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## Scalp Eeg and Tms Based Electrophysiological Study of Brain Function of Motor Control in Aging

Mehmed Satuk Bayram  
*Cleveland State University*

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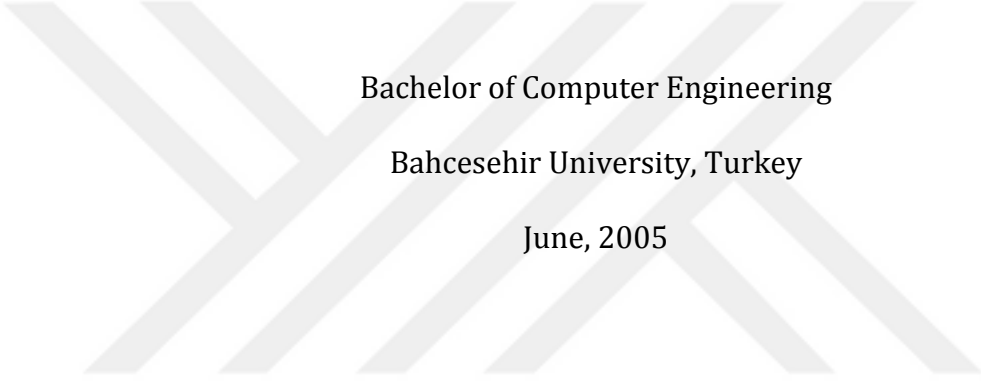
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SCALP EEG AND TMS BASED ELECTROPHYSIOLOGICAL STUDY OF BRAIN  
FUNCTION OF MOTOR CONTROL IN AGING

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at the

CLEVELAND STATE UNIVERSITY

April, 2013



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This dissertation has been approved  
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and the College of Graduate Studies by

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To Ege...

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ABSTRACT

Voluntary movements of human body are controlled by the brain through corticomuscular pathways. Although neuromuscular control mechanisms of voluntary movements have been studied extensively, many remain to be learned, especially neuromuscular adaptations related to clinical conditions such as neurological disorders and aging. This research aims at a better understanding of functional connection between the brain and muscle during voluntary motor activities in aging and the extent to which this connection can be changed by training the neuromuscular system. Three research projects were conducted to achieve this aim. The analyses in the first two projects are based on comparisons of non-invasive electroencephalographic (EEG) and electromyographic (EMG) signals recorded in young and elderly individuals performing voluntary muscle contractions whereas the third project is based on transcranial magnetic stimulation (TMS). The first project examines the relationship between EEG frequency power and muscle force to identify an EEG or brain signal parameter directly related to voluntary motor action. The second project investigates further the strength of functional brain-muscle connectivity by quantifying EEG-EMG coherence and effects of aging on the connectivity. The third project identifies the

representation of the biceps brachii muscle in primary motor cortex with TMS; examine its excitability of corticospinal tracts, intra-cortical excitability reflecting activity of both inhibitory and facilitatory inter-neurons and inter-hemispheric inhibition.

This research reveals that aging brain has impaired coupling between the central and peripheral neuromuscular systems and also significantly different intra-cortical excitability; both may have an influence for weakened muscle output in the elderly. This research will contribute to a better understanding of neural mechanisms underlying voluntary movement deficit in aging and its recovery following training the neuromuscular system.

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## CHAPTER I

### INTRODUCTION

#### 1.1. Aging Brain

Corporal Seyit (Seyit Onbaşı, in Turkish) is a real life Turkish hero from Battle of Gallipoli of the First World War, who was serving in Ottoman army as an artilleryman. On 18<sup>th</sup> March 1915, when Allied navy fleet attempted to open up The Dardanelles Strait, a very strategic point for both sides, the cannon gun he was serving had its shell crane damaged, but still remained operational. Seyit accomplished something beyond belief: he carried three 258kg (~568lbs) shells and loaded in the cannon, by himself. The third shell reputedly hit the HMS Ocean, a British battleship, and helped it sunk by directing the ship to the mines nearby... The next day, they wanted photograph him while carrying the same shell, but he tried and said he couldn't even move the shell from where it is standing. Thus, this photograph (Figure 1, see Appendix A for copyright permission) is taken with a wooden replica of the shell.

