool, caused by a decrease in muscle spindle activity and/or increased inhibition originating from GTOs, the motor unit's RTs slightly increase and the firing rates decrease. This resultant decrease in FR_{MAX} would also explain the ~9% reduction in maximal strength.
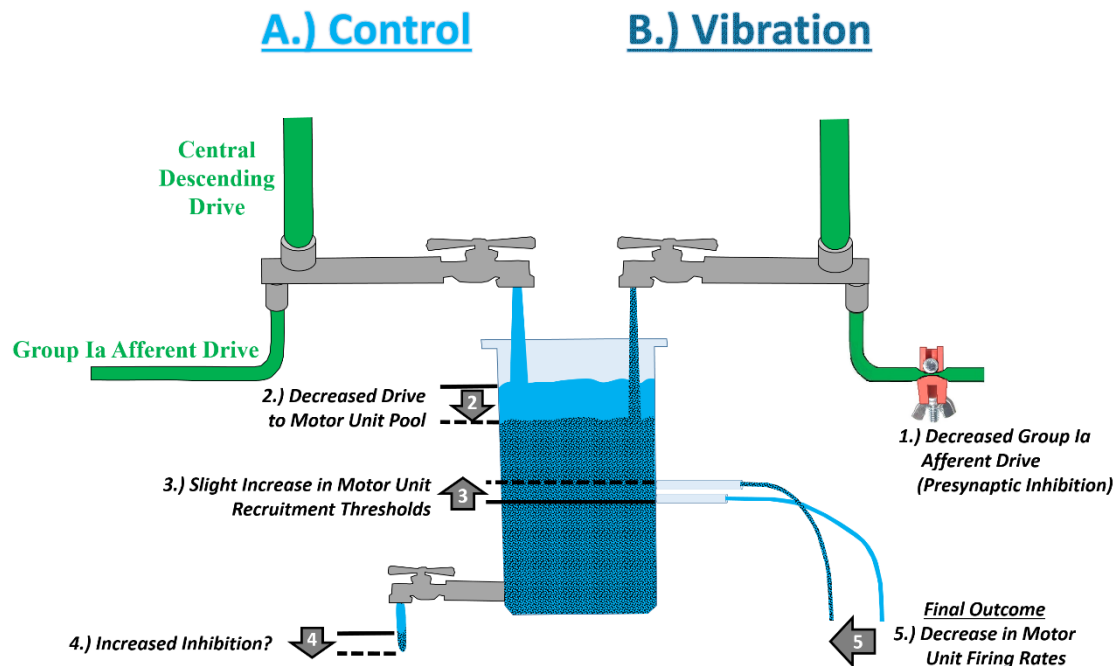
Figure 5. Proposed model for the effects of vibration on motor unit outputs. This model is a revised and modified version of the Hydraulic Model of Common Drive, original presented by De Luca and Erim (1994). The water pouring from the faucet into the beaker represents input excitation to the motor unit pool while the faucet at the bottom left represents inhibition, and the level of water in the beaker would be the total net excitation. The spouts on the right side represent the recruitment threshold (i.e. the MU will not activate until the net excitation reaches the level of the spout), and the distance the water projects from the spout would be the firing rate. The light blue water and solid lines are the control condition, while the dark shaded water and dashed lines are during or after vibration. **1.)** Decreased drive from Group Ia afferents, possibly due to presynaptic inhibition, which would then cause **2.)** a reduction in the net excitation to the motoneuron pool. 3.) A slight increase in motor unit recruitment thresholds (small to moderate effect size). **4.)** A possible increase in inhibition due to activation of Golgi tendon organs. **5.)** Mechanisms 2-4 combined lead to a decrease in motor unit firing rates (large effect size). The decreased firing rate then leads to a decrease in maximal voluntary strength.

2.4.5 Limitations

First, while the short (5 sec) ramp up to 100% effort was necessary to avoid fatigue, it may have made it difficult for the decomposition algorithm to precisely locate

20

recruitment times; the 20% MVC/s represents the fastest ramp up that is in the recommended range (Nawab, Chang, & De Luca, 2010). Second, the muscle spindles of the agonist muscle produce a reciprocal inhibition of the antagonist muscle (Corcos et al. 1989). Due to the significant increase in reflex latency after both brief and prolonged vibration, as previously reported (Pope & DeFreitas, 2015), we have reason to believe that muscle spindle activity was diminished; so it is possible that antagonist coactivation might have increased, thus also contributing to the decrease in agonist maximal voluntary strength. Thirdly, we did not have any GTOs discharge frequency data, so our proposal of the GTO's potential role is based on previous studies.

2.4.6 Recommendations for future studies

Further research is needed to determine the precise moment when vibration-induced muscle spindle facilitation shifts to suppression during submaximal and maximal contractions, while controlling for vibration frequency. In addition, future studies examining muscle spindle function should account for potential changes in antagonist coactivation.

2.5 Conclusions

Altering the gain of the stretch reflex pathway via muscle vibration influences motor unit behavior and motor output. The resultant reduction in excitation to the MU pool altered MU behavior by slightly increasing recruitment thresholds, decreasing firing rates, and ultimately reducing maximal strength. These results show the importance of afferent

feedback to the alpha-motoneuron in the production of maximal force, as attenuation of spindle function reduces excitation to the alpha motoneuron pool and reduce motor unit output.

CHAPTER III

SENSORY AND MOTOR FUNCTION ACROSS THE LIFESPAN

3. Barrera-Curiel, A., Colquhoun, R.J., Hernandez-Sarabia, J.A. & DeFreitas, J.M. Sensory and Motor Function Across the Lifespan

3.1. Introduction

It is known that with aging, the neuromuscular system undergoes structural and functional changes that affect performance[7,12,27,28]. To understand these modifications, Papegaaij and collaborators[7] classified age-related changes into three main categories, structural, functional, and behavioral changes. Structural changes, refer to the degeneration of neuromuscular system; such as, loss of muscle mass and quality[16-20]; degradation of the somatosensory system including muscle spindles and cutaneous receptors[6,21,22]; decrease in myelinated and unmyelinated fiber density[23]; decrease in cortical gray and white matter volume[24,25], etc. Functional changes, refer to the modification in how the neuromuscular structures operate, these include, decrease

somatosensory receptors sensitivity[26], decrease in peripheral nerves conduction velocity [27], change in muscle activation patterns[7,28-30], decreased spinal and cortical inhibition[31,32], among others. Behavioral changes denote the changes in performance, including poorer postural control[6,10,11], slower and weaker movements[13-15].

Since aging affects several domains of movement control, it is important to study these changes as whole. To our knowledge the studies analyzing the relationship between age-related changes, are limited to one or two categories[21,40-43] or involve a review of other studies[6,7,28,38]. Moreover, research has shown that sensory degradation precedes motor degradation [6,27]. Within sensory information, recent studies have shown the role of muscle spindles on motor unit excitation; it seems that muscle spindles provide 8 – 30% of the total excitation that alpha-motoneurons receive[8,33,34]. Therefore, understanding the role of muscle spindle on morphophysiological variables and on performance could further our understanding of the aging process. Therefore, the purpose of this study was to analyze structural (muscle mass and quality) and functional (spindle function) changes associated with aging, their relationships, and how they may affect performance (balance, strength, and rate of torque development).

3.2 Methods

3.2.1 Participants

One hundred and forty-three volunteers (females: 61 and males: 82) aged 19 – 88 years old (mean ± SD; 39.7 ± 19.9 years) were divided into three groups, young (range, mean, sample size; 19 – 35 years old, 23.6 ± 3.7, 78); middle-age (36 – 64 years old, 51.2 ± 8.8;

42); and old (65 and older, 72.9 ± 6.9, 22). Their average height and weight was 171.1 ±

0.1 cm and 76.9 ± 17.5 kg, respectively. Prior to testing, each participant was informed

about the experimental procedures, risks, and their ability to withdraw at any moment and

participants gave their written consent prior to any testing. To be included in this study,

participants had to be completely free of any musculoskeletal knee injury or any

diagnosed neurological disorder. This investigation was conducted in accordance with the

Declaration of Helsinki and approved by the University's Institutional Review Board.

Table 1.
Demographic data for each group

Variable	Young	Y vs MA	Middle-Age	MA vs O	Old	Y vs O
	$\bar{X} \pm s$	Mean diff.	$\bar{X} \pm s$	Mean diff.	$\bar{X} \pm s$	Mean diff.
Age (yrs.)	23.7 ± 3.7	-27.5*	51.2 ± 8.8	-21.7*	72.9 ± 6.9	-49.2*
Height (m)	1.74 ± 0.09	0.04	1.7 ± 0.11	0.07*	1.63 ± 0.09	0.11*
Weight (kg)	75.4 ± 16.3	-4.6	80 ± 16	3.6	76.4 ± 17.5	-0.9

* = Significant differences to the 0.05 level

3.2.2 Research design

This study was a non-experimental, cross-sectional analysis. Only one visit to the lab

was required. Each participant started with a brief familiarization of the protocol.

Following, each participant's height and weight were measured. To start the testing

protocol, ultrasound assessments were performed to quantify muscle size and quality

followed by postural sway to assess balance. Participants were then seated on a dynamometer where tendon taps were delivered to their patellar tendon, followed by participants' voluntary maximal and submaximal knee extensions.

3.2.3 Instruments and Procedures

3.2.3.1 Muscle Imaging

Participants laid supine on a comfortably padded, adjustable-height exam table for five minutes with their legs extended, their knees supported by a pillow, and the right foot placed in a custom made foot mold to prevent external rotation at the hip. Panoramic ultrasound images of the rectus femoris (RF) muscle were obtained using a diagnostic US imaging device (GE Logiq S8, Milwaukee, WI, USA) with a linear array probe (Model ML6-15-D 4-15 MHz, 50-mm field of view) at 50% of the distance from the anterior superior iliac spine and the superior border of the patella. The probe was placed at the medial beginning of the RF muscle and slowly moved laterally, until the entire muscle was captured. The equipment settings for all participants were a gain of 46dB and a frequency of 12Hz; except for depth which was adjusted individually depending on the size of the participant's thigh. Two scans were collected, and the image with the greatest quality was used for further analysis; in addition, images were calibrated from pixels to cm, by drawing a one centimeter line on the ultrasound.

RF muscle cross-sectional area (CSA_{RF}; cm^2) and Muscle Quality (MQ_{RF}; au) were analyzed by defining a region of interest that included as much muscle as possible, using

the polygon function in the image analysis software (ImageJ, version 1.50i, National Institutes of Health, Bethesda MD, USA). MQ_{RF} was determined using computer-aided gray scale analysis using the standard histogram function and was measured in arbitrary units with values ranging from 0 (black) to 255 (white).

3.2.3.2 Balance

The Modified Clinical Test of Sensory Interaction in Balance was used. Participants stood on the platform (Biodex SD 950-440, Biodex Medical Systems, Inc. Shirley, NY, USA) with their feet shoulder-width apart and their hands on the hips. They were asked to hold still for 30 seconds under four different conditions: 1-Eyes open on a firm surface (EOFS); 2-Eyes closed on firm surface (ECFS); 3-Eyes open on a soft surface (EOSS); and 4-Eyes closed on a soft surface (ECSS). Sway index was measured as the standard deviation of the averaged position from the center [44]. Under the assumption that the ECFS condition relies the most on proprioception input, and the ECSS condition relies on it very little (mostly vestibular), Proprioceptive contribution (PC; %) was calculated as (ECSS – ECFS) / (ECSS – EOFS).

3.2.3.3 Stretch Reflex (Tendon Taps)

Subjects were seated on an isokinetic dynamometer (Biodex System 4, Biodex Medical Systems, Inc. Shirley, NY, USA) with a knee and hip angle of 90° and ~110°, respectively. Subjects were restrained with straps over the trunk, hips, and thigh to prevent any countermovement. The dynamometer's axis of rotation was aligned with the

participant's lateral malleolus. A total of 5 successful taps were delivered to the center of the patellar tendon with a mallet-type reflex hammer (Trömner 555, MDF Instruments, Malibu, CA, USA) customized to swing 165° before hitting the tendon. The subject was instructed to performed the Jendrassik maneuver (hands pulling apart) with eyes closed during the taps. The best three responses were visually identified, averaged, and used for further analysis. Surface electromyography (sEMG) was recorded during the strikes from the RF muscle. To detect the hammer strike, an accelerometer ('EG' accelerometer; Entran Sensors and Electronics, Fairfield, NJ) was placed 20 mm above the location of the strike. The following variables were measured: 1) Tendon taps magnitude, calculated as the maximal reflex torque normalized to each subject's MVC (R_{MAG}; %MVC); 2) Reflex latency was measured as the total latency from the mechanical strike to the torque onset and then femur length was divided by this latency (R_{LAT}; m/s) (for detailed information read [45]).

B.
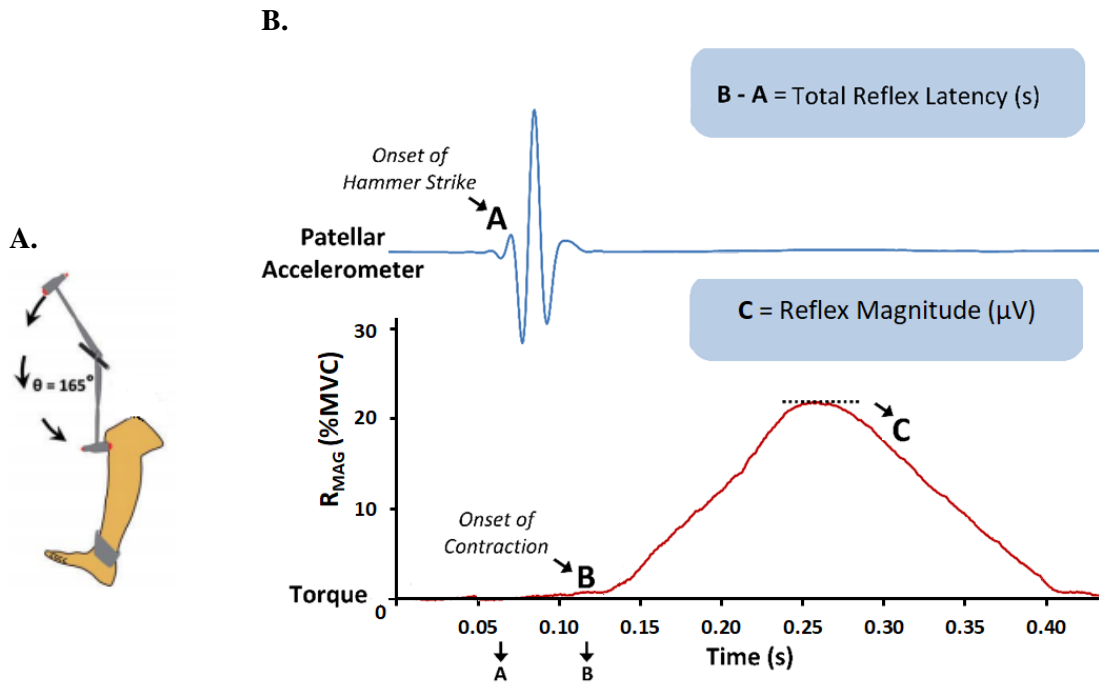
Figure 1. Example of a reflex response. A. Tap delivery over tendon. B. Measurement of reflex magnitude and latency; reflex latency, calculated as the time between the hammer strike to the onset of the reflex contraction; and reflex magnitude, maximal reflex torque normalized to each subject's MVC.

3.2.3.4 Maximal and submaximal contractions

While sitting on the dynamometer, subjects performed 3 unilateral isometric maximal knee extensions using the dominant leg at a knee angle degree of 120°. Participants were instructed to push as hard as possible for 3 – 4 seconds; the highest force value measured during a 1 second epoch from the 3 extensions was designated as the subject's maximal voluntary contraction (STR; Nm). Rate of torque development was calculated as the

linear slope of the force-time curve (Δforce/Δtime) from torque onset to 50% MVC (RTD; Nm/s).

3.2.3.5 Electromyography

For sEMG of the tendon taps, two surface electrodes, (38 mm in diameter) (Blue Sensor Electrodes; Ambu, Denmark) were placed over each participants RF belly with 20 mm interelectrode distance, according to recommendations from the SENIAM project; and a reference electrode was placed over the tibial tuberosity.

3.2.3.6 Signal Processing

Torque, sEMG, and accelerometry were sampled simultaneously during the tendon taps at a rate of 2kHz using Biopac data acquisition system (MP150WSW, BIOPAC Systems, Inc., Santa Barbara, CA, USA). sEMG signals were filtered with a zero-phase 8th order Butterworth filter (cutoffs 10 – 500 Hz). A 50-point (25ms) moving average window (with a single datum point shift) was applied to smooth the signals. Each signal was processed offline with custom written software (LabVIEW, National Instruments, Austin, Texas).

3.2.4 Statistical Analysis

The variables were categorized as either structural, functional, or behavioral changes using Papegaaij et al. [7] model. Table 2 shows how the variables measured in this study were classified.

Table 2.
Classification of Neuromuscular changes across age

Structural	Functional	Behavioral
CSA_{RF} (cm^2)	R_{MAG} (Nm; %MVC)	STR (Nm)
MQ_{RF} (au)	R_{LAT} (s; m/s)	RTD (Nm/s)
	PC (%)	Balance

For each variable measured, outliers were removed when the standardized score was higher than ± 2.5 standard deviations. A one - way MANOVA was used [group (young vs middle-age vs old)] was performed between age - groups in the predictor variables (CSA_{RF}, MQ_{RF}, balance, and PC). Significant multivariate interactions were identified using Wilk's Lambda test. However, Pillai-Bartlett test was used with small sample sizes and/or the assumption of homogeneity of variance-covariance was violated. One –way ANOVAs [group (young vs middle-age vs old)] was used in those dependent variables that had smaller sample sizes. Bonferroni adjusted alpha ($\frac{\alpha}{no.of\ groups}$) was used to assess significance difference in these variables, which were grouped into STR and RTD and R_{MAG} and R_{LAT} . Pearson correlation coefficients were used to examine the relationships between the predictor variables (age, structural and/or functional) and each dependent variable (functional and/or behavioral) collapsed between age groups. Additionally, separate correlations were performed to examine the relationship between the predictor variables (age, structural, and/or functional) and each dependent variable (functional and/or behavioral) in each age group. Following the Pearson correlation coefficients, stepwise multiple regression analysis examined which of the predictor variables (age,

structural and/or functional) independently explained a significant proportion of the total variance in behavioral variables across groups. Only variables that significantly related to each behavioral changes across each age groups were used in the regression analysis. All analyses were performed using SPSS software (version 21, IBM, Inc., Chicago, IL, USA).

3.3 Results

3.3.1 Structural, Functional, and Behavioral Changes across the Life-span

Each category and its relationships will be discussed in the following paragraphs. Look at Table 3 and 4 for each variable's mean, standard deviation, and sample size; as well as the mean differences between the three groups.