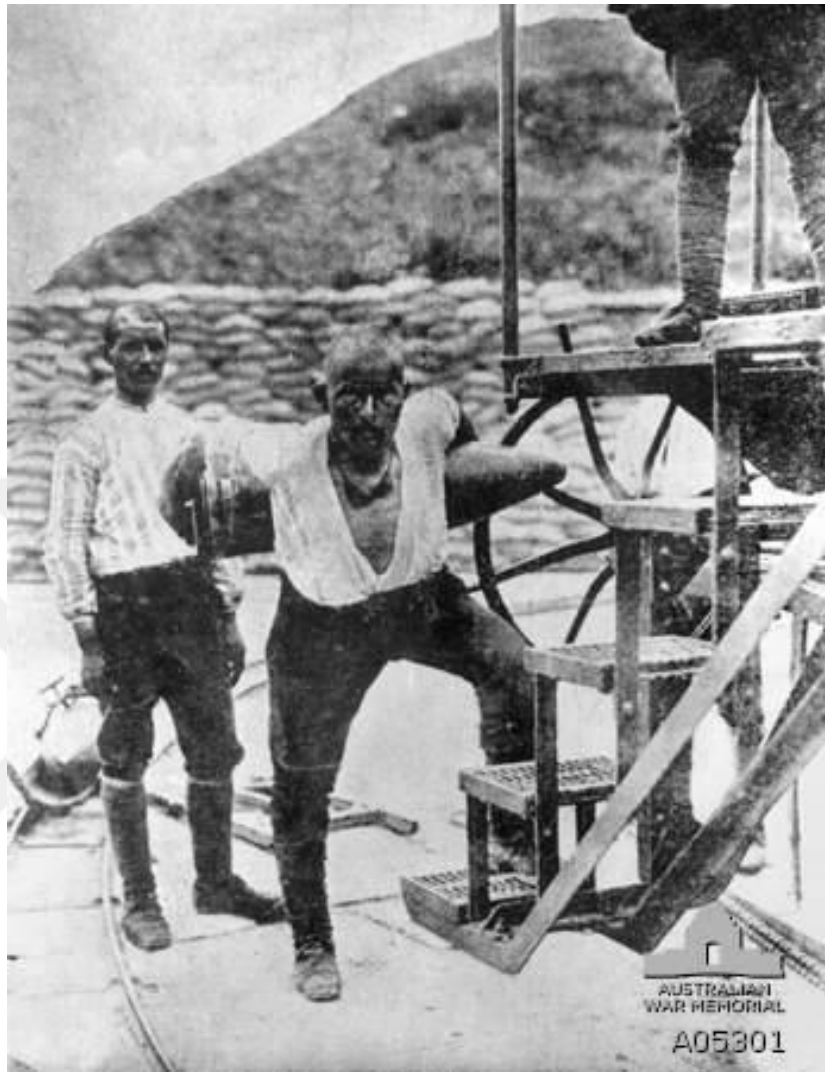


Figure 1. Corporal Seyit, posing, c 1915 (AWM A05301).

The above story clearly describes a human body can perform extraordinarily and push its limits to the edge, when in need. The central nervous system, which consists of the brain and spinal cord, is the main player. Brain receives, executes and sends information while spinal cord helps in retrieving and transmitting that information to most parts of the body, in addition to carrying some of its own independent duties, such as controlling reflexes. Normally, these neural mechanisms control human behavior for the daily activities. But for some instances, they will kick in and

adjust the parameters as in this story: adrenaline secretion, excessive muscle firing, pain management and the most importantly; a mental state which is isolated from outer conditions. Although the secondary part of the nervous system, peripheral nervous system, has been studied and answered a lot of questions about the neuromuscular part, questions about control mechanisms behind central nervous system for voluntary movement are largely unanswered.

On the other hand, aging is inevitable. According to United Nations (United Nations 2011) world population is getting older rapidly, with an estimation of 2 billion people being 65 years or older in 2050 - up from 600 million in 2000. Aging comes with muscular, neuromuscular and musculoskeletal system degeneration thus has a direct effect on performance and quality of daily lives.

An elderly person may possibly not accomplish muscle related activities in the same degree, compared to when he/she was younger. Muscular degeneration part is due to loss of muscle mass and muscle strength. This decline may range up to 1/3 in humans between the ages 30 to 80 (Tzankoff and Norris 1977). Elderly adults experience significant deterioration in muscle strength ranging from 20% to 50% or even higher (Doherty 2003; Grabiner and Enoka 1995; Hopp 1993; Lindle et al. 1997). Although it is shown that weight training may help by increasing the endurance (Ades et al. 1996), it may not be feasible or healthy for an elderly person to maintain its muscle mass by having constant physical exercise.