3.3.1.1 Structural Changes

One-way MANOVA revealed a main effect of age group on CSA_{RF} and MQ_{RF}, $F_{(4,258)}$ = 11.431, $p < 0.001$, $\eta p^2 = 0.151$. Post hoc Tamhane test revealed significant larger CSA_{RF} in the young group when compared to the middle-age and older groups (mean difference, 2.22 cm^2 and 4.76cm^2); also, there was significant difference between the middle-age and old group (2.53cm^2). Regarding MQ_{RF} grey scale was significantly higher in the older group when compared to the young group (13.85 au) and middle-age groups (-15.09 au) (Fig 2).
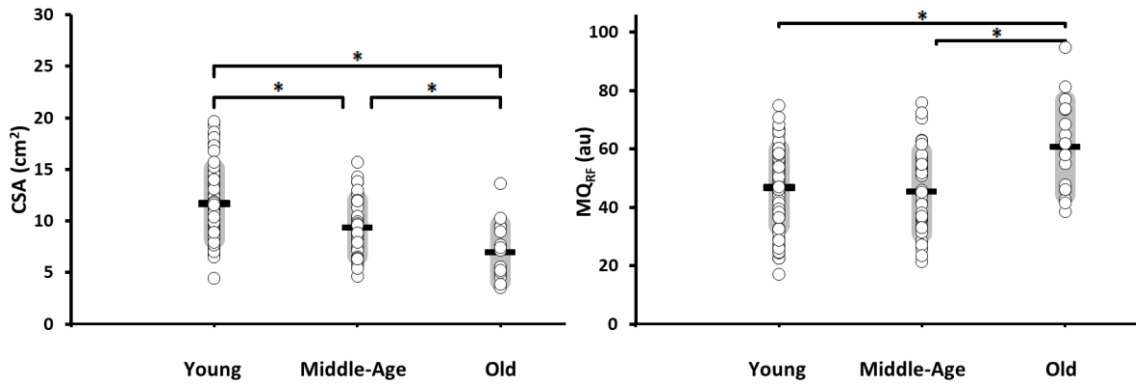
Figure 2. Age differences in muscle size (CSA) and quality (MQ) between the young, middle-age and old groups. * = Significant relationships to the 0.05 level.

3.3.1.2 Functional Changes

One – way ANOVA revealed a main effect of age on R_{MAG} (2, 81) = 7.64, p < 0.001, ηp^2 = 0.159. Post hoc analysis using Bonferroni adjusted alpha (0.0125) revealed that the young group R_{MAG} was on average 0.09 %MVC less than old group (Fig. 3).
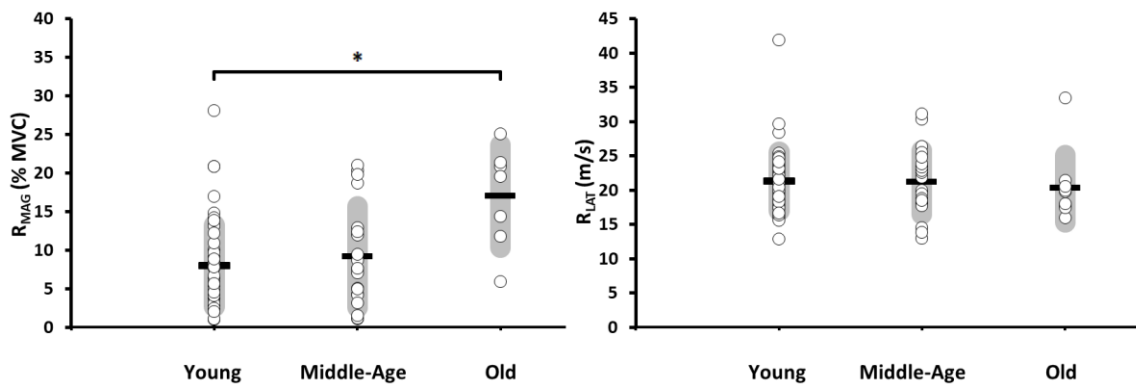
Figure 3. Age differences in normalized reflex magnitude (R_{MAG}) and latency (R_{LAT}) between the young, middle-age and old groups. * = Significant relationships to the 0.05 level.

3.3.1.3 Behavioral changes

One – way ANOVA revealed a main effect of age on STR, $F_{(2,122)} = 16.884$, $p < 0.001$, $\eta p^2 = 0.217$. Post hoc analysis using Bonferroni adjusted alpha (0.025) revealed a significant difference between the three age groups, the young group was on average 38.5 Nm and 101.32 Nm stronger than the middle-age and older groups, respectively. Also, the middle-age group was 62.83 Nm stronger than the older group. One – way ANOVA revealed a main effect of age on RTD, $F_{(2,61)} = 8.329$, $p < 0.001$, $\eta p^2 = 0.215$. Post hoc analysis using Bonferroni adjusted alpha revealed a significant decrease in RTD when comparing the middle-age, - 415.23 Nm/s, and older group, -554.74 Nm/s to the young group. One-way MANOVA revealed a main effect of age group on sway index $F_{(10, 118)} = 7.26$, $p < 0.001$, $\eta p^2 = 0.36$. Post hoc Tamhane's test revealed a significant more sway on all the balance conditions, in the older group when compared to the young (mean difference per condition, EOFS: 0.21, ECFS: 0.25, EOSS:0.46, and ECSS 1.2). In addition, the middle-age group had greater sway in the conditions EOFS, ECFS and ECSS when compared to the young group (0.14, 0.23, 0.51). The two conditions that showed a significant difference between the middle and older group were EOSS and ECSS with a greater sway in the older group (0.42 and 0.69) (Fig. 4).
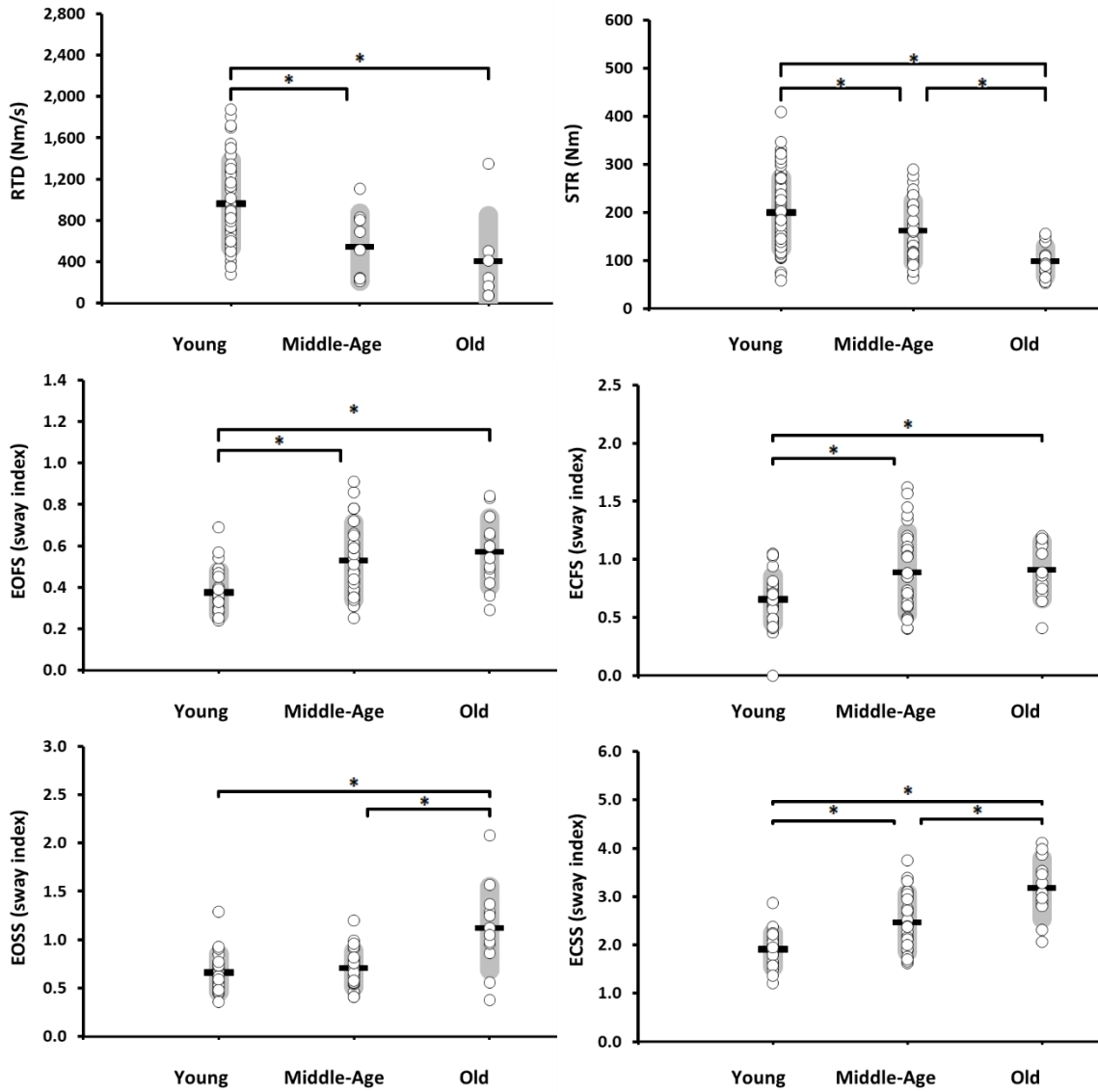
Figure 4. Age differences in strength (STR), rate of torque development (RTD) and balance eyes open and closed firm surface and soft surface (EOFS, ECFS, EOSS, ECSS) between the young, middle-age and old groups. * = Significant relationships to the 0.05 level.

Table 3.

Variables means and standard deviations per group

Variable	Young $\bar{X} \pm s$	Young n	Middle-Age $\bar{X} \pm s$	Middle-Age n	Old $\bar{X} \pm s$	Old n
CSA_{RF} (cm^2)	11.67 ± 3.4	78	9.45 ±2.6	38	6.91 ± 2.72	17
MQ_{RF} (au)	46.69 ± 12.94	78	45.45 ± 13.92	38	60.54 ± 16.01	17
R_{MAG} (%MVC)	7.934 ± 5.27	57	9.14 ± 6.56	20	16.99 ± 6.63	7
R_{MAG} (Nm)	14.53 ± 8.82	58	10.86 ± 6.43	22	12.95 ± 5.28	10
R_{LAT} (m/s)	21.28 ± 4.26	56	21.11 ± 4.64	24	20.21± 4.93	10
R_{LAT} (s)	0.042 ± 0.007	56	0.043 ± 0.008	24	0.042 ± 0.006	10
PC (%)	82.06 ± 11.37	26	80.68 ± 9.81	28	88.04 ± 10.35	12
STR (Nm)	198.55 ± 71.79	76	160.05 ± 63.24	33	97.22 ± 30.44	16
RTD (Nm/s)	956.8 ± 417.02	48	541.57 ± 330.34	9	402.06 ± 447.47	7
EOFS	0.37 ± 0.1	26	0.51± 0.18	28	0.58 ± 0.18	12
ECFS	0.64 ± 0.2	26	0.87 ± 0.34	28	0.89 ± 0.25	12
EOSS	0.65 ± 0.19	26	0.68 ± 0.18	28	1.1 ± 0.45	12
ECSS	1.9 ± 0.34	26	2.42 ± 0.57	28	3.11 ± 0.6	12

Table 4.
Variables mean differences across groups

Variable	Young vs Middle-Age	Middle-Age vs Old	Young vs Old
CSA_{RF} (cm^2)	**-2.22***	**-2.53***	**-4.76***
MQ_{RF} (au)	1.23	**15.09***	**13.85***
R_{MAG} (%MVC)	-1.21	7.85	**9.06***
R_{MAG} (Nm)	2.86	3.7	1.58
R_{LAT} (m/s)	0.18	0.9	1.07
R_{LAT} (s)	0.001	0.001	-0.0001
PC (%)	1.4	-7.4	-6.0
STR (Nm)	**-38.5***	**-62.83***	**-101.32***
RTD (Nm/s)	**- 415.23***	-139.51	**- 554.74***
EOFS	**0.14***	0.08	**0.21***
ECFS	**0.23***	0.02	**0.25***
EOSS	0.03	**0.42***	**0.46***
ECSS	**0.51***	**0.69***	**1.2***

* = Significant differences to the 0.05 level

3.3.2 Relationships between Age and Structural, Functional, and Behavioral Variables

Age correlated weekly with MQ_{RF} (au) (r = 0.256), R_{MAG} (r = 0.348); moderately with

CSA_{RF} (r = -0.543), the balance conditions EOFS, ECFS, EOSS (r = 0.579; r = 0.492; r =

0.497), RTD (r = -0.457), and STR (r = -0.466); and strongly with the balance condition

ECSS (r = 0.729). All of these correlations where significant at the p < 0.001. Table 5,

shows the relationships between age and all the variables measured in this study.

Table 5.
Relationship between age and structural, functional, and behavioral variables

	Structural and Functional									
	CSA_{RF} (cm^2)	n	MQ_{RF} (au)	n	R_{MAG} (%MVC)	n	R_{LAT} (m/s)	n	PC (%)	n
	-0.543[**]	134	**0.256**[**]	134	**0.348**[**]	84	-0.078	90	0.085	64
Age	Behavioral									
	Balance (sway index)							RTD (Nm/s)	n	STR (Nm)	n
	EOFS	n	ECFS	n	EOSS	n	ECSS	n			
	0.579[**]	72	**0.492**[**]	73	**0.497**[**]	70	**0.729**[**]	70	**-0.457**[**]	64	**-0.466**[**]	125

** Correlation is significant at the 0.01 level

3.3.3 Relationships between structural, functional, and behavioral variables across the life-span

When collapsing functional variables across groups, we see a negative relationship between R_{MAG} normalized to each subjects MVC and CSA_{RF} (r = -0.271, p = 0.014) and a positive relationship with MQ_{RF} (r = 0.329; p = 0.003). When the absolute R_{MAG} was used (Nm), we see a significant positive correlation with CSA_{RF} (r = 0.245; p = 0.023) (Table 6).

Table 6.
Relationship between structural and functional variables

Functional	Structural			
	CSA_{RF} (cm^2)	n	MQ_{RF} (au)	n
R_{MAG} (%MVC)	**-0.271**[*]	82	**0.329**[**]	82
R_{MAG} (Nm)	**0.245**[*]	86	-0.0271	86
R_{LAT} (m/s)	-0.0418	86	0.1375	86
R_{LAT} (s)	0.168	86	**-0.255**[*]	86
PC (%)	0.070	62	0.093	63

** Correlation is significant at the 0.01 level
* Correlation is significant at the 0.05 level

When structural variables were collapsed across group, CSA_{RF} was negatively correlated to each balance condition EOFS ($r = -0.366$; $p < 0.01$), ECFS ($r = -0.411$; $p < 0.01$), EOSS ($r = -0.328$; $p < 0.01$) and ECSS ($r = -0.517$; $p < 0.01$). Also, it was positively correlated to RTD ($r = 0.538$; $p < 0.01$) and STR ($r = 0.732$; $p < 0.01$) (Fig. 5). In contrast, MQ_{RF} was negatively correlated to three balance conditions, ECFS ($r = 0.248$; $p < 0.05$), EOSS ($r = 0.353$; $p < 0.01$) and ECSS ($r = 0.358$; $p < 0.01$), and negatively correlated with RTD ($r = -0.555$; $p < 0.01$) and STR ($r = -0.55$; $p < 0.01$) (Fig. 6). Regarding functional variables, R_{MAG} correlated with two balance conditions and negatively correlated with EOSS ($r = 0.643$; $p < 0.01$) and ECSS ($r = 0.497$; $p < 0.05$), and negatively correlated with RTD ($r = -0.326$; $p < 0.05$) and STR ($r = -0.481$; $p < 0.01$) (Table 7).

Table 7.
Relationship between predictor variables and behavioral variables

	Behavioral											
	Balance (sway index)								**RTD (Nm/s)**	**n**	**STR (Nm)**	**n**
	EOFS	**n**	**ECFS**	**n**	**EOSS**	**n**	**ECSS**	**n**				
CSA_{RF} (cm^2)	**-0.366****	67	**-0.411****	68	**-0.328****	66	**-0.519****	65	**0.538****	62	**0.732****	120
MQ_{RF} (au)	0.230	68	**0.248***	69	**0.353****	67	**0.358****	66	**-0.555****	61	**-0.550****	120
R_{MAG} (%MVC)	0.311	24	0.302	24	**0.643****	24	**0.497***	24	**-0.326***	59	**-0.481****	84
R_{MAG} (Nm)	-0.043	26	-0.007	26	0.282	26	0.058	26	0.244	61	0.202	84
R_{LAT} (m/s)	-0.120	26	-0.106	26	-0.160	26	-0.069	26	-0.103	61	-0.124	85
R_{LAT} (s)	-0.006	26	0.033	26	-0.036	26	-0.130	26	0.235	61	**0.258***	85
PC (%)	-0.025	66	**-0.614****	66	0.157	66	0.1	66	-	0	-0.153	55

** Correlation is significant at the 0.01 level* Correlation is significant at the 0.05 level
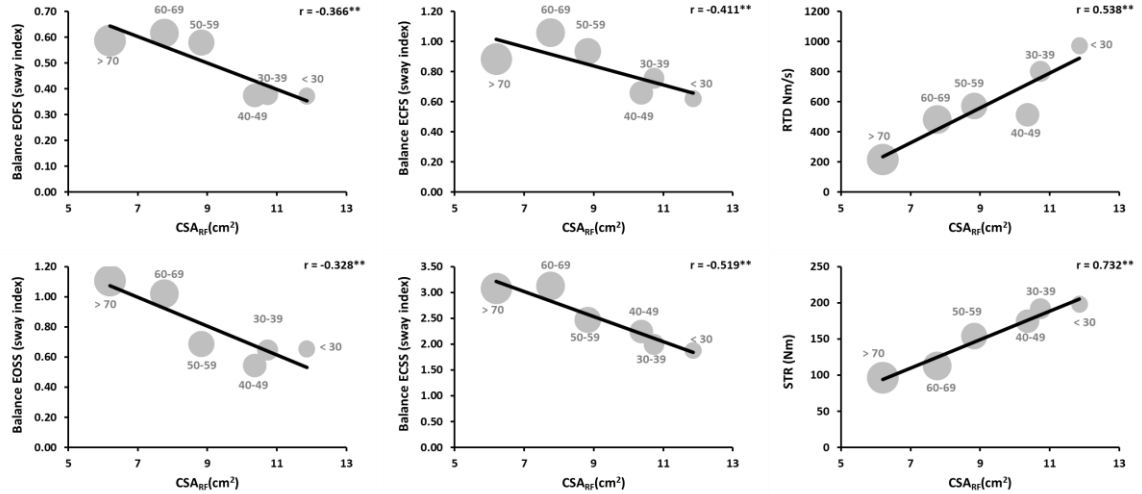
Figure 5. Significant relationships between CSA_{RF} and behavioral variables (balance, strength, rate of torque development). Person correlation r value is displayed for each linear regression. For visual purposes, groups have been collapsed into six age groups <30 years, 30 – 39 yrs., 40 – 49 yrs., 50 – 59 yrs., 60 – 69 yrs., and >70 yrs. For each group, the average of each variable was calculated and plotted. The size of the bubble represents the mean age, the bigger the bubble the older the group. ** = Significant relationships to the 0.01 level.
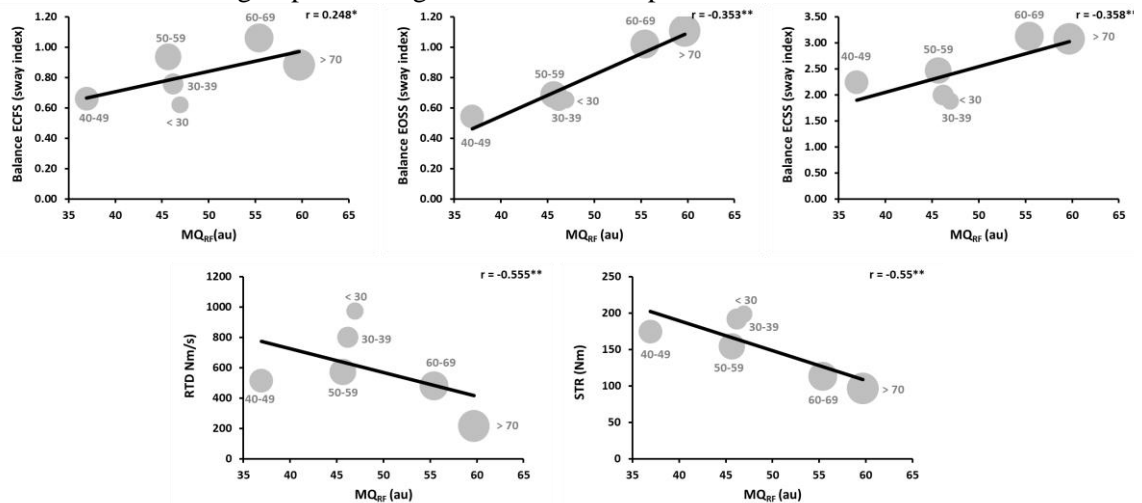
Figure 6. Significant relationships between MQ_{RF} and behavioral variables (balance, strength, rate of torque development). Person correlation r value is displayed for each linear regression. For visual purposes, groups have been collapsed into six age groups <30 years, 30 – 39 yrs., 40 – 49 yrs., 50 – 59 yrs., 60 – 69 yrs., and >70 yrs. For each group, the average of each variable was calculated and plotted. The size of the bubble represents the mean age, the bigger the bubble the older the group. * = Significant relationships to the 0.05 level. ** = Significant relationships to the 0.01 level.
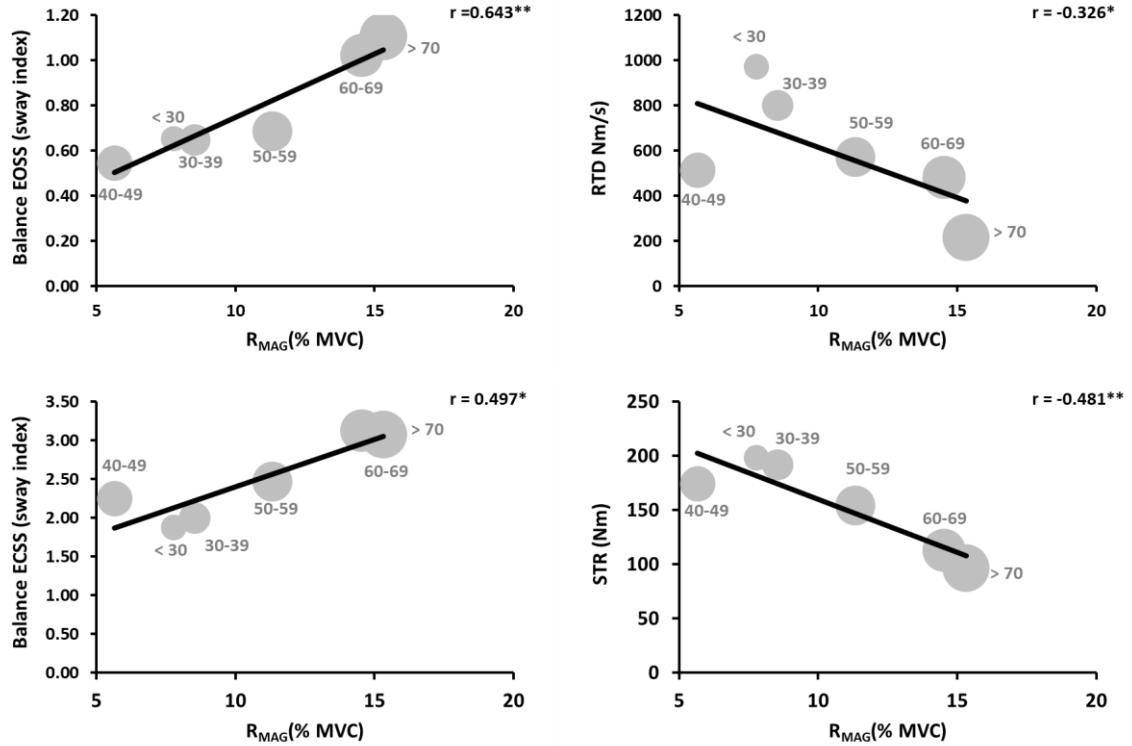
Figure 7. Significant relationships between R_{MAG} and behavioral variables (balance, strength, rate of torque development). Person correlation r value is displayed for each linear regression. For visual purposes, groups have been collapsed into six age groups <30 years, 30 – 39 yrs., 40 – 49 yrs., 50 – 59 yrs., 60 – 69 yrs., and >70 yrs. For each group, the average of each variable was calculated and plotted. The size of the bubble represents the mean age, the bigger the bubble the older the group. * = Significant relationships to the 0.05 level. ** = Significant relationships to the 0.01 level.

3.3.4 Determinants of Performance

3.3.4.1 Determinants of Balance

No multicollinearity was detected, independent predictor variables correlation was less than 0.85. Each stepwise multiple regression only examined the functional and/or structural variables that were significantly related to each balance condition. The stepwise multiple regression model for EOFS when collapsed across groups was significant. The

primary determinant was age, independently explaining 27% ($R^2 = 0.27$; p = 0.011. When the regression analysis was performed per group, only the middle-age group had a significant model. The primary determinant for this group was age, independently explaining 41.1% ($R^2 = 0.411$, p ≤ 0.001) of the variance.

The stepwise multiple regression model for ECFS when collapsed across groups was significant. The primary determinant was age, independently explaining 23.8% ($R^2 = 0.238$; p ≤ 0.001). When the regression analysis was performed per group, only the middle-age group had a significant model. The primary determinant for ECFS was age, independently explaining 41.1% ($R^2 = 0.411$, p ≤ 0.001) of the variance.

The stepwise multiple regression model for EOSS when collapsed across groups was significant (p ≤ 0.001). The primary physiological determinant for EOSS was R_{MAG}, independently explaining 41.1% ($R^2 = .411$, p ≤ 0.001) of the variance. When the regression analysis was performed per group, only the middle-age group had a significant model. The primary determinant for EOSS for this group was age, independently explaining 28.8% ($R^2 = 0.288$, p = 0.003) of the variance.

The stepwise multiple regression model for ECSS when collapsed across groups was significant (p ≤ 0.05). The primary physiological determinant for ECSS was CSA_{RF}, independently explaining 29.7% ($R^2 = .297$, p = 0.007) of the variance. In the younger group, the multiple regression model was not significant. In the middle- age group, the model was significant and the primary physiological determinant for ECSS was CSA_{RF}, independently explaining 36.6% ($R^2 = 0.366$, p = 0.048) of the variance. In the older

group, the model was significant and the primary determinant for ECSS was MQ_{RF}, independently explaining 99.9% ($R^2 = 0.999$, p = 0.014) of the variance. However, CSA_{RF} further explain 0.1% of the variance.

3.3.4.2 Determinants of Rate of Torque Development

The stepwise multiple regression model for RTD when collapsed across groups was significant (p ≤ 0.001). The primary physiological determinant for RTD was MQ_{RF}, independently explaining 31.9% ($R^2 = .319$, p ≤ 0.001) of the variance. However, R_{MAG} and CSA_{RF} further explained the change in variance by 7.8% (p = 0.01) and 4.8% (p = 0.037), respectively. Altogether, these variables explained 44.5% of the change in RTD variance. When divided between groups, only in the younger group, showed a significant model. The primary physiological determinant for RTD was CSA_{RF}, independently explaining 22.8% ($R^2 = 0.228$, p ≤ 0.001) of the variance.

3.3.4.3 Determinants of Strength

The stepwise multiple regression model for STR when collapsed across groups was significant (p ≤ 0.001). The primary physiological determinant for STR was CSA_{RF}, independently explaining 55.7% ($R^2 = .557$, p ≤ 0.001) of the variance. However, R_{MAG} further explained the change in strength variance by 9.3% (p ≤ 0.001). Altogether, these variables explained 65% of the change in STR variance. When divided between groups, the three groups showed significant models. The primary physiological determinant for STR in the young was CSA_{RF}, independently explaining 51.9% ($R^2 = 0.519$, p ≤ 0.001) of

the variance. However, R_{MAG} further explained the change in STR variance by 5.3% (p = 0.013). Altogether, these variables explained 57.2% of the change in STR variance. The primary physiological determinant for STR in the middle-age group was R_{MAG}, independently explaining 49% ($R^2 = 0.49$, p =0.002) of the variance. However, CSA_{RF} further explained the change in STR variance by 16.5 % (p = 0.0022). Altogether, these variables explained 65.5% of the change in STR variance. The primary physiological determinant for STR in the older group was R_{MAG}, independently explaining 65.4% ($R^2 = 0.654$, p =0.028) of the variance. However, CSA_{RF} further explained the change in STR variance by 33.3 % (p = 0.001). Altogether, these variables explained8.7% of the change in STR variance.

3.4 Discussion

We identified structural, functional, and behavioral changes associated with aging and their relationships to one another. Older adults had a smaller CSA_{RF} (~5cm2), lower MQ_{RF} (~14 au), greater R_{MAG} (~10% MVC), less STR (~101Nm), slower RTD (~554 Nm/s), and poorer balance performance (~ 0.5 sway index) when compared to the younger. The middle-age group had smaller CSA_{RF} (~2 cm^2), less STR (~ 39 Nm), slower RTD (~ 415 Nm/s), and poorer performance in all the balance conditions, except EOSS, (~0.29 sway index) when compared to the young group. Finally, when comparing the middle-age group to the older group, the older group had smaller CSA_{RF} (~3cm²), less STR (~63 Nm) and poorer balance performance in the balance conditions EOSS and ECSS (~0.55 sway index). Each change will be discussed in the following paragraphs.

3.4.1 Age-related structural and functional changes

Sarcopenia, known as loss in muscle mass, is a major well-studied age-related change. It seems to start, as early as, the age of 25 years old and progresses rapidly. One factor related to smaller CSA is due to a loss of fibers, mainly type II [16,20]. In this study we showed a significant decrease in RF's muscle size across each age group, where the young group had the largest CSA_{RF} and the old showed a reduction of ~5 cm^2.

Muscle quality was measured using ultrasound echo intensity. Echo intensity has been strongly correlated with higher percent of interstitial fibrous tissue (r = 0.87) [46] and subcutaneous fat (r = 0.8) [47]. Our results showed a significant lower quality in the old when compared to the young and middle age, but no differences were seen when comparing the young and middle-age group. Studies analyzing echo intensity have studied only one age group [17,48-50], or they have compared young versus older adults [18,19]. Similar to our finding, Nishira and collaborators[19] reported a significant lower muscle quality in the older group when compared to the young. However, to our knowledge, no study has looked at the middle-age group. From our results it seems that muscle quality seems to change at a slower rate that accentuates with the older group. This was also evident in our Figure 7 where we split our participants into six groups. In this figure we can see similar averages between the young and middle –age groups (30 – 59 years old) but it was until the age of 60 that the distinction between the groups was apparent. Yet, the lack of statistical significance might be due to the middle-aged groups being underpowered, which led to an outlier bin (40 - 49 yrs. old).

In this study we measured reflex responses through tendon taps, where reflex magnitude was normalized to each subject's MVC. While normalization aided the comparison across subjects and groups, the results might be misleading. The normalized values showed a higher R_{MAG} in the older group; yet, in reality the absolute numbers demonstrate lower R_{MAG} in the older group. Therefore, both values will be discussed here. When comparing the young and old groups we discovered a significant difference in R_{MAG} normalized. One factor behind this phenomenon was the significant difference in maximal strength between the young and the old (Y = 198.55 and O = 97.22 Nm), which resulted in an apparent higher R_{MAG} in the older group. However, the opposite interpretation might also hold true. Muscle spindles provide a reflexive excitation of 7 – 30% to the motoneuron pool [33-35,51]. However, they undergo a morphological, biochemical, and function degradation with aging, [15,21]. In this study, R_{MAG} raw values showed a ~2 Nm weaker response in the old when compared to the young. As a result, there might be less excitation sent to the motor unit pool which reduces motor output resulting in less STR [8,33,34], hence higher normalized R_{MAG}. Even though, there was not a significant difference in R_{MAG} raw values, it is possible that it was due to the age of our participants and/or due to the middle-age group being underpowered. In Liu et al [21] muscle spindle comparison study, their young group was 19 – 48 years old and the old subjects were aged 69 – 83 years old.

3.4.2 Behavioral changes and its relationship to structural and functional changes

In line with previous studies, we saw a significant decrease in STR associated with aging [50,52]. Interestingly, the two variables that explained the variance in STR were CSA_{RF} and R_{MAG}. The reason behind this, might again be explained by the muscle spindle degradation associated with aging. Previous studies have shown a detrimental effect of age on muscle spindle morphology and function [6,15,21]. In addition, suppression of muscle spindle activity has resulted in decreased motor unit excitation [33,34] affecting higher threshold motor units the most [8]; and one factor related to smaller CSA is loss type II fibers[16,20] Therefore, it seems possible that the altered spindle function could have led to atrophy of higher threshold motor units, thus the smaller CSA_{RF} and the significant relationship between CSA_{RF} and R_{MAG}, making these variables important predictors of STR. Furthermore, in the young group CSA_{RF}, explains most of the variance and R_{MAG} was secondary. However, with the latter groups, R_{MAG} becomes the main determinant of STR and CSA_{RF} secondary.

Similarly, RTD variance was explained by MQ_{RF}, R_{MAG}, and CSA_{RF}. In this case, MQ_{RF} was the main predictor. As mentioned earlier echo intensity has been strongly correlated with non-contractile tissue[46,47], so the higher the score the lower the muscle quality and possibly less contractile tissue. This explains why CSA_{RF} and MQ_{RF} are crucial determinants of RTD [17,18,50]. In addition, regarding R_{MAG}, studies have shown that spindle function suppression leads to slower RTD results. Therefore, our results are in accordance with previous research [35].

Balance requires a complex integration between sensory input and motor output; where the sensory input allows the system to adapt to the environment. During vertical standing, there are three main sources of sensory feedback, vision, vestibular system, and proprioception[52,53]. In this study we assessed balance using the Modified Clinical Test of Sensory Interaction, which involves four different conditions. We discovered moderately to strong correlations between each balance condition and age. In addition, when comparing the young and old groups, the older group's sway index was significantly greater in every balance condition; also when comparing the middle-age group with older group, the older group demonstrated greater sway in the conditions EOSS and ECSS. These results are consistent with previous studies demonstrating that altering somatosensory and/or visual input resulted in greater balance errors associated with aging [6,10,11,54]. After the stepwise regression, we discovered that R_{MAG} was the functional variable explaining most of the variance in EOSS condition; greater normalized R_{MAG}, seen in older adults, resulted in greater sway. In this condition, one of the somatosensory inputs that was altered was stretch reflex. As we discussed before, muscle spindle undergoes a structural and functional degradation [6]. Even though, somatosensory input was altered in this condition, it was still present; so it explains why it was one important factor in postural control and why performance significantly decreased across each age group. On the other hand, the strongest correlation that was found between aging and sway index was during the condition ECSS; this condition involves altering somatosensory and visual information which resulted in greater sway, which is in accordance with previous literature [6,10,11]. The primary structural variable related to this

condition was CSA_{RF}. Research has suggested that when balance is challenged, a hip

strategy is used, where trunk and thigh muscles are activated first instead of the ankle

muscles (ankle strategy) [52,55]. The condition ECSS, was the most challenging condition

because two sources of feedback were altered, vision and somatosensory input. If

subjects used a hip strategy, it explains why CSA_{RF} was the main determinant in this

condition. Furthermore, with older adults, MQ_{RF} explained most of the variance in this

condition. Indicating that the quality of the muscle was crucial for this specific condition.

3.4.5 Limitations

The middle-aged and old groups sample size for some variables was small, which led to

being underpowered. Another limitation was that even though tendon taps involve a

natural muscle response, it might still not reflect muscle spindle behavior during

voluntary movements. Another limitation was that since we wanted to study correlation

and variance, our groups' physical fitness status was not controlled. This could have led

to greater variability that we saw on the variables measured here.

3.5 Conclusions

Age alters the control of voluntary movement. One prominent change related to motor

control and output is a functional and structural degradation of muscle spindles. There is

evidence indicating that suppression of muscle spindle activity leads to a reduced motor

unit excitation. In this study, we saw a reduced reflex magnitude that related to muscle

size, strength, rate of torque development, and balance. Therefore, it is possible that

muscle spindle degeneration could be the underlying mechanism behind other structural,

functional and behavioral changes associated with aging.

CHAPTER IV

CENTRAL AND PERIPHERAL DETERMINANTS OF COACTIVATION

4.1 Introduction

Since experiments conducted by Sir Charles Sherrington, where stimulation of one

muscle caused the relaxation of the opposing [56], it has been accepted that voluntary

movements are organized around a dual balanced system of muscle pairs that act at a

joint[2,3,57-60]. These muscle pairs activities are mediated by central and peripheral

mechanisms; where supraspinal mechanisms, such as motor cortex, midbrain,

cerebellum, and basal ganglia, seem to be primarily involved in decision making and

planning of movement [1] ; whereas peripheral feedback provide reflexive assistance[8,60,61]

and aid in assessing the internal and external conditions of a specific task[6,9,62,63]. The

efferent drive, from supraspinal mechanism, and afferent feedback, from peripheral

mechanisms, are translated by complex spinal networks to exert the desired movement

according to the task specifications [4,9]. Muscle activation varies according to the nature of

the task. During single-joint movements there seems to be two possible activation patterns between opposing muscles, reciprocal inhibition and antagonist coactivation[2,3,40]. Factors such as velocity, load[40,64], rhythm[4], and fatigue[65], among others seem to dictate the control mechanism that was facilitated[66]. It has been generally accepted that lower velocities and resistances are associated with higher levels of reciprocal inhibition [40,64]. On the other hand, higher velocities and/or loads and during unstable conditions, a higher antagonist coactivation is seen [64,67]. Inhibitory Ia interneurons, seem to be the main mechanism mediating reciprocal inhibition, these interneurons are facilitated by central and peripheral pathways such as Renshaw cells, muscle spindles Ia afferent, among others [2-4]. When reciprocal inhibition is favored, it seems that alpha motoneurons and their corresponding Ia inhibitory interneurons are controlled in parallel[3]. On the other hand, during tasks with agonist – antagonist cocontraction, Ia inhibitory interneurons are centrally depressed [3,63] while agonist and antagonist motoneuron pools are controlled as one [68].