Numerous studies have reported evidence of age-related structural and functional degenerations in the central nervous and muscular systems that contribute to motor function impairment. While the most commonly implicated

mechanism involves muscle atrophy (Doherty 2003; Faulkner et al. 2007), following death of spinal motor neurons (Faulkner et al. 2007), peripheral degeneration only partially explain aging-related weakness (Doherty 2003; Young et al. 1985). Changes within the central nervous system, both microscopic and macroscopic, exaggerate the deficit. Degenerative processes include reduction in gray matter volume (Good et al. 2001), fewer motor cortical neurons (Henderson et al. 1980), decrease in synaptic density (Haug and Eggers 1991), loss of white matter integrity (Davis et al. 2009; Lindberg et al. 2010), lowered neurotransmitter levels (Gu 2002) and greater variability in motor unit (Laidlaw et al. 2000).

## **1.2. Functional Measures**

Understanding the motor function impairments in aging is important, yet there are many unknowns regarding the central and peripheral systems' connection. The dissertation overall focused upon evaluating aging-related effects upon brain and its communication with muscle. These effects were evaluated using three modalities: EEG (electroencephalography), EMG (electromyography) and TMS (transcranial magnetic stimulation), several combinations of which provide unique methods to address the questions. For instance, EEG signal, especially, the power of its frequencies represents how a certain frequency and/or frequencies contribute to the overall signal. While EEG power discusses overall signal of brain, brains' commands to muscle can only be examined with EEG's combination with EMG and TMS and EMG. Brain-to-muscle coupling can be studied during voluntary tasks (using EEG applied to the scalp and EMG collected from muscle) and during rest

(using TMS and EMG). Both strategies have been employed here since they are complementary but unique. Although EEG-EMG can describe shift in binding of brain's commands to ongoing muscle activity, TMS can describe these relations in resting state of muscle and help infer actual conduction of brain's signals via the descending motor tracts dedicated to the muscle. Thus, while EEG-EMG defines the relation between activity of brain and activity of contracting muscle, TMS-EMG studies the direct substrate underlying this relation. Both methods offer functionally complementary information about relation of brain to muscle in movement control and both methods were used to evaluate changes in brain-to-muscle relation in aging, to potentially identify parameters that may reflect aging-based weakness and incoordination, carrying implications for therapeutics.

Power analysis on EEG signals is a unique method of establishing brain's role in muscle activation (Schwilden 2006). Power of EEG frequencies is correlated to the intensity of muscle contraction which suggests the EEG power reflects brain signals that control the levels of muscle force/strength (the higher the signal, the greater the strength). Thus, power spectrum is a quantitative representation which shows how a certain frequency and/or frequencies contribute to the overall signal of brain activity. Frequencies in EEG generally divide into brain bands/rhythms including, Delta (0-4Hz), Theta (4-8Hz), Alpha (8-12Hz), Beta (12-35Hz) and Gamma (35+ Hz). Beta rhythms have been mostly linked with movement on-site, especially with voluntary motor actions for upper limb muscles (Conway et al. 1995; Brown 2000; Bayram et al. 2010; Moraes et al. 2011; Lim et al. 2011; Ho et al. 2012; Gola et al. 2012). EEG collected over the primary motor cortex with an isometric voluntary

motor action has been found to happen in upper Beta rhythm region (Lalo et al. 2007; Baker 2007; Bayram et al. 2010). Literature shows high correlations between force and frequency power of EEG signals recorded from a number of scalp locations overlying cortical regions related to sensorimotor function. These results indicate that cortical signal oscillations vary systematically with muscle output. The oscillatory changes may represent modulations of the cortical control signals for weaker or greater descending command for lower or higher muscle output. The findings of this study may offer the possibility of using the EEG frequency power as an objective parameter for monitoring how the aging brain is changed.

Techniques that generate real-time information of central-peripheral communication, such as EEG-EMG, in voluntary motor control may best address functional coupling of brain's signals to muscle activity. Functional coupling between the brain and muscle can be estimated by calculating coherence in frequency domain between brain and muscle signals. This coherent measure has been suggested to solve the "binding" problem, acting as a mechanism to link information related to the same function but processed in different neural populations (Salenius et al. 1997; Thiele and Stoner 2003). Coherence between EEG (from brain) and EMG (from muscle) signals at particular frequency bands has been reported by many studies (Baker et al. 1997; Gross et al. 2000; Yang et al. 2011) to demonstrate functional coupling between the brain and muscle. It has been previously shown that the level of brain-muscle or corticomuscular coherence (CMC) increases with the level of voluntary activation of a muscle (Kilner et al.

2000), indicating a relation between voluntary muscle output and strength of brain-muscle functional coupling or CMC.