Nevertheless, these activation patterns seem to be affected by the neuromuscular reorganization[39,42] associated with aging. Specifically, it seems that older adults execute many voluntary movements using a disproportionately heightened coactivation[7,28-30,38]. The underlying mechanisms behind this heightened antagonist cocontraction are not completely understood. In Hortobágyi and De Vita's[28] study supraspinal and spinal mechanisms that can be related to the increased antagonist activation are described through the review of several studies; yet, these studies have focused only on one component, the mechanisms[31,39] (i.e. reciprocal inhibition) or on the behavior[29] (increased

antagonist electrical activity). The possible cortical and spinal mechanisms related to increased coactivation include decreased reciprocal[39] and presynaptic inhibition[31]; decreased muscle spindle sensitivity[38]; higher cortical bilateral activation[32]; decreased interhemispheric and cortical inhibition[12,41]; and dispersed muscle representation areas[43]. Still, to our knowledge, there is no study that measures central and peripheral mechanisms in relationship to increased antagonist coactivation. Furthermore, these central and peripheral changes have been shown to affect performance[12,32,40,41,43,69]. Increased brain activation has been associated with improved performance[7], shown by an inverse relationship between activation and reaction times[32,43]. In contrast, decreased cortical inhibition has been associated with worse performance[7], where shorter cortical silent periods are associated with poorer performance during complex tasks[12].

4.1.2 Purpose of the Study

The purpose of this study was twofold: first, to identify the central and peripheral determinants behind the age-related changes in antagonist muscle coactivation; and second, to determine the effects of the identified changes on performance.

4.1.3 Research Questions and Hypotheses

This study has the potential to provide new information regarding the age – related central and peripheral changes associated with performance. The following research questions and hypotheses have the potential of being answered:

- Research Question 1: Which central or peripheral mechanisms explains variance, if any, in the level of coactivation? If so, which mechanism explains the greatest

variance?

- o Hypotheses:

    - ▪ The amount of agonist and antagonist's muscle representation areas overlap (FCR-ECR$_{OVERLAP}$) will be a significant predictor of antagonist coactivation.

    - ▪ Decreased cortical inhibition will be related to higher antagonist coactivation.

    - ▪ Decreased presynaptic inhibition will be associated with higher coactivation levels.

    - ▪ Decreased muscle size and quality will be associated with higher coactivation levels.

- RQ 2: Is there a relationship between peripheral (muscle size and quality) and central (brain excitation and inhibition, cortical representation area) changes?

    - o Hypotheses:

        - ▪ Decreased muscle size and quality will be associated with increased cortical excitation.

- RQ 3: Is there a significant relationship between increased antagonist coactivation and performance?

    - o Hypotheses:

        - ▪ Reaction time will be significantly related to antagonist coactivation levels.

4.1.4 Significance of the Study

Due to the sociodemographic change that is happening in the USA; where there will soon

be elder adults that young people, it is imperative to understand the functional and behavioral changes that can impair an older adult's quality of life. Previous literature shows an increased muscular coactivation related to diminished reaction capacity, which increases the older adult's fall risk. Therefore, it is crucial to determine the underlying mechanisms behind these behavioral changes and their roles. This information has the potential to be the guide for creating effective interventions to decrease falls and increase quality of life of the older population.

4.1.5 Limitations

1. Randomization: The process of subject participation was voluntary and the group division was based on their age. Therefore, the selection was not truly random.

2. Transcranial magnetic stimulation (TMS) has many limitations:

   a. Since this still a recent technology, protocols have not been standardized. Furthermore, the replication of studies was harder due to insufficient methodological descriptions[70].

   b. TMS has shown great variability in motor evoked potential (MEP) amplitudes, slightest move of the position of the coil and/or the person's emotional state can alter the results[7].

   c. TMS mapping involves at least 100 stimuli; therefore, it can create annoyance, which in turn can affect cortical excitability and performance[71].

3. Coil limitations:

   a. A figure-eight coil can reach a depth of 1.5 – 2.5 cm.; this depth was not enough to stimulate any leg muscles[72]. Therefore, the results found here might not apply

to weight bearing muscles, such as the legs.

4. Cortical and spinal stimulation:

   a. The study of cortical excitation and inhibition, was made through artificial stimulation. It is possible that evoked contractions did not reflect the behavior during voluntary movements.

4.1.6. Assumptions

1. Subjects answer health and pain questionnaire honestly

2. Maximal effort was given during maximal contraction and reaction tasks

3. The EMG detected accurately represents the behavior of the whole muscle with little crosstalk

4.1.7 Threats to validity

The following was potential threats to validity:

1. Intra-subject variability: due to the TMS variability, it may be difficult to perform consistent measurements. To account for this:

   a. All cortical measurements were done in one day

   b. MEPs were normalized to M-wave

   c. Silent periods (CSP) was normalized to normalized maximal MEP

   d. The position of the coil was marked on the cap, to maintain the consistent positioning

   e. Subjective annoyance was rated to use as a covariate in case it affects the measurements

2. Stimulants and fatigue effect

   a. Participants were asked to refrain from any stimulant, such as coffee, and/or avoid any exercise 48 hours before visiting the lab

4.2. Methods

4.2.1 Participants

This study required at least 30 healthy subjects, 15 for each age group (18 – 44 & 65 years or older) from the local community. Inclusion criteria included ability to walk independently without aid and ability to communicate and follow testing procedures. Exclusion criteria included severe cognitive impairment, known cardiovascular or neuromuscular disease, and/or arm or leg injury in the last year, and/or have any contraindications regarding transcranial magnetic stimulation (TMS) use. All subjects completed an informed consent, a pre-exercise health, an exercise status questionnaire, and a TMS screening questionnaire. This study was approved by the University's Institutional Review Board.

4.2.2 Research Design

Each subject visited the lab on three separate occasions. The first visit consisted of familiarization and cortical and peripheral excitability measurements. The second visit involved anthropometric measurements and performance tasks. The primary muscles of interest are the flexor carpi radialis (FCR) and extensor carpi radialis (ECR).

Table 1
Summarized activities for each visit

Visit 1 (60 min.)	Visit 2 (30 - 45 min.)	Visit 3 (60 – 90 min.)
• Ultrasound: muscle size and quality (Peripheral) • Maximal strength and EMG amplitude (Performance) • Reaction Tasks (Performance)	• M-wave (Peripheral)	• Cortical excitation (Central) • Cortical silent period (Central) • TMS M1 Mapping (Central)

4.2.3 Instruments and Procedures

The main goal of this study was to determine the central and peripheral determinants of

antagonist coactivation associated with aging. Therefore, the following sections were

divided into cortical and subcortical measurements.

4.2.3.1 Central

Hot spot identification: a cap was placed over the participants scalp to allow marking of

stimulation locations, and the location of the vertex was determined (a point on the

midsagittal line, midway between the nasion and inion and right and left pre-auricular

points). Subjects laid supine on a comfortable bed and kept their arms relaxed at a 90°

shoulder abduction and with the arm in a supine position. A figure-eight coil connected to

a Magstim 200 (Magstim Inc., MN, USA) was be held tangentially at a 45°-degree angle

to the sagittal plane with the handle pointing in the posterior direction to induce a

posterior – anterior current flow, which is the optimal coil position for left primary motor

cortex excitation[73]. To identify the optimum scalp position, first the coil was placed 5cm

lateral and 1 cm anterior relative to the vertex[74]. A subthreshold intensity was used to elicit motor evoked potentials (MEPs), then the coil was shifted 1 cm in the anterior, posterior, medial, and lateral direction while evoking three MEPs at each site[75,76]. The site with the largest MEP was used as the hot spot[75,77]. Once the hot spot has been identified, the rim of the coil was marked to maintain coil position.

Cortical resting motor threshold (CRMT): to calculate the RMT, the adaptive method was used[78] due to its accuracy and efficiency[75,76]. This method predicts a TMS intensity that yields a 50% probability of evoking a MEP. Using Awiszus and Borckard Motor Threshold Assessment Tool (version 2.0), an upper boundary of 100% and a lower boundary of 0% was used. Based on the boundaries, the program selects the TMS intensity that was used, then the researcher has to fed back whether the MEP was evoked or not. The program estimated the stimulus intensity of the next TMS based on the maximum-likelihood threshold-tracking algorithm. Using this method, only 14 – 17 stimuli are needed to accurately estimate CRMT[75].

Motor cortical representation areas mapping: topographic organization of FCR and ECR was quantified using MEPs from single-pulse TMS. A 7 x 7 cm rectangular grid with 1 cm spacing was placed over the scalp. The center of the grid was placed over the identified hot spot. To determine the order for stimulation, the grid was divided into columns and these seven columns' order was randomized for each participant. While participants are relaxed, four MEPs was elicited at 130% of CRMT [12,76,79,80] separated by at least 4 - 6 seconds[43,81]. EMG was monitored to ensure the participants relaxation and

each MEP P-P amplitude was recorded in real – time. MEP_{MAX}, map area, map volume, center of gravity (CoG), and map overlapping was calculated. The amplitude of each MEP was calculated as the peak – to – peak amplitude between the onset and offset of the MEP, and it was expressed relative to the maximal M-wave for each muscle (MEP_{MAX}; % M_{MAX}). MEP latency was measured as the time between the start of the square impulse and to the highest peak and normalized to each subject's height (MEP_{LAT}; s/m). The largest MEP with the shortest latency was used to assess cortical excitability. Map area was calculated as the sum of the active sites. A site was considered active if at least one MEPs out of four MEPs are larger than 24% of the largest MEP_{MAX}[82] (Map_{AREA}; cm^2). Map volume was calculated by adding mean normalized to M_{MAX} amplitudes of each stimulated site divided by the mean MEP amplitude, normalized to M_{MAX}, at the site where the largest response was obtained (Map_{VOL}; %M_{MAX}). CoG was computed for the mediolateral (x) and anteroposterior (y) coordinates relative to vertex (expressed in cm) using the following formula $CoGx = (\sum x_i \times MEP_i)/\sum MEP_i$; and $CoGy = (\sum y_i \times MEP_i)/\sum MEP_i$; where MEP_i represents the mean amplitude of the MEPs produced at one site[81,82]. The CoG provides a spatial average optimal site; also, it has allowed the distinction of the representation areas of two limb muscles[74,76] (CoG; cm^2). Map overlap was calculated for the ECR and FCR, it was quantified as the shared number of active sites (as identified before) as a percentage of the total number of active sites that the two muscles overlaid in M1. The following formula was used; where overlap refers to a grid site (active site) shared by both muscles and *active sites* represents a grid site > 0 on the map (OVERLAP; %).

$$Overlap = \frac{number\ of\ shared\ active\ sites}{total\ number\ of\ active\ sites} * 100$$

Cortical silent period (CSP): the TMS coil was placed on the FCR hot spot, then ten

MEPs was elicited at intensity of 130% of RMT while the participants perform a tonic

wrist flexion at 20% of their maximal voluntary contraction (MVC)[79] lasting 40 – 60

seconds. The CSP was measured as the time between the MEP to the recurrence of EMG

activity. To improve the accuracy in identifying the recurrence of EMG, EMG was

rectified and the recurrence was identified through visual inspection[75,76]. To reduce inter-

subject variability the ratio of CSP duration was calculated and averaged across the ten

trials (CSP; ms/ μV).

4.2.3.2 Peripheral measurements

M-wave: a bipolar probe connected to a stimulation cart (Cadwell Sierra Summit,

Cadwell Industries, Inc., Kennewick, WA, USA) was used to stimulate the median and

radial nerve at the level of the elbow[83]. Median nerve was stimulated at the cubital fossa[74]

medial to the biceps' tendon[84-86], this stimulation does not cause stimulation on the ECR[87]

and radial nerve stimulation was elicited laterally to the brachioradialis[88]. Each muscle

was identified and marked using ultrasound imaging. The cathode was placed proximally

and the optimal probe position was determined by delivering single stimulus at a low

intensity (5 – 10mA). The location that elicited the largest M-wave was marked and used

for the entire nerve stimulation protocol. To identify the maximal M-wave, the intensity

was increased in a stepwise fashion, by five mA increments, until the M-wave peak – to –

peak reaches a plateau. The largest M-wave peak – to – peak was defined as the maximal M-wave (M_{MAX}; mV). M-wave max was confirmed by increasing stimulation level by 15 mA with no changes in M-wave amplitude[83]. The latency of the M_{MAX} was measured as the time between the onset of the stimulus artefact up to the first deflection and normalized to subject's height[27] (M_{LAT}; s/m).

Electromyography: Central and peripheral measurements were performed while participants were sitting arm with their arm abducted to 90°; the elbow was at 160° of extension with a neutral wrist position. Two bipolar bar electromyographic (EMG) electrodes (DE-2.1; Delsys, Inc., Boston, MA) with 1 cm in interelectrode distance were placed on each subject's forearm. The EMG sensors were placed over the FCR, at 1/3 the distance of the medial epicondyle to the distal of the head of the radius [89]; and over the ECR, 1/5th between the lateral epicondyle to second metacarpal[85]. The location of both muscles was confirmed through ultrasound imaging and EMG activity. To confirm electrode placement using EMG, the participants performed resisted wrist extension with radial deviation and finger flexion (ECR) and a resisted flexion with radial deviation (FCR)[85]. A reference electrode (Dermatrode; American Imex, Irvine, CA) was placed on C7. Prior to electrode placement, the skin was prepared by shaving, removing the dead skin and cleaning the skin. The sensors were firmly secured with hypoallergenic surgical tape.

Signal processing: analog EMG signals was collected using a Bagnoli EMG system (Delsys Inc., Boston, MA) and digitized using a Data Acquisition system (DAQ NI A-D

card USB- 6251, National Instruments, Austin, TX, USA) with a customized LabVIEW

program (LabVIEW v. 19.0, National Instruments, Austin, TX, USA). EMG signal was

amplified (gain = 100), sample at a frequency of 4 kHz and filtered using band-pass filter

(8th Butterworth; cut-offs of 20 and 999 Hz).

Ultrasonography: Ultrasound (US) images of the dominant FCR and ECR muscles was

obtained using a diagnostic US imaging device (GE Logic S8, Milwaukee, WI, USA)

with a linear array probe (model ML6-15-D, 4-15 MHz, 50-mm field view). Participants

rested their arm on a table at 90° of shoulder abduction and flexion. Panoramic US

images of the right FCR and ECR was taken at 1/3 the distance of the medial epicondyle

to the distal of the head of the radius[89] and over the ECR, at two fingerbreadths distal to

the lateral epicondyle[90]. The probe was placed perpendicular to the skin and it was

advanced laterally along the skin above the muscles in a slow, consistent manner. Water-

soluble transmission gel was applied to the skin to enhance acoustic coupling[48]. Muscle

cross-sectional area (CSA) and echo intensity (MQ) were optimized for image quality

using musculoskeletal mode prior to all image acquisitions using a gain of 50 dB and a

frequency of 12Hz. Depth was adjusted according to participants' adipose tissue.

Panoramic US images was captured until two uniform scans with acceptable image

quality are collected by the same investigator.

US image analysis was performed using Image-J software (National Institutes of Health,

USA, Version 1.50i). Each image was individually calibrated from pixels to cm using the

straight-line function in Image-J. FCR and ECR CSA and EI were analyzed by defining a

region of interest that includes as much muscle as possible, without including any bone or fascia, using the polygon function in the Image-J software (CSA; cm^2). EI was determined using computer-aided gray scale analysis using the standard histogram function and was measured in arbitrary units (au) with values ranging from zero (black) to 255 (white) (MQ; au). CSA and EI was recorded, averaged and used for further analysis.

4.2.3.3 Performance measurements

Voluntary Maximal Contractions: participants were comfortably seated on a calibrated isokinetic dynamometer (Biodex system 4; Biodex Medical Systems, Inc. Shurley, NY, USA) with the trunk stabilized in the chair by abdominal straps. The forearm was supported and strapped in a prone position with the hand over the wrist attachment. The axis of rotation of the dynamometer head was aligned with the stylus process of the ulna. Participants warmed up by performing three, five second contractions at 50% and 75% of what they believe is their maximal effort with 30 seconds of rest between contractions. Following, participants performed 3 – 4 seconds maximal voluntary contractions (MVC) of the wrist flexors and extensors. Participants were instructed to "push as hard as possible". The amplitude of each EMG signal was assessed as the root-mean-square and normalized to M_{MAX} (RMS; %M_{MAX}). Antagonist coactivation (CoA) was calculated for the FCR and ECR. The CoA was calculated as the highest RMS 40 ms window and it was normalized to the corresponding M_{MAX} (CoA; %M_{MAX}).

Reaction task: Following the maximal strength testing, participants performed the reaction task. For this test, there was three conditions, single, and dual-task congruent and dual-task incongruent and each participant performed each one twice. During the single task, participants performed a reaction task while fixating a point located at the center of a white cardboard placed in front of them (RT_C). In the dual – task conditions, participants performed the Stroop Test (congruent, RT_{Cn} and incongruent RT_I). The order of the three tasks was randomized across participants. Before the test, the wrist range of motion (ROM) of each participant was assessed; the largest wrist angle that can be comfortably held was used as the maximal ROM for the reactive task. Starting in a prone neutral position (hand parallel to the floor), the wrist was suddenly displaced at a velocity of 90°/s and a torque of 20 N. The participant was instructed to stop the lever as fast and as hard as possible. Each participant repeated each task twice, the trial with the shortest reaction time was used for the statistical analysis. For each of these tasks we measured the following variables: FCR and ECR latencies, which was the time between the onset of the displacement to the point where the rectified smoothed EMG signal deviates two standard deviations from the baseline (FCR_{LAT} and ECR_{LAT}; s); antagonist coactivation was measured, as the maximal 40ms RMS window of the antagonist muscle normalized to M_{MAX} (ECR_{CoA}; %M_{MAX}); and ECR RMS max location, as the time between the onset and the maximal 40ms RMS window ($ECR_{RMS-LOC}$; s).

4.2.3.4 Annoyance and pain rating

Since TMS and electrical nerve stimulation (ENS) might involve painful stimulus, at the end of each day, participants was asked to rate the annoyance and pain. To determine annoyance, participants was asked, "How annoying were the TMS pulses?" zero, meant "not at all annoying;" while ten meant "highly distracted and unable to do the task". For pain, the participants were asked, "if the stimulus was painful, how intense was the pain;" zero meant "no pain at all;" while ten meant "the worst pain they could tolerate during the experiment."

4.2.4 Statistical Analysis

A repeated measures MANOVA was used [reaction task (control, congruent, and incongruent) x CoA)] was performed. Significant multivariate interactions were identified and further divided into simple main effects on dependent variables that showed significance. If the Wilk's Lambda test or a given univariate interaction was not statistically significant, the main effects was analyzed. When the main effect was significant, the corresponding F test for each dependent variable was analyzed. For any given significant univariate F test, a pairwise comparison was done. Bonferroni adjusted alpha ($\frac{\alpha}{no.of\ groups}$) was used to asses significance. Pearson correlation coefficients were used to examine the relationships between the predictor variables (central and peripheral measurements) and each reactive measurement (FCR_{LAT}, ECR_{LAT}, $ECR_{CoA;}$ $ECR_{RMS-LOC}$). Following the Pearson correlation coefficients, stepwise multiple regression analysis examined which of the predictor variables (central and peripheral variables)

independently explained a significant proportion of the total variance in reactive measurements (FCR$_{LAT}$, ECR$_{LAT}$, ECR$_{CoA}$; ECR$_{RMS-LOC}$). Only variables that were significantly be related were used in the regression analysis.

4.3 Preliminary Findings

4.3.1 Descriptive statistics

Twelve young adults participated in this study, 8 females and 4 males. Demographic data is presented on Table 2; central determinants of coactivation on Table 3; peripheral determinants of coactivation on Table 4 and performance measurements on Table 5. Only six participants were able to finish the third visit involving TMS; the six participants that were not included were due to reporting having a concussion in the past.

Table 2.
Participants Demographics

Variable	$\bar{x}$	s
Age (yrs.)	21	1
Height (m)	1.70	0.09
Weight (kg)	78.54	22.37
Hand Grip	34.25	9.61

Table 3.
Central physiological variables

Variable	$\bar{x}$	s
FCR$_{CSP}$ (s)	0.134	0.02
FCR$_{CSP}$ (s/µV)	0.092	0.040
FCR$_{MEP-MAX}$ (%FCR$_{M-MAX}$)	10.615	10.266
FCR$_{MEP-LAT}$ (s)	0.032	0.005
FCR$_{MEP-Lat}$ (s/m)	0.019	0.004
ECR$_{MEP-MAX}$ (%ECR$_{M-MAX}$)	5.522	4.403
ECR$_{MEP-LAT}$ (s)	0.027	0.005

Variable	$\bar{x}$	s
$ECR_{MEP\text{-}Lat}$ (s/m)	0.016	0.003
FCR_{CoGx} (cm)	4.855	0.819
FCR_{CoGy} (cm)	1.134	0.709
ECR_{CoGx} (cm)	4.886	0.686
ECR_{CoGy} (cm)	1.225	0.605
$FCR_{MAP\text{-}AREA}$ (cm^2)	18.667	5.645
$ECR_{MAP\text{-}AREA}$ (cm^2)	26.000	7.321
$FCR_{MAP\text{-}VOL}$ (cm^3)	15.400	3.608
$ECR_{MAP\text{-}VOL}$ (cm^3)	17.158	4.359
$FCR\text{-}ECR_{OVERLAP}$ (%)	75.834	15.769

Table 4.

Peripheral structural and functional variables

Variable	$\bar{x}$	s
FCR_{CSA} (cm^2)	2.438	0.968
FCR_{MQ} (au)	69.455	8.879
ECR_{CSA} (cm^2)	4.095	1.883
ECR_{MQ} (au)	62.410	9.442
$FCR_{M\text{-}MAX}$ (μV)	7.014	2.559
$FCR_{M\text{-}LAT}$ (s)	0.0023	0.0009
$FCR_{M\text{-}LAT(n)}$ (s/m)	0.0013	0.0005
$ECR_{M\text{-}MAX}$ (μV)	9.874	0.969
$ECR_{M\text{-}LAT}$ (s)	0.0015	0.0002
$ECR_{M\text{-}LAT(n)}$ (s/m)	0.0009	0.0001

Table 5.

Behavioral variables

Variable	$\bar{x}$	s
$WF\text{-}FCR_{RMS}$ (%$FCR_{M\text{-}MAX}$)	6.0747	3.2544
$WF\text{-}FCR_{RMS\text{-}LOC}$ (s)	2.0026	1.0632
$WF\text{-}ECR_{CoA}$ (%$ECR_{M\text{-}MAX}$)	1.1699	0.6458
$WF\text{-}ECR_{CoA\text{-}LOC}$ (s)	1.7852	1.0121
$WE\text{-}FCR_{CoA}$ (%$FCR_{M\text{-}MAX}$)	0.9154	0.5426
$WE\text{-}FCR_{CoA\text{-}LOC}$ (s)	2.7951	1.3388
$WE\text{-}ECR_{RMS}$ (%$ECR_{M\text{-}MAX}$)	3.9685	1.7492
$WE\text{-}ECR_{RMS\text{-}LOC}$ (s)	2.3765	1.5806
$RT_{C}\text{-}FCR_{LAT}$ (s)	0.1077	0.0706
$RT_{C}\text{-}FCR\text{-}ECR$ (s)	0.0457	0.0901
$RT_{C}\text{-}ECR_{LAT}$ (s)	0.1533	0.1029
$RT_{C}\text{-}FCR_{RMS}$ (%$FCR_{M\text{-}MAX}$)	4.9285	2.5341
$RT_{C}\text{-}FCR_{RMS\text{-}LOC}$ (s)	0.7875	0.4574
$RT_{C}\text{-}ECR_{CoA}$ (%$ECR_{M\text{-}MAX}$)	0.7677	0.4589
$RT_{C}\text{-}ECR_{CoA\text{-}LOC}$ (s)	0.8800	0.5736

RT_{Cn}-FCR_{LAT} (s)	0.0896	0.0583
RT_{Cn}-FCR-ECR (s)	0.1113	0.1569
RT_{Cn}-ECR_{LAT} (s)	0.2009	0.1626
RT_{Cn}-FCR_{RMS} (%$FCR_{M\text{-}MAX}$)	4.3999	2.6601
RT_{Cn}-$FCR_{RMS\text{-}LOC}$ (s)	0.7230	0.4187
RT_{Cn}-ECR_{CoA} (%$ECR_{M\text{-}MAX}$)	0.4715	0.2197
RT_{Cn}-$ECR_{CoA\text{-}LOC}$ (s)	0.7961	0.4728
RT_{I}-FCR_{LAT} (s)	0.0885	0.0846
RT_{I}-FCR-ECR (s)	0.0412	0.0996
RT_{I}-ECR_{LAT} (s)	0.1166	0.0729
RT_{I}-FCR_{RMS} (%$FCR_{M\text{-}MAX}$)	5.4319	3.7073
RT_{I}-$FCR_{RMS\text{-}LOC}$ (s)	0.7635	0.3980
RT_{I}-ECR_{CoA} (%$ECR_{M\text{-}MAX}$)	0.5402	0.2556
RT_{I}-$ECR_{CoA\text{-}LOC}$ (s)	0.6444	0.4550
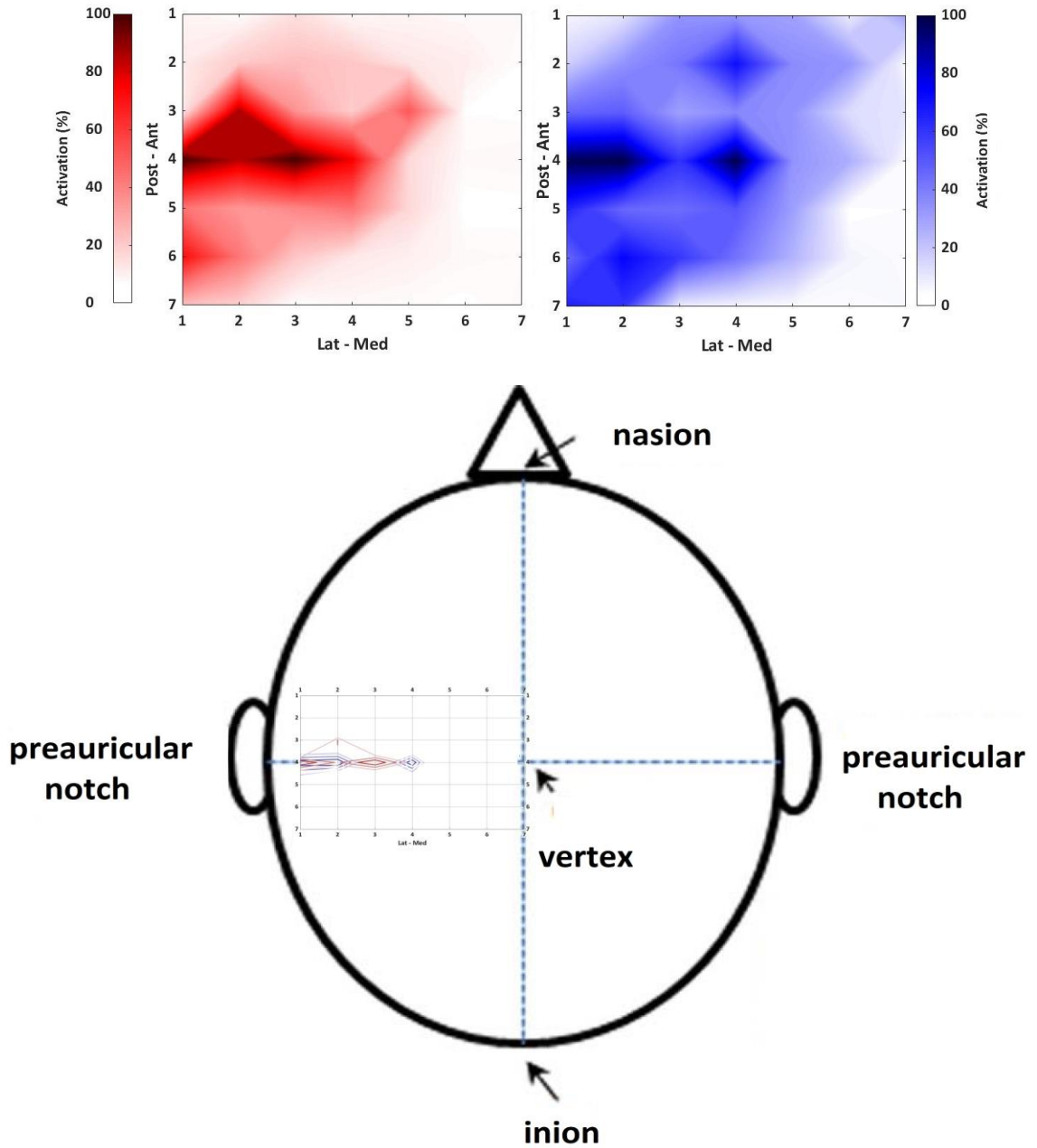
Figure 1. TMS mapping using MATLAB. For visual purposes the responses were rescaled from 0% - 100%; where 100% was the site with the largest averaged response. (A)ECR map (red), and (B) FCR map(blue). (C) Overlap, both muscles were plotted in the same graph, only responses that where 80% or higher are shown.

Figure 2. Subject's ECR (red) and FCR (blue) maps. The areas represented here are those that had 80% of activation or more. Areas where both muscles are present represent the zones where both muscles overlap.

3.3.2 Relationships between central and peripheral determinants of antagonist

coactivation during maximal and reactive tasks

4.3.2.1 Reactive tasks

This experiment involved three conditions, control (RT_C), congruent (RT_{Cn}) and

incongruent (RT_I). For each of these tasks we measured the following variables: FCR_{LAT},
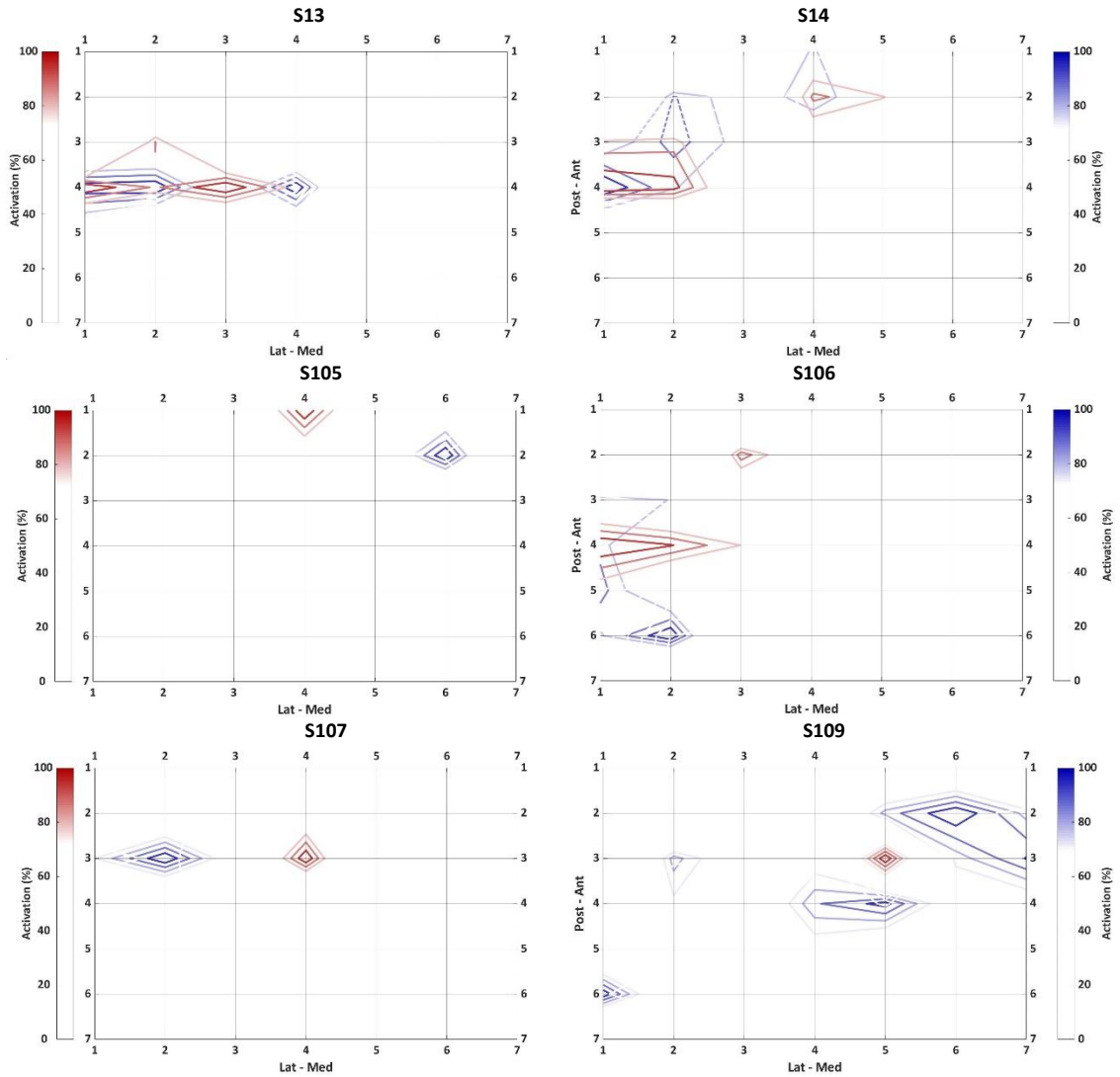
ECR_{LAT}, ECR_{CoA}, and $ECR_{RMS-LOC}$. One-way RM MANOVA indicated a main effect of

type of reactive test on one of the dependent variables, $F(10,36) = 2.303$, $p = 0.033$.

Pairwise comparisons revealed a significant difference in ECR_{CoA}, which was

significantly larger in the control condition (0.77% M_{MAX}) when compared to the

congruent condition (0.47 %M_{MAX}; $p = 0.03$) (Figure 1).
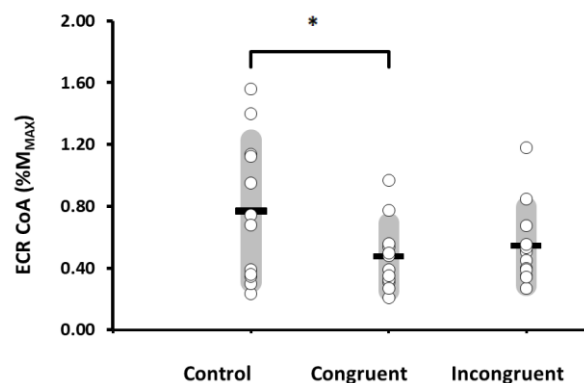

Figure 3. Antagonist coactivation across the 3 reactive tasks, control, congruent, and
incongruent. * = Significant relationships to the 0.05 level.

The relationships between central/peripheral variables and coactivation were identified

(Figure 1). The central relationships were, FCR_{CSP} was significantly correlated to RT_C-

$ECR_{CoA-LOC}$ (r =0.949; p = 0.004) and $RT_{Cn-CoA-LOC,}$ (r = 0.891; r = 0.01). Also, it was correlated to $RT_{Cn}-ECR_{COA}$ (r = 0.825; p = 0.043). Overlap correlated negatively to RT_{C}-ECR_{CoA} (r = -0.872; p = 0.024), $RT_{Cn}-ECR_{COA}$ (r = -0.850; p = 0.032). $CoGy_{FCR}$ and $CoGy_{ECR}$ were positively correlated to RT_{C} -$ECR_{CoA-LOC}$ (r = 0.921; p = 0.009 & r = 0.951; p = 0.04). $FCR_{MEP-LAT}$ correlated negatively with $RT_{I}-FCR_{LAT}$ (r = -0.876; p = 0.022). The peripheral relationships identified were FCR_{M-LAT} was positively correlated to $RT_{C}-ECR_{CoA}$ (r = 0.599, p = 0.04). ECR_{M-LAT} correlated positively with RT_{C} -$ECR_{CoA-LOC}$ (r = 0.939, p < 0.001). ECR_{MQ} had a negative correlation with $RT_{C}-ECR_{CoA}$ (r = -0.655, p = 0.021).