Aging related effects on functional coupling have been explored preliminarily. Few recent studies have attempted to investigate CMC in aging. Kamp et al. (Kamp et al. 2011) showed slowed and shifted CMC in people with more advanced ages compared with young individuals but they did not address different force levels exerted and whether the relation changes when people get the force levels get higher. Others (James et al. 2008) compared CMC among subjects in ages from infancy to elderly and reported prominent differences during motor development in children. Although CMC changes with aging, there is lack of knowledge on whether CMC modulates similarly with increased muscle activation in aging or whether there is a break-down of this relationship. Moreover, it is unknown if a positive relationship between the CMC and muscle output is maintained in the elderly. Addressing these questions will help understand whether changes in functional coupling across increasing muscle output may partly explain muscle weakness in the elderly.

Transcranial magnetic stimulation (TMS) is another technique that can be used to evaluate brain-to-muscle connection and excitability of the corticomuscular system. TMS is a non-invasive exploratory technique which can be used to study the excitability of the human motor cortex, such as primary motor cortex for motor actions, at rest. TMS uses electromagnetic induction through an induction coil by changing its magnetic field thus creating an electric current which then causes depolarization in the neurons (Theodore 2002). Since it is non-invasive and has

minimal discomfort to the subject, it is one of the most influential new methods to explore intra-cortical or corticomuscular functional connectivity. When TMS is delivered to certain motor cortex regions in the brain, Motor Evoked Potentials (MEP) can be recorded from muscles as a form of EMG; following the TMS delivery to the motor cortex region associated with that muscle (Kammer et al. 2001). Since MEP amplitude is correlated with motor excitability and electromagnetic output from the TMS delivery equipment can be increased or decreased, the MEP response from the muscle is changed accordingly, thus TMS offers a quantitative way to detect induced muscle activity (Pitcher et al. 2003). Age-related adaptations have almost invariably been explored for representations in M1 that are devoted to dexterity, such as ones representing distal hand/wrist muscles (McGinley et al. 2010; Sale and Semmler 2005; Peinemann et al. 2001; Pitcher et al. 2003; Talelli et al. 2008b; Marneweck et al. 2011). However, since strength is a stronger predictor of disability than dexterity (Canning et al. 2004) and greater proximal strength can help compensate for lack of dexterity (Canning et al. 2000), studying age-related adaptations in M1 that explain proximal muscle weakness will carry important implications. Further, by defining what specific markers, i.e. whether an increase or a decrease in corticospinal, intra-cortical and inter-hemispheric mechanisms predicts age-related muscle strength, discrepancies between findings in the literature can be resolved.

### **1.3. Thesis Purpose**

Given the significance of understanding motor control mechanisms and neuromuscular mechanisms behind muscle weakness in aging, it is crucial to better understand aging brain motor control functions by analyzing brain and muscle signals. Still, little is known whether functional coupling between the two (central [brain] and peripheral [muscle]) systems during voluntary motor activities is intact in individuals with advanced age. Effects of aging brain for motor control pathway from peripheral to central have been investigated separately, however, the relationship of these changes on various sites has never been directly addressed. This dissertation had three objectives: to investigate EEG frequency power and muscle force relationship in healthy elderly compared to healthy young subjects; to quantify CMC changes with aging during voluntary muscle contractions; to visually represent biceps brachii muscle in the brain with TMS technique.

It was hypothesized that with aging, descending brain command would be weaker which would have a direct negative effect muscle output. Findings of this research are likely to contribute to a better understanding of neural mechanisms underlying motor function deficit in aging and its possible recovery following training the neuromuscular system.

### **1.4. Thesis Organization**

First, an EEG frequency power and muscle force relationship was evaluated to learn the pattern of the leading frequency band for voluntary muscle actions and what EEG frequency band is active during the voluntary force tasks (Chapter 2).

Based on the pattern, it was further investigated the strength of functional brain-muscle connectivity by quantifying CMC and effects of aging, if the coherence is prominent in the same frequency bands (Chapter 3). Based on the hypothesis of reduced CMC in aging, the third project identifies if this reduction is caused by a change in M1 excitability by quantifying the representation of the biceps brachii muscle in M1 with TMS; examine its excitability of corticospinal tracts, intra-cortical excitability reflecting activity of both inhibitory and facilitatory inter-neurons and inter-hemispheric inhibition (Chapter 4). Finally, Chapter 5 concludes the studies and discusses the future directions.