4.3.2.2 Maximal contractions

The relationships between central functional variables and antagonist coactivation were WF-$ECR_{COA-LOC}$ correlated positively with $FCR_{MEP-MAX}$ (r = 0.843; 0.035), $ECR_{MAP-AREA}$ (r = 0.827; p = 0.042). WE-FCR_{CoA} correlated FCR_{CSP} (r = 0.848; p = 0.033), FCR_{CoGy} (r = 0.841; p = 0.036). The WE-$FCR_{CoA-LOC}$ negatively correlated to FCR-$ECR_{OVERLAP}$ (r = -0.863; p = 0.027). The relationships involving peripheral variables were WF-$ECR_{COA-LOC}$ negatively correlated with FCR_{M-MAX} (r = -0.6; p = 0.039); whereas it correlated positively with FCR_{M-LAT} (r = 0.652; p = 0.022). WE-FCR_{CoA} correlated with FCR_{M-LAT} (r = 0.653; p = 0.021(Figure 2).
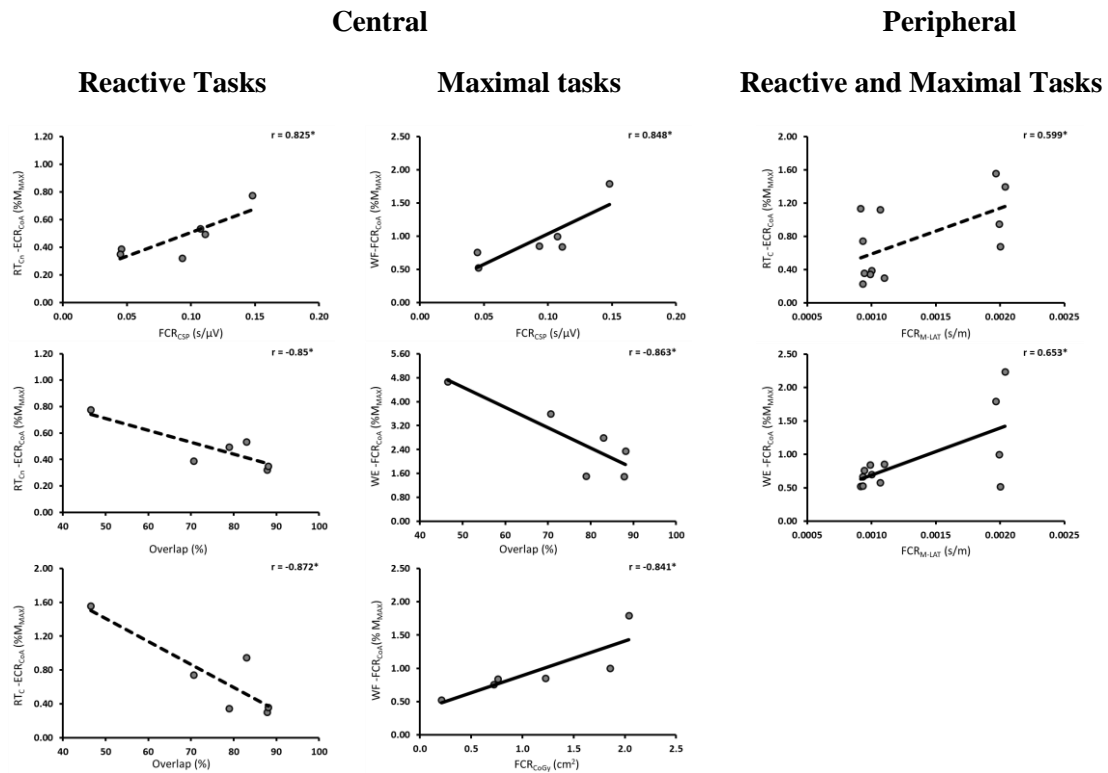
Figure 4. Significant relationships between predictor variables and coactivation during a reactive and maximal efforts.

4.3.3 Determinants of coactivation during reactive and maximal tasks

Each stepwise multiple regression only examined the physiological variables that were significantly related to coactivation. The stepwise multiple regression model for RT_C-ECR_{CoA} was significant ($p \leq 0.05$). The primary central determinant for coactivation was FCR-$ECR_{OVERLAP}$, independently explaining 76% ($p = 0.024$) of the variance in ECR coactivation. The stepwise multiple regression model for RT_C-$ECR_{CoA-LOC}$ was significant ($p \leq 0.05$). The primary central determinant for RT_C-$ECR_{CoA-LOC}$ was ECR_{CoGy}, independently explaining 90.4% ($p = 0.004$) of the variance in location where

ECR coactivation was the highest. However, FCR_{CSA} (p = 0.03) further explained 9.2%,

of the variance in RT_C-$ECR_{CoA-LOC}$. Altogether, the central and peripheral variables

accounted for a total of 99.6% of the variance in RT_C-$ECR_{CoA-LOC}$. The stepwise multiple

regression model for RT_{Cn}-ECR_{CoA} was significant (p ≤ 0.05). The only central

determinant for coactivation was FCR-$ECR_{OVERLAP}$, independently explaining 72.2% (p =

0.032) of the variance in ECR coactivation. The stepwise multiple regression model for

RT_{Cn}-$ECR_{CoA-LOC}$ was significant (p ≤ 0.05). The only central determinant for

coactivation was FCR_{CSP}, independently explaining 79.3% (p = 0.017) of the variance in

ECR coactivation. The stepwise multiple regression model for RT_I-ECR_{CoA} was

significant (p ≤ 0.05). The only peripheral determinant for coactivation was ECR_{M-LAT},

independently explaining 78.6% (p = 0.018) of the variance in ECR coactivation. The

stepwise multiple regression model for WF-$ECR_{CoA-LOC}$ was significant (p ≤ 0.05). The

primary central determinant for coactivation was FCR_{MEP}, independently explaining

71.1% (p = 0.035) of the variance in ECR coactivation. However, $ECR_{MEP-LAT}$ (p =

0.031) and $FCR_{MAP-AREA}$ further explained 24% and 4.8% of the variance in WF-ECR_{CoA-}

$_{LOC,}$ respectively. In addition, $FCR_{CSP,}$ and ECR_{M-MAX}, accounted for an additional 0.1%

of the variance in WF-$ECR_{CoA-LOC.}$ Altogether, the variables accounted for a total of

100% of the variance in WF-$ECR_{CoA-LOC}$. The stepwise multiple regression model for

WE-FCR_{CoA} was significant (p ≤ 0.05). The primary central determinant for coactivation

was FCR_{CSP}, independently explaining 71.9% (p = 0.033) of the variance in FCR

coactivation. However, $ECR_{MAP-VOL}$ (p = 0.033) further explained 23.2%, of the variance

in WE-FCR_{CoA}. Altogether, the variables accounted for a total of 97.5% of the variance in

WE-FCR$_{CoA}$. The primary peripheral determinant for WE-FCR$_{CoA-LOC}$ was ECR$_{MQ}$,

independently explaining 95.4% (p = 0.001) of the variance in FCR coactivation.

CHAPTER V

DISCUSSION

5.1 General Discussion

The general purpose of this dissertation was to analyze structural, functional, and

behavioral changes of sensorimotor integration.

Study 1 (2.1) was designed to analyze the effects of altered stretch reflex sensitivity, via

brief and prolonged vibration, on motor unit behavior during maximal contractions. We

discovered that altering muscle spindle function resulted in altered MU behavior, where

there was a slight increment in recruitment thresholds, accompanied by a decrease in

firing rates, and ultimately reducing motor output seen by a 9% reduction in maximal

strength. These results show the importance of afferent feedback to the alpha-motoneuron

in the production of maximal force, as attenuation of spindle function reduces excitation

to the alpha motoneuron pool and reduce motor unit output.

Study 2's (2.2) goal was to analyze structural (muscle mass and quality) and functional

(spindle function) changes associated with aging, their relationships, and how they affect performance (balance, strength, and rate of torque development). The results showed that older adults had smaller $CSA_{RF,}$ less STR, and poorer balance, during the altered proprioceptive feedback conditions, when compared to the younger and middle-age group. When compared only to the young group, older adults also exhibited lower MQ_{RF}, greater R_{MAG}, slower RTD, and poorer balance performance in every condition. Variance in STR was explained by CSA_{RF} and R_{MAG}; due to the role of spindle function on motor unit excitation[8,33,34], we believe that the altered spindle function seen with aging could have led to atrophy of higher threshold motor units, thus explaining the smaller CSA_{RF}, the significant relationship between CSA_{RF} and R_{MAG}, and their relationship to strength. Similarly, RTD variance was explained by R_{MAG}, and CSA_{RF}, but mostly by MQ_{RF} which has been strongly correlated with non-contractile tissue 46[47], so the higher the score the lower the muscle quality and possibly less contractile tissue. This explains why CSA_{RF} and MQ_{RF} are crucial determinants of RTD [17,18,50]. In addition, regarding R_{MAG}, studies have shown that spindle function suppression leads to slower RTD results [35]. Regarding balance, EOSS and ECSS, were the two conditions where the older group was worse than the young and middle-age group, which is in accordance with previous research that states that altering somatosensory and/or visual input resulted in greater balance errors associated with aging [6,10,11,54]. R_{MAG} was the functional variable explaining most of the variance in EOSS condition; greater normalized R_{MAG}, seen in older adults, resulted in greater sway. Regarding ECSS; the primary structural variable related to this condition was CSA_{RF}. Research has suggested that when balance is challenged, a hip strategy is

used, where trunk and thigh muscles are activated first, explaining why it was the main variable related to this condition.

Study 3 (Chapter III) was designed for two purposes: first, to identify the central and peripheral determinants behind the age-related changes in antagonist muscle coactivation; and second, to determine the effects of the identified changes on performance. The study is still in progress and further subjects are needed to make any conclusions, so far it seems that the variables related to greater coactivation depend on the task. This study involved maximal efforts and three different reactive tasks. It seems that during maximal efforts, the central determinants of coactivation are cortical agonist-antagonist representation areas overlap and the location of the muscles center of gravity. This is in accordance with previous studies that have related spatial organization of muscle representation areas with muscle activation latencies[40]. During the different reactive tasks, agonist-antagonist overlap and silent period seem to be related to higher coactivation levels. Some researchers believe that the silent period is caused by spinal mechanisms[75,76,91], while the later part is caused by cortical inhibition[92,93] generated by $GABA_B$ receptors. If this is true, then it seems that greater the FCR inhibition is related to greater antagonist coactivation. The only significant relationship regarding reaction time was $FCR_{MEP-LAT}$, which strongly correlated with reaction time in the incongruent reactive test, the most difficult task. $FCR_{MEP-LAT}$ indirectly reflects cortical excitation, so it seems that longer latencies are associated with less coactivation. Still the sample size was too small to assure these conclusions. Moreover, we also wanted to study this phenomenon in an older group. Studies have shown that older adults use a heightened coactivation;

however, this functional compensation might be detrimental to performance[7,28,29].

Therefore, once this study is successfully completed we will further our knowledge

regarding motor control and aging.

5.1 General Conclusion

The general purpose of this dissertation was to analyze structural, functional, and

behavioral changes of sensorimotor integration. In study 1, we discovered that altering

muscle spindle function resulted in altered MU behavior and output. Through study 2, we

saw a structural (muscle size and quality) and functional (reflex magnitude) detriment

associated with aging. These changes affected performance where older adults showed

slower and weaker movements and poorer balance, when compared to a young and

middle-age group. Study 3 was designed to identify the determinants behind the age-

related changes in antagonist muscle coactivation. The study is still in progress; but so far

it seems that the variables related to greater coactivation are: cortical agonist-antagonist

representation areas overlap, the location of the muscles center of gravity and cortical

inhibition. In conclusion, age alters many dimensions in the control of voluntary

movement; therefore, to understand the aging process, it is important to analyze plasticity

of sensorimotor integration as a whole.

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APPENDICES

A. DFINITION OF TERMS

Agonist: principal muscle during a contraction

Alpha-motoneuron: Spinal neuron that innervates muscle fibers

Antagonist: muscle opposing the action of the agonist

Coactivation: antagonist activation during isolated contractions

Golgi tendon organs: sensory receptors located between the muscle and the tendon and is sensible to muscle tension

Efferent fiber: an axon transmitting signals from a more central structure to a more peripheral structure.

Electromyography (EMG): a method for recording action potentials created by the muscles fiber.

Evoked contraction: contraction elicited using stimulation (magnetic or electrical)

Firing rates: a motor unit's discharge rates.

Hip strategy: a pattern of hip and trunk muscles activation in response to an external perturbation.

Ia afferents: sensory fiber associated with muscle spindles.

Latency: the delay between a stimulus and a reaction.

M-wave: direct muscle response to an electrical stimulation on the peripheral nerve.

Maximal voluntary strength: a participant's maximal effort with the limb at a fixed position

Motor cortex: region of the cerebral cortex involved in planning, control and execution of voluntary movements.

Motor evoked potential: muscle response after stimulation of the motor cortex.

Motor unit: a motoneuron and all the muscle fibers it innervates.

Motor unit action potentials: an electrical signal produced by the summation of all muscle fiber action potentials belonging to that motor unit.

Motor unit action potential size: largest peak to peak motor unit amplitude.

Motor unit behavior: a motor unit's recruitment thresholds and firing rates.

Muscle spindles: stretch receptors within the muscle.

Proprioception: awareness of body's limbs position and movement.

Ramp contractions: 15 seconds isometric contractions with a descending and ascending rate of + 20 and -20% maximal voluntary contraction (MVC), respectively, with a 5 second plateau at 100% MVC in between.

Recruitment threshold: absolute torque level (Nm) at which the MU began discharging.

Silent period: a period of EMG silence between a motor evoked potential and the EMG resumption.

Stretch reflex: a muscle contraction in response to stretching within the muscle.

Transcranial magnetic stimulation (TMS): non-invasive stimulation of the motor cortex.

APPENDICES

B. LITERATURE REVIEW

The literature review is organized into two subsections. The article summaries are

provided in chronological order within each section and a summary of each subsection is

provided at the end.

2.1 Isolated activation versus coactivation and underlying mechanisms

<u>Wislow, 1776[94]</u>

One of the first insights into the coordination of opposing muscles is provided by this

short passage:

> "To move any part or to maintain it in a fixed position, involves a cooperation of
> all the muscles capable of moving it. Some muscles guide this motion directly to
> its position or fixed attitude, others modify it by counterbalancing it in the
> opposite direction; still others direct it laterally. The first of these principal
> muscles I have called motors, the others moderators, and the last directors of the
> fixed movement. The moderators are, in general, those called "antagonists," and
> often the heaviness or the resistance of some foreign body and even the weight of
> the part to which they are attached compensates for the deficiency of their
> operation."

This is one of the first muscle coordination conceptualizations, where the roles of the
muscles around a joint are described.

<u>Bell, 1823[95]</u>

The conception originally from Descartes[96], was supported by Bell, who was the first to establish not only a reciprocal control of muscles, but also, establishing a neural connection between opposing muscles.

> "Through the nerves is established the connection between the muscles, not only that connection by which muscles combine to one effort but also that relation between the classes of muscles by which the one relaxes and the other contracts. I appended a weight to a tendon of an extensor muscle which gently stretched it and drew out the muscle; and I found that the contraction of the opponent flexor was attended with a descent of the weight, which indicated the relaxation of the extensor."

<u>Sherrington, 1907 – 1952[56,97]</u>

Sherrington was able to study reflexes in motor cortex of the cat and monkeys[97] and in purely spinal preparations of the cat[56]. By applying electrical stimuli to the peripheral nerve, he discovered that the excitatory afferent going to the antagonist muscle was ineffective, when the "inhibitory" afferent of the agonist muscle was stimulated[56]. Later on he discovered that when the extensor's motor cortex was stimulated, an immediate relaxation of the biceps with an active contraction of the triceps was seen[97]. This led him to the concept of reciprocal inhibition, where an interaction between opposing muscles exists, excitation of the agonist muscle is followed by relaxation of the antagonist[56,97].

<u>Tilney and Pike, 1925[57]</u>

The goal of this study was to examine the interaction between antagonistic muscles and determine the role of the cerebellum in this interaction. In this experiment, animals' limbs were immobilized, the motor cortex was exposed and myographic recordings were taken before and after a cerebellar lesion. The authors described an unequal activation of opposing muscles, where one muscle's activity predominated. After the cerebellar lesion, a disassociation between opposing muscles was seen. Therefore, it was concluded that the cerebellum was involved, at least partially, in the coordination of opposing muscles.

<u>Lloyd, 1941 - 1946[58,98]</u>

Lloyd developed several experiments to test the monosynaptic reflex in cats. He demonstrated that stimulating large muscle afferents resulted not only on monosynaptic excitation, but also on reciprocal inhibition of antagonist's motoneurons. The author proposed a two-neurons excitatory arch, responsible for direct inhibition from Ia agonist's afferents to antagonist's motoneurons[58].

<u>Hultborn et al., 1972[59]</u>

This is a thesis that summarizes Hultborn's finding from 1971 – 1972. The aim was to analyze the excitatory and inhibitory inputs onto Ia interneurons. In prepared spinal cords in cats Ia inhibitory postsynaptic potentials (IPSPs) were evoked by stimulating antagonist's Ia afferents while conditioning stimuli were given to the skin, joint or

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supraspinal centers. Recurrent depression was tested through antidromic stimulation of the ventral root to depress Ia inhibitory pathway. The effect of Ia afferents on recurrent inhibition of Ia inhibitory interneurons was measured through the stimulation of cut dorsal roots conditioned by stimulation of motor fibers. The author compiled a list of various neuronal systems converging on to Ia inhibitory interneurons:

- Ib afferents have an excitatory effect on Ia interneurons, shown by a clear separation into a fast and a slow response when group I volley (Ia and Ib) was stimulated.

- Flexor reflex afferents inhibit flexors and extensor' Ia inhibitory interneurons, seen by a depression in Ia IPSPs.

- Cutaneous low threshold afferents facilitate transmission of Ia inhibition in both flexors and extensors, seen by an increase in IPSPs following cutaneous nerve stimulation.

- Ipsilateral interneurons activated from flexors, receive excitation from the contralateral flexor reflex afferent. This phenomenon was shown when a direct measurement of interneurons IPSPs was recorded after contralateral cutaneous and high threshold afferents were stimulated.

De Luca and Mambrito, 1987[68]

The purpose of this study was to quantify the relationship between firing rates of motor units among an agonist-antagonist muscle's pair. Participants performed three different types of contractions, one involving isolated flexion or extension, one involving stiffness and one involving random movements at 15% of their maximal effort. Intramuscular EMG was collected from the flexor pollicis longus and extensor pollicis longus. Firing rates were greatly cross – correlated with each other within the same muscle and among motor units of the antagonist during the voluntary coactivation. The authors concluded that the motoneurons pools of an agonist and antagonist muscle pair possess a common drive of central origin.

Gottlieb et al., 1989[67]

In this study, the researchers aimed to identify patterns of muscle activation for single-joint movements. The subjects' goal was to position a cursor on a target, as accurately and as quickly as possible. This movement required an elbow flexion or extension from different starting angles to a 9° target, with and without an added load. Even though, a clear pattern was not identified, there were important behaviors discovered. Agonist EMG rise rate was similar for different loads and distances. On the other hand, antagonist EMG onset and activity varied depending on peak velocity and acceleration.

<u>De Serres and Milner, 1991</u>[99]

The goal of this study was to determine the role of antagonist cocontraction and reflex responses on wrist stiffness. Participants were asked to maintain a wrist angle under different stability conditions (constant, elastic or unstable). Surface EMG was recorded from three wrist flexors and one wrist extensor. Increased agonist and antagonist activity and greater stretch reflex were seen under the unstable condition. The researchers concluded that cocontraction was the main strategy to maintain wrist stiffness. In addition, they concluded that reflex activity depended on agonist motoneuron excitability, seen by the increment of reflex activity parallel to the increment in agonist activity.

<u>Macefield et al., 1991</u>[51]

The purpose of this study was to examine discharge behavior of single muscle spindle afferents during sustained isometric contractions. Ia spindle and muscle activity was recorded from the TA during a dorsiflexion for one to two minutes. The force target was double that at which the afferent was recruited. A progressive decline in spindle discharges was seen, related to a progressive increase in EMG to maintain the required force level. The authors concluded that muscle spindles provide facilitate their homonymous alpha motoneurons.

<u>Nielsen and Kagamihara, 1992</u> [3]

The aim of this study was to investigate the supraspinal control of the disynaptic Ia reciprocal pathway during simultaneous activation of two antagonistic muscles. Disynaptic reciprocal inhibition was measured as the percentage difference between a test H-reflex and a conditioned H- reflex. The H-reflex stimulus was applied to the common peroneal nerve at rest, during a dorsal and plantar flexion, and during an antagonist cocontraction. The amount of reciprocal inhibition was significantly less pronounced during the plantar flexion compared to rest, and significantly smaller during the cocontraction when compared to rest. A similar result was obtained during an ischemic period, blocking peripheral feedback. The authors concluded that there is a central control of Ia inhibitory interneurons and their corresponding alpha motoneurons.

<u>Macefield et al., 1993</u>[8]

The purpose of this study was to quantify the net influence of muscle afferent feedback on the firing rates of motoneurons. Single motor unit maximal firing rates were obtained from the tibialis anterior muscle after a complete nerve block. During sustained maximal voluntary contractions, deafferented motoneurons firing rates significantly decreased (from 28.2 ± 0.6 Hz to 18.6 ± 1.9 Hz). The main finding from this study is that Ia afferents provide a net facilitation to the tibialis anterior motoneuron pool, reflexively increasing motor output.

Crone and Nielsen, 1994[2]

This is publication is a review paper that summarizes the modulation of Ia disynaptic reciprocal inhibition tested in humans through short-latency depression and H-reflex following a conditioning stimulation of antagonist nerve. The authors analyzed their previous publications, along with other studies, and concluded that Ia inhibitory interneurons and their corresponding motoneurons (alpha and gamma) are controlled in parallel by supraspinal mechanisms during single-muscle contractions. This parallel mechanism would ensure that the excitability of antagonist would always be adjusted to the activity level of the agonist. In previous studies, the researchers demonstrated a linear reduction in the test reflex related to an increase in agonist strength. In contrast, during tasks that require agonist-antagonist cocontraction reciprocal inhibition is relatively constant and independent of the strength level. The authors concluded that there is a supraspinal agonist - antagonist facilitation, while inhibitory pathways between these muscles become less effective.

Amiridis et al., 1996[100]

The aim of this study was to compare torque production capacity, antagonist contribution, and agonist activation during eccentric and concentric maximal actions, in highly skilled and sedentary individuals. Subjects performed three maximal eccentric and concentric knee extensions at 14 random angular velocities (range 15 – 300°/s). Surface EMG was

recorded from the VL, vastus medialis (VM) and semitendinous (ST) muscles. Their

results showed that highly skilled participants produce significantly higher peak torques

with lower antagonist EMG_{RMS} amplitudes (12%) when compared to the sedentary group

(38%). On the other hand, antagonist coactivation was lower during eccentric

contractions. The authors concluded that the lower coactivation levels seen in trained

participants might be related to an increase in neuromuscular efficiency.

Weir et al., 1998[65]

The aim of this study was to examine the effect of fatigue on the coactivation response

during isokinetic contraction and different speeds. After a fatiguing protocol of 50

maximal knee extensions, subjects performed three maximal knee extensions and

flexions at 100 and 250°/s while EMG activity was recorded from the biceps femoris

(BF) and VL. The main finding was that coactivation of the BF increased as VL fatigue

increased relatively to the force produced. In addition, stable ratio between VL and BF

activity was seen during the fatiguing protocol. The authors suggested that the increase of

coactivation may be in part responsible for the diminished agonist force production and

that the stable ratio between agonist and antagonists suggests a central control of

opposing muscles.

Christensen, et al., 2001[101]

The goal of this study was to investigate the stretch reflex modulation in the TA during walking and the mechanism mediating this modulation. Surface EMG was recorded from the TA and soleus while participants walked on a treadmill. During the different stages of the walk, swing versus stand, muscular stretches and MEPs were superimposed on the TA. During the early stance phase, the largest stretch reflexes were produced with the shortest latency. In contrast, small responses at two different latencies were seen during the swing phase. After ischemia, these responses were abolished. In addition, MEPs were facilitated during the peak of the stretch response during the stance. The conclusion was that muscle afferents are involved in the generation of the stretch and the modulation of the stretch reflex has a central cortical component.

Suzuki et al., 2001[99,102]

The purpose of this study was to assess the muscle coactivation in relationship to movement kinematics (movement amplitude) and phasic EMG activity. Surface EMG was recorded from eight different opposing muscles at the elbow and shoulder joints while participants performed single-joint movements. Tonic EMG was defined as EMG in a 100ms window after the movement was completed. In contrast, phasic EMG was defined as the first initial EMG burst detected during the movement. In addition, to assess agonist central activation in the absence of any voluntary or afferent feedback, agonist

EMG was analyzed in the first 30 ms window. A clear increase in tonic and phasic EMG from agonists and antagonists' muscles was seen with higher movement velocities and amplitudes. Moreover, a strong relationship ($r > 0.63$) was seen between phasic EMG, measured during the movement, and tonic EMG, after the movement. The authors believed that the cocontraction is centrally specified. The proposed central command is that tonic EMG activity is scaled according to phasic EMG activity.

<u>Baret et al., 2003[103]</u>

The goal of this study was to study reciprocal inhibition in the tibialis anterior (TA) by activation of soleus group I afferents. A test H-reflex was conditioned by two stimuli applied to the posterior tibial nerve, one with the purpose of activating Renshaw cells, and the second one with the purpose of causing reciprocal inhibition. The time interval between the two conditioning stimuli was systematically varied between –5 and 50 ms, while the test stimuli interval was constant. The amount of reciprocal inhibition was 33%; however, Renshaw cells activation strongly depressed reciprocal inhibition at time intervals of +20 and +30 ms the closer the two conditioning stimuli were, greater reciprocal inhibition was seen. Therefore, reciprocal inhibition of antagonist is depressed or suppressed by agonist Renshaw cells activation.

Gribble et al., 2003

The purpose of this study was to examine the relationship between antagonist cocontraction and accuracy during arm movements. They hypothesized that greater cocontraction increased joint stiffness which would be beneficial for accuracy. Surface EMG was recorded from seven different muscles at the elbow and shoulder joints. Cocontraction, measured through "wasted contraction" consisted of removing the EMG portion in one muscle that was not matched by the opposite muscle; it was measured during the movement and in 200 ms window at the end of the movement. Accuracy was measured as constant error with respect to target position and variable error as endpoint variability. The experiment demonstrated how cocontraction varied as a function of target size, as target size decreased, cocontraction increased. In addition, higher level of cocontraction were associated with decreased movement error. The authors suggested a central modulation of cocontraction in order to increase joint stability, which increases accuracy.

Angel et al., 2005[104]

The aim of this investigation was to locate and examine interneurons mediating group I disynaptic excitation of extensor motoneurons. Averages of extensor nerve group I afferent-evoked disynaptic EPSPs were made during the extension and flexion phases of locomotion in decerebrate and paralyzed cats and interneurons activity was recorded.

Candidate excitatory interneurons were located in mid to caudal parts of the L7 segments. These interneurons might mediate group I-evoked disynaptic excitation of extensor motoneurons.

Bassa et al., 2005[64]

The objective of this study was to examine the effect of angular velocity and muscle contraction type on antagonist coactivation. Surface EMG was recorded from the VL and BF while participants performed knee flexion and extensions at concentric and eccentric angular velocities of 45, 90 and 180 deg·s⁻¹. Antagonistic activation was expressed as a percentage of the respective muscle when it was acting as an agonist during the same contraction type and velocity. The results showed a lower antagonistic EMG activity during eccentric contractions and during slower contractions. In addition, during concentric contractions, antagonistic EMG activity increased with angular velocity. Therefore, the level of coactivation is dependent on the type and velocity of the contraction.

Biro et al., 2007[105]

The goal of this study was to measure muscle force and EMG responses to tendon taps and single motor units during voluntary and reflex contractions. Reflex contractions were elicited through 30 seconds of vibration pre and post fatigue. Motor unit recruitment thresholds showed a significant difference during the reflex contraction. In addition, the

time interval between the electrophysiological muscle response and force during a tendon tap was significantly increased. The authors concluded that during fatigue, the gamma loop might provide a peripheral compensation to its own agonist in order to preserve force.

Barthélemy et al., 2011[1]

The purpose of this review was to prove the role of cortical areas in the control of human gait. Since it is a review, it will not be thoroughly summarized. Still, the cortical involement presented here is of great relevance for our study. The evidence suggesting a supraspinal control of movement is:

- Primary sensorimotor areas, supplementary motor area, basal gangli and cerebellum activated during walk.
- Significant MEPs modulation has been seen when the muscle is active suggesting a corticospinal facilitation[101].
- Motor unit syncrhonization during isolated movements is absent or greatly reduced in patients with spinal cord injury.
- The longer latency responses seen after stretch reflexes superimposition might suggest a cortical tract involment[101]; the cortical mechanisms suggested are brain stem, cerebellum or motor.
- Changes in corticospinal excitability precede changes in EMG.

<u>Dimitriou, 2014[60]</u>

The purpose of this study was to examine the balance between agonist and antagonist muscles' activity through muscle spindle responses. Single muscle spindle afferents from the extensor digitorum muscle were recorded, along with surface EMG from extensor and flexor digitorum, torque, and kinematics while subjects passively or actively moved the finger at a 1 Hz pace. Participants performed these movements under. The kinematics of the finger movement was controlled and equal for every condition; while, different external torques were applied to differentially load the extensor or flexor digitorum muscle. Even though the movement was identical between conditions, muscle spindle's response was different. When the loaded antagonist was stretched, firing rates from its own afferent increased. In contrast, when the antagonist muscle was stretched but the agonist, muscle was being loaded; afferent firings from the antagonist were lower. The results showed a positive relationship between extensor muscle activity and extensor spindle sensitivity (β regression coefficient = 1.53) and a negative relationship between flexor muscle activity and extensor spindle sensitivity (β = -0.48). In addition, instantaneous velocity showed a significant effect on spindle afferent responses. The authors concluded that the monosynaptic stretch reflex might reflect balance activity across antagonistic pairs in single joint movements.

Aguiar and Baker, 2018[106]

The purpose of this study was to examine the spinal circuits' convergence from FCR and ECR afferents. An H – reflex on the median nerve, innervating the FCR, was conditioned by different types of stimuli to quantify Ia and Ib afferent activity. The conditioning stimuli were an H – reflex on antagonist muscle; a tap on ECR's tendon; a tap to FCR's tendon; and cutaneous stimulation to two digits. In addition, the condition of the muscle was manipulated through maxima flexions or passive movements to modulate afferent feedback from FCR. Overall, a significant depression was seen at 1.5, 3 and 5 ms, followed by a facilitation at 30 ms and a significant suppression at 70 ms. The facilitatory effect occurring at 30 ms was further investigated. The authors discovered that the twitch time of the ECR was consistent with the facilitation. They suggest that ECR Ib afferents and FCR afferents participated concurrently in producing the H-reflex facilitation in FCR.

Cote et al., 2018[4]

This is a systematic review over the spinal interneurons functions. The interesting thing about this article for our research is the detailed description of each interneuron and their excitatory or inhibitory effect on either their homonymous muscle or the opposite muscle. These interneurons are:

- Ia interneurons: these are crucial interneurons in reciprocal inhibition phenomenon occurring in the first milliseconds (0 – 3ms). These have multiple synaptic contacts with each antagonist motoneuron, suggesting a powerful control on antagonist; also, they synapse with contralateral side interneurons, suggesting a participation in the right-left limb coordination. They are subject to recurrent inhibition from Renshaw cells, which seems to control the depth of reciprocal inhibition and presynaptic inhibition from Ia afferents. The role of Ia interneurons has been indirectly measured through conditioning H-reflexes and/or based on soleus H – reflex depression after antagonist tonic muscle activity.

- Renshaw cells: the cells are responsible for the recurrent inhibition of its homonymous motoneuron pool with a delay of 0.5 to 50 ms. The function of recurrent inhibition is to inhibit motoneurons to slow down contracting fibers, synchronize motoneuron discharge patterns, and prevent persistent inward currents. In humans, recurrent inhibition has been estimated through conditioning an agonist H-reflex with a supramaximal stimulus to the same nerve at an interval of 10 ms.

- Ib interneurons: The main effect is the inhibitory postsynaptic potential they exert onto their homonymous and synergistic motoneurons. Known as autogenic inhibition. These interneurons receive multimodal inputs from group I and II afferents, corticospinal, rubrospinal, and reticulospinal descending tracts. They

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project to alpha and gamma motoneurons, and to other Ib interneurons. In humans Ib actions has been assessed by testing the effects of electrically induced group I volleys, on agonist muscle. The latency between the stimulation and the inhibition is five – six milliseconds and the duration of the inhibition is less than ten milliseconds.

- II interneurons: contacted by primary and secondary muscle spindle afferents and other interneurons. These interneurons exert excitatory and inhibitory actions on motoneurons; mainly they are responsible for coordination of contractions of the stretched muscle. It is possible that these interneurons are involved in various types of reflex circuits such as the transcortical-mediated stretch reflex. The study of these interneurons in humans is less clear due to lack of selective stimulation.

2.1.1 Summary of "Agonist – Antagonist Interactions and Underlying Mechanisms"

During single-joint movements there seems to be two possible activation patterns between opposing muscles, reciprocal inhibition and agonist - antagonist coactivation. Factors such as velocity, load, and fatigue, among others seem to dictate the control mechanism that will be facilitated[66].

Reciprocal inhibition is apparent during:

- Agonist muscle contraction, as muscle contraction increases, reciprocal inhibition increases[3,39,56,58,80]

- Lower velocities and resistances [64,66]

- Training status, highly-trained individuals showed lower coactivation levels when compared to sedentary participants[100]

- Type of contraction, it seems that during eccentric contractions, lower levels of coactivation are apparent[64,100]

Coactivation of antagonist muscle is apparent during:

- Tasks with increasing resistance and/or higher velocities [64,67]

- Unstable conditions, where antagonist cocontraction aids in stabilizing the joint[99]

- Novel tasks or accuracy-demanding tasks, when the goal of a movement is accuracy, coactivation is the preferred strategy[107]. Furthermore, lower-skill levels use higher levels of coactivation [66,100,107]

- Fatigue, there is a linear relationship between agonist fatigue and antagonist coactivation relatively to force produced[65]

The activation patterns between opposing muscles are facilitated or inhibited by cortical and spinal, and peripheral mechanisms. Supraspinal components, such as, brain, midbrain, hindbrain, cerebellum and basal ganglia are involved in decision making and planning for movement initiation[1]. The motor cortex is responsible for the control of the muscles involved[68,101] and has been shown to intervene in the modulation of spinal

reflexes[101]. The peripheral mechanisms include muscle spindles (Ia and II afferents),

GTOs (Ib afferents), and cutaneous receptors. Muscles spindles Ia and II afferents acting

on their homonymous motor unit pool provide a reflexive assistance to the muscle[8,51]. Ia

afferents synapsing with Ia interneurons cause a disynaptic reciprocal inhibition of the

antagonist[2-4]. In contrast, GTOs Ib afferents disynaptically excite antagonist alpha

motoneurons[108]. The descending commands from the supraspinal mechanisms, along

with feedback from the periphery are then translated by complex spinal networks to exert

the desired movement according the external and internal conditions[2,4,9]. Interneurons

related to reciprocal inhibition and/or agonist – antagonist coactivation include Ia

interneurons, II interneurons, Renshaw cells, and Ib interneurons. Ia interneurons are the

most important interneurons in the disynaptic reciprocal inhibition pathway[2-4]. Renshaw

cells regulate the activity of their own motoneuron through recurrent inhibition[4]; and

control the depth of the reciprocal inhibition [2,103,109]. PSI of Ia terminals is increased

during agonist – antagonist cocontraction [3]. Ib interneurons cause a short-latency

depression of the homonymous and synergistic motoneurons[4] and a disynaptic excitation

of the antagonist muscle[59,108]. Therefore, depending on the action, these complex

mechanisms combine to enable a certain activation pattern, either reciprocal inhibition or

agonist – antagonist coactivation.

2.2 Neurophysiological changes associated with aging and performance

Earles et al., 2001[31]

The aim of this study was to examine the role of presynaptic inhibition (PSI) on reflexes during voluntary contractions in young and elderly subjects. H – Reflexes and M-responses were elicited from the soleus and TA muscles during low tonic contractions (10 – 20% of MVC). PSI was quantified as the difference between a control H-reflex and a conditioned H – reflex by a stimulation of the common peroneal nerve. Young subjects showed greater inhibition of the conditioned soleus H – reflex (5.3% M – max) when compared to the older subjects (13. 2%). In addition, the young group demonstrated a significantly greater conditioned reflex during rest when compared to voluntary effort. In contrast, the older group showed similar amplitude of the conditioned H-reflex and at 10% of MVC; it was until 20% of MVC that the amplitude was significantly different. It was also observed that across different levels of voluntary contractions, young subjects demonstrated higher PSI gain. The authors suggested that the older population use a different control strategy, where a higher direct motor activation is used and less PSI.

Mattay et al., 2002[32]

The purpose of this study was to explore the effect of aging on brain networks associated with reactive tasks. This study involved two groups, young ($\mu = 30$ years old) and old group ($\mu = 50$). Subjects were required to press a specific button, from four

possible options, in a random order while blood oxygen level – dependent (BOLD) fMRI was conducted. The spatial activation areas for the young were contralateral primary sensorimotor cortex, parietal cortex and thalamus; bilateral premotor and supplementary areas; and ipsilateral cerebellum. The older group showed, not only, greater activation in the aforementioned areas, but also, the ipsilateral sensorimotor cortex and putamen, and contralateral cerebellum areas were activated. In addition, older adults exhibited a significant negative correlation between activation and reaction time, where shorter reaction times were seen with greater activation. The authors concluded that the greater activation in areas involved with motor execution, afferent processing, motor processing, motor planning and timing were the result of a compensation due to less effective brain processes, or due to neurotransmitter imbalances and cytoarchitectural changes.

Scaglioni et at., 2003[27]

This study was designed to study the effects of aging on the M-wave and H-reflex on the soleus muscle. There were 10 young (μ = 22 years old) and 9 older adults (μ = 73). By applying one millisecond square0wave stimuli over the posterior tibial never, the following measurements were collected, Hfree: largest H – reflex without a M-wave response; H latency: time between stim to first deflection normalized to participant's height; M – wave at H max; M – max; and M latency. Older adults' showed a smaller H – reflex (y: 5.37 vs o: 1.74 mV) and M-wave amplitude (y: 8.29 vs o: 3.97 mV), a greater M response during H max (y: 4.89 vs o: 28.57% Mmax), a M peak-to-peak longer

duration (y: 2.57 vs o: 3.63 ms) and a slower H – reflex (y: 0.176 vs o: 0.211 s/m). The

authors concluded that longer duration of the M-wave could be due to a loss of high

threshold motor units and or changes in the excitation-contraction coupling processes. In

addition, the slower H-reflex response with no change in M-wave latency ant the larger

M response during H max was evidence of a sensory degradation preceding the motor

degradation seen with aging.

Chalmers and Knutzen, 2004[110]

The aim of this study was to compare resting recurrent inhibition in younger versus older

adults. A conditioning electrical stimulus was delivered to Ia afferent fibers, which was

conditioned by successive stimulus applied to the same nerve 10 ms after. The level of

recurrent inhibition for both groups was not significantly different.

Kido et al., 2004[39]

The main purpose of this study was to investigate spinal excitatory and inhibitory across

the lifespan. EMG was recorded from the TA and soleus muscles while subjects were

asked to perform a voluntary plantar flexion or dorsiflexion. In addition, reciprocal

inhibition and M-waves were elicited by stimulating the common peroneal or tibial nerve

during standing or walking and during different levels of agonist contraction. Both H_{max}

(r = 0.62) and M_{max} (0.76) become smaller with age, and H-reflex latency is longer (r =

0.78). Still, during walking similar H-reflex modulation patterns are similar. The amount

of reciprocal inhibition decreased with increasing age during standing (r = 0.57) and

walking (r = -0.61) for both muscles. Even though, not significant, task-dependent

modulation of H-reflex was less pronounced in the older subjects. The authors concluded

that the reduction in H-reflex and the longer latencies could be associated with an altered

presynaptic inhibition or a reduced spinal and (or) supraspinal input to α-motoneuron.

The linear reduction of reciprocal inhibition with aging could be associated with a

reduced efficacy of disynaptic reciprocal inhibition pathway.

Mackey and Robinovitch, 2004[30]

The purpose of this research was to assess the relationship performance levels, strength

versus speed, and ability to recover balance. Two groups were used in this experiment,

young and older adults. Participants were supported in an incline standing position, the

inclination was either progressively increased (static) or participants were suddenly

released (dynamic). Participants were asked to recover their balance by contracting the

muscles at the ankle joint. In the dynamic trials, older adults muscle response latency was

longer, accompanied by longer reaction times. The ability to recover balance was

associated with strength (r = -0.657) and reaction times (r = -0.571) in both groups. The

authors concluded that elderly women have both impairments in strength and reaction;

longer reaction times are explained by longer muscle response latencies. In addition,

these performance measurements were strongly correlated with the ability to recover

balance. Therefore, older women are at a higher risk of falling.

<u>Hortobágyi and DeVita, 2006[28]</u>

This is a review article summarizing the mechanisms responsible for the age-associated increase in antagonist coactivation. The author examined changes in antagonist coactivation by dividing underlying mechanisms into supraspinal and spinal mechanisms:

Spinal mechanisms:

- Disynaptic reciprocal inhibition: an inverse relationship between reciprocal inhibition an age was seen during walking and standing [39].

- Presynaptic inhibition: lower levels of presynaptic inhibition are seen in the older populations. This lower inhibition might affect the access to the motoneuron pool[31].

Cortical mechanisms:

- Cortical excitation: increased activity in agonist and antagonist representation areas before movement initiation and a spread of motor command from agonist muscle's cortical representation area[41,43]. Higher bilateral activation in motor cortex, sensorimotor cortex, lateral premotor area, supplementary motor area, and cerebellum in the older individuals[32].

- Cortical inhibition: degradation of central inhibitory processes[12]

- Sensory cortex activation: greater activation in sensory cortex areas is seen with older adults.

- Sensorimotor integration: greater activity in older adult' caudate and putamen. Modification in globus pallidus circuits associated with agonist facilitation and antagonist inhibition through the cortico-putamino-pallidal-thalamos-cortical path.

Olivero et al., 2006[111]

The purpose of this study was to determine the changes in excitability of the cerebral cortex associated with aging. Subjects were divided into two groups, young and old. MEPs were delivered to the optimum scalp position to elicit motor responses on the FDI. Researchers compared young versus older adults' cortical silent period, short latency intracortical inhibition, and short latency afferent inhibition. The main differences were MEP amplitude was significantly smaller in older than young (1.3 ± 0.8 mV vs 2.7 ± 1.1 mV); CSP duration was shorter in the older group (87 ± 29 ms versus 147 ± 39 ms), but when the ratio between CSP and MEP was calculated, both groups were similar. The authors suggest that in order to achieve the necessary excitability, older adults show a reduced activity of some inhibitory circuits.

Shaffer and Harrison, 2007[6]

This review study summarizes the structural and functional declines of the somatosensory system and its relationship with postural instability seen in older adults. The significant morphological changes associated with age were:

- Muscle spindles: there is a reduction in the number of muscle spindles, intrafusal fiber, nuclear chain fibers, and muscle spindle sensitivity.

- Golgi Tendon organs and articular receptors: there is a general decline in the number of mechanoreceptors.

- Cutaneous receptors: studies show a decline in the number of Meissner's corpuscle and Pacinian corpuscle; also, Meissner's corpuscles cross-sectional area is reduced and impaired touch thresholds have been reported.

- Peripheral sensory axons: a reduction in the number, density, and velocity of myelinated peripheral nerve fibers has been reported in animal species. The slower conduction has also been shown also in humans, with sensory fibers affected prior to motor fibers.

The significant functional changes associated with aging are:

- Joint kinesthesia: older adults show a decline in joint position sense during dynamic and static tasks, with and without load. This decline was strongly associated with proprioceptive decline ($r^2 = 0.92$) and increased plantar flexors and dorsiflexors cocontraction.

- Discriminative touch: discriminative touch was compromised with aging. In addition, this impairment has been associated with fallers and increased mediolateral sway (28% more).

Tsang et al., 2008[69]

The objective of this study was to assess muscle responses during downward stepping between older adults with and without a history of falls. Based on their fall history, older adults were divided into fallers and non-fallers. Then older adults were asked to step down with and without a concurrent cognitive task while surface EMG was recorded from the TA and medial gastrocnemius. The main findings were that there were similar pre-landing muscle response latencies during the single task. However, when a concurrent cognitive task was done, fallers' TA muscle response onset was significantly shorter than without the task (79.1 ms vs 141.1ms), and significantly shorter when compared to the non-fallers (79.1 ms vs 98.6 ms). The authors concluded that fallers might use antagonist cocontraction as a compensatory mechanism to increase joint stability when the attention demands of a task increase.

Bernard and Seidler, 2012[43]

The purpose of this study was to motor cortical representation areas of the first dorsal interosseous muscle related to performance. Contralateral and ipsilateral cortical mapping, MEP onset, latency, and amplitude and reaction time were measured in younger and older adults. The older adults exhibited larger contralateral and ipsilateral representation areas. In addition, a significant relationship between contralateral representation and reaction time was seen (Spearmans' rank correlation $p = 0.59$). The

author proposed that this extensive spatial representation area is the indicative of a phenomenon called dedifferentiation, rather than a compensatory mechanism. Dedifferentiation refers to the decrease distinctiveness results in performance deficits.

Boisgontier et al., 2012[112]

The purpose of this study was to examine the proprioceptive performance during single and dual matching tasks in young and older adults. Participants had to match the same joint angle set by the investigator on their non-dominant leg with their dominant leg. This was done during a single task, where they would only pay attention to a white board and during a dual-dual task where they would have to match the joint angle while doing a congruent and incongruent Stroop test. Matching performance was measured by total error and matching times; and cognitive performance was measured as speed index and accuracy. The main findings were that older adults had longer matching times only during dual-tasks. This increased matching time might suggest that during dual-tasks, older adults might need to recruit more cortical areas.

Fujimaya et al., 2012[12]

The goal of this study was to assess corticospinal excitatory and inhibitory processes in younger and older adults during coordination of upper and lower limbs. This research involved two groups, one older ($\mu = 69$ years) and one younger ($\mu = 21$) group. Surface EMG from the ECR was recorded while participants performed four conditions requiring

coordination of hand flexion/extension and foot plantar flexion/dorsiflexion. The conditions were contralateral isodirection, where both limbs moved in the same direction; contralateral non-isodirectional, where the limbs moved in opposite directions, ipsilateral isodirection and ipsilateral non-isodirection. Single transcranial magnetic pulses were delivered at 0°, 9° and 18° during the extension phase and motor evoke potentials (MEPs) were recorded. Younger adults showed longer silent periods during ipsilateral limb coordinating tasks. In contrast, older adults exhibited no modulation of silent period across conditions, except in the ipsilateral non-isodirectional conditions. A reduced silent period was seen when ipsilateral limbs moved in opposite directions. This shorter silent period was more pronounced in those older adults with poorer performance. The authors concluded that older adults exhibit a decreased ability to control corticospinal inhibition, which affected performance during the most complicated task. Furthermore, the differences in corticospinal inhibition distinguished high and lower performing older adults.

Nelson-Wong et al., 2012

The purpose of this study was to determine the relationship between agonist - antagonist cocontraction and fall risk. Surface EMG was collected from TA and gastrocnemius while participants performed different static tests, Romberg Test and Sharpened Romberg with eyes open and closed, and Single Leg Standing with eyes open. In addition, a dynamic balance test, called the Four Square Step Test, was performed to categorized

participants as being at-risk or not-at risk of falling. Cocontraction index (CCi) was calculated by integrating the ratio of the EMG magnitudes of both muscles. A significant association between CCi and the fall risk category was seen in all conditions except Romberg eyes closed. Findings from this study showed that cocontraction might be an ineffective postural control strategy that strongly that affects performance during dynamic balancing tasks.

Coppi et al., 2014[41]

The aim of this study was to investigate interhemispheric interaction in physiological aging motor cortex and its correlation to performance. Abductor pollicis brevis (APB), abductor digiti minimi's (ADM) cortex maps, and ipsilateral silent period (ISP) were measured using TMS. In addition, participants hand performance was measured through mirror movements, nine-hole peg test, finger tapping and grip strength. The main findings in this study were smaller ISP (old = 38.05 ms vs young = 46.48 ms); significantly more mirror movements (9 vs 1); worse nine-hole peg test performance; less finger tapping; and lower grip strength in the older when compared to the young. In addition, the young group showed significant effect of muscle representation areas, with the APB showing a greater area. However, this difference was not seen in the older group. When the researchers correlated the physiological and performance measurements, they discovered a significant correlation between ISP associated with worse performance in the peg test and grip strength. The authors concluded that the

decrease in ISP and increase of MM represent a reduction in transcallosal inhibition. Concluding that aging might mark a dissociation of motor cortices, characterized mainly in the non-dominant hemisphere.

Papegaaij et al., 2014[7]

This review summarizes and relates the structural, functional and behavioral changes associated with age. The important contribution of this article to this review are the age-related behavioral changes associated to the structural and functional reorganization seen in older adults. These are:

- Three percent reduction per year in joint position sense has been reported, possibly due to loss in the number of muscles spindles.

- There seems to be a greater upregulation of PSI in older adults. Greater PSI is accompanied by greater sway amplitude and greater coactivation.

- Greater activation of M2 areas, prefrontal, and premotor areas is associated with better task performance.

- Cortical inhibitory circuits seem to be less active in older adults; shown by shorter silent periods, reduced short – interval intracortical inhibition and reduced cortical reciprocal inhibition. This decrease might be related to the decline white (2.5 percent per decade) and gray matter integrity (4 – 16 percent). The shorter silent

periods have been associated with lower performance and increased antagonist coactivation.

- Gray and white matter degeneration is associated with slower information–processing speed shown by slower gait speeds.

- Reduced conduction velocity could be explained by loss of nerve fiber density (~37 percent loss). Afferent fibers seem to be the most affected, H – reflex latency is ~3.39 ms slower in older adult. The smaller and slower H-reflexes could be associated with longer muscle onset latencies during balance perturbations response.

- Increased activation of motor and premotor areas, including antagonist representation area might be related to the increased antagonist coactivation associated with aging.

Overall, the authors concluded that age-related reorganization is characterized by a greater cortical activation and by a differential modulation of spinal reflexes.

Baudry, 2016[38]

This is a hypothesis driven review, where the researchers suggest an increased corticospinal resilience to control balance. The summarized findings supporting this hypothesis are of great importance for this study.

- Negative relationship between H-reflex amplitude and age during standing (r2 = 0.34)

- There was a significant reduction in H-reflex amplitude from sitting to standing across all ages (20 – 80 years old). The reduction was significantly greater in older adults.

- Progressive increase in MEP amplitude with age (r2 = 0.33).

The authors concluded that there is an age-related progressive shift in the reliance on spinal to supraspinal pathways to control leg muscles.

Smith and Fisher, 2018[40]

The purpose of this study was to compare temporal and spatial characteristics of anticipatory postural adjustments between older and younger adults and characterize this behavior between older adults' fallers and non-fallers. Participants performed rapid arm abductions while surface EMG was recorded from agonist muscle (deltoid) and anticipatory muscles (gluteus medius, external oblique, thoracic longissimus). Measurements of reaction time, movement time, coactivation, anticipatory postural adjustment (APA) latency, balance, and mobility were taken. In addition, each muscle was mapped using TMS and center of gravity, horizontal distance between muscle pairs and volume of representation areas were calculated. APAs were significantly later and representation areas were more lateral in the older population when compared to the

young group. When dividing the older group between fallers and non-fallers, the greatest age-related changes were evident in the non-fallers. The authors suggested that the greatest spatial and temporal changes seen in the non-fallers might be a potential compensation associated with aging.

2.2.2 Summary of "Neurophysiological Changes Associated with Performance"

Aging causes a cortical structural and functional reorganization of voluntary movements[7] with increased excitation[32,40,43,111] and a decreased inhibition[12,41,111,113]. The higher cortical activity has been seen in the ipsilateral and contralateral premotor and supplementary cortex; ipsilateral putamen and sensorimotor cortex; contralateral primary sensory cortex, cerebellum, parietal cortex, and thalamus[32]. In addition, muscle representation areas are more disperse[43]. This increased cortical activation and dispersion have been correlated with better performance levels[32,40]. In contrast, reduced cortical inhibition, seen with shorter silent periods, has been associated with poorer performance[12,41,113].

At the spinal level a decreased reciprocal[39] and presynaptic inhibition[31] has been identified; with a strong relationship between RI and aging (r = 0.67). Furthermore, during voluntary movements, older adults lack the modulation of PSI[31] and RI[39] seen with the younger groups.

A somatosensory decline has been seen in older adults. For example, a reduction in the number of muscle spindles, intrafusal fibers, Golgi tendon organs, articular receptors, cutaneous receptors and nerve fibers has been demonstrated in animals or postmortem humans[6]. In addition, older adults have exhibit smaller H – reflexes[39], reduced joint kinesthesia[62] and discriminative touch[6].

Muscular and motor decline is also apparent with aging. The elderly population has showed reduced muscle cross – sectional area[114] and quality[115], lower strength levels[14,30,115] and rate of force developement[14]. These lower values have been associated with increased reaction times[30] and lower balance scores[14]. In addition, it appears that during activities such as standing and stepping, older adults use a coactivation strategy in order to control body sway and stiffen the joint, compensating for the decrease in sensory and motor function[7,28,29,38].

In summary, researchers have suggested that due to structural decline, in cortical and subcortical areas associated with aging[7,14,115], older adults experience functional changes. These can be compensatory, such as increased excitation[32,39,43,69] or can be the result of the structural deterioration such as decreased inhibition[12,41]. Furthermore, these functional changes affect performance levels[7,32,43].

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Oklahoma State University Institutional Review Board

Date:	05/23/2019
Application Number:	ED-19-71
Proposal Title:	Central and Peripheral Muscle Activation Pairs during Maximal Efforts and Reaction Tasks
Principal Investigator:	Ale Barrera Curiel
Co-Investigator(s):	Jesus Hernandez Sarabia
Faculty Adviser:	Jason Defreitas
Project Coordinator:	
Research Assistant(s):	
Processed as:	Expedited
Expedited Category:	

Status Recommended by Reviewer(s): Approved

Approval Date:	05/20/2019

The IRB application referenced above has been approved. It is the judgment of the reviewers that the rights and welfare of individuals who may be asked to participate in this study will be respected, and that the research will be conducted in a manner consistent with the IRB requirements as outlined in section 45 CFR 46.

This study meets criteria in the Revised Common Rule, as well as, one or more of the circumstances for which continuing review is not required. **As Principal Investigator of this research, you will be required to submit a status report to the IRB triennially.**

The final versions of any recruitment, consent, and assent documents bearing the IRB approval stamp are available for download from IRBManager. These are the versions that must be used during the study.

As Principal Investigator, it is your responsibility to do the following:
1. Conduct this study exactly as it has been approved. Any modifications to the research protocol must be approved by the IRB. Protocol modifications requiring approval may include changes to the title, PI, adviser, other research personnel, funding status or sponsor, subject population composition or size, recruitment, inclusion/exclusion criteria, research site, research procedures and consent/assent process or forms.
2. Submit a status report to the IRB when requested
3. Promptly report to the IRB any harm experienced by a participant that is both unanticipated and related per IRB policy.
4. Maintain accurate and complete study records for evaluation by the OSU IRB and, if applicable, inspection by regulatory agencies and/or the study sponsor.
5. Notify the IRB office when your research project is complete or when you are no longer affiliated with Oklahoma State University.

If you have questions about the IRB procedures or need any assistance from the Board, please contact the IRB Office at 405-744-3377 or irb@okstate.edu.

Sincerely,
Oklahoma State University IRB

VITA

Alejandra Barrera Curiel

Candidate for the Degree of

Doctor of Philosophy

Dissertation: THE STRUCTURAL, FUNCTIONAL, AND BEHAVIORAL PLASTICITY OF

SENSORIMOTOR INTEGRATION

Major Field: Health and Human Performance

Biographical:

Education:

Completed the requirements for the Doctor of Philosophy in Health and Human Performance at Oklahoma State University, Stillwater, Oklahoma in July, 2020

Completed the requirements for the Masters of Science Dual Degree Program in Leisure Studies at Oklahoma State University, Stillwater, Oklahoma in May 2015 and Management and Marketing at Universidad Popular Autonoma del Estado de Puebla, Puebla, Mexico in August 2015.

Completed the requirements for the Bachelor of Science in Physical Education at Benemerita Universidad Autonoma del Estado de Puebla, Puebla, Mexico in December, 2012

Experience

Graduate Teaching/Research Assistant at Oklahoma State University, School of Kinesiology, Applied Health and Recreation, Stillwater, OK