## CHAPTER II

### EEG POWER OUTPUT IS IMPAIRED IN AGING

#### 2.1 Introduction

Scalp Electroencephalography (EEG) is a non-invasive technique which is used to record electrical activity of the brain, produced by neurons' firing and synaptic activities (Wolpaw et al. 2002). It was named by German researcher Dr. Hans Berger in 1924, who invasively recorded the first EEG on man. He also named the first brain waves he recorded as the "alpha waves", which are 8 - 12 Hz and faster waves as "beta waves". These terms are still used to distinguish different brain wave/rhythm frequencies. Although there is no universally acclaimed standard to differentiate brain rhythms' frequency ranges in the literature, Table I shows the nominal ranges and the associated names, which will be referred to in this study.

<b>Delta</b>	<b>Theta</b>	<b>Alpha</b>	<b>Beta</b>	<b>Gamma</b>
0.1 - 4	4 - 8	8 - 12	12 - 35	35 - 100+

Table I. Brain rhythms are classified as in their frequency responses (in Hertz).

Power spectrum is a quantitative representation which shows how a certain frequency and/or frequencies contribute to the overall signal (Schwilden 2006). EEG, being a real time recording technique, can be easily transformed from time domain into frequency domain with Fourier Transform or its variants such as Fast Fourier Transform (FFT) (Rosenberg et al. 1989) or Short-time Fourier Transform (STFT) (Allen and MacKinnon 2010). Recorded EEG waves, like any signal over time, are a superposition of sine waves of multiple frequencies thus its power becomes the square of its magnitude.

Power analysis for EEG has been investigated thoroughly. Delta rhythms, the slowest of the brain waves (0.1-4 Hz) although having the highest amplitude, should be seen dominantly in deep sleep state (Berry et al. 2012) whereas Theta rhythms (4-8 Hz) are linked with spatial learning, short-time memory and navigation tasks (Vertes 2005; Buzsaki 2005). Alpha rhythms (8-12 Hz), should indicate a relaxed but aware state for adults (Niedermeyer 1997) and an overlapping set of these rhythms called Mu rhythms (8-13 Hz) may indicate a preparation stage for movement which also makes them a hot research topic for EEG-based Brain-Computer Interfaces (BCI) (Machado et al. 2010). Gamma rhythms (35-100+ Hz), being the least understood in all brain waves, have been recently linked with sensory processing in the visual cortex (Swettenham et al. 2009). Beta rhythms (12-35 Hz), have been mostly linked with movement on-site, especially with voluntary motor actions for upper limb muscles (Conway et al. 1995; Brown 2000; Bayram et al. 2010; Moraes et al. 2011; Lim et al. 2011; Ho et al. 2012; Gola et al. 2012). EEG collected over the primary motor cortex (M1) with an isometric voluntary motor

action has been found to happen in upper Beta rhythm region (Lalo et al. 2007; Baker 2007; Bayram et al. 2010). Recently, it was suggested that, Beta band oscillations play an important role in the stability level of finger-muscle contraction for distal hand muscles (Lim et al. 2011).

Previously, it was demonstrated that in healthy young people not only is there a linear relationship between the amplitude of motor activity-related cortical potential (on EEG) and voluntary activation of upper limb muscles (Siemionow et al. 2000), but there is also an association between the power of EEG oscillations and the output of human lower limb muscles (Siemionow 2003). These relationships, however, have not been investigated in aging. In this study, the relationship between EEG-recorded cortical waves and frequency modulation of upper limb muscles has been explored at different levels of voluntary effort in elderly subjects to determine the association between brain waves and levels of force. It is suggested that in the process of voluntary muscle output, frequency modulations of the cortical neurons involved as well as the magnitude of the descending command.

## **2.2 Methods**

### **2.2.1 Subjects**

Table II shows the demographics of 28 healthy elderly and 20 young individuals participated in the study. All recruited subjects were right handed (Oldfield 1971) and screened by a physician to ensure they were free of neurological, musculoskeletal, cardiovascular or other body system disorders/impairments. All enrolled subjects did not have any systematic upper-extremity motor training in the

last 5 years. Elderly subjects had a minimum score of 25 or more on the Mini Mental State Examination (Folstein et al. 1983). The research study and its procedures were approved by the Institutional Review Board at the Cleveland Clinic and all subjects signed an informed consent prior to their participation.

### 2.2.2 Elbow Flexion Strength and Submaximal Elbow Flexion Contractions

Maximal elbow flexion (EF) force was measured at the beginning of the experiment, indicating the subject's Maximal Voluntary Contraction (MVC) force of the joint. This was used as a baseline for subsequent calculation of 20%, 50% and 80% EF MVC force. The forces (maximal and sub-maximal) were measured by a force transducer (0-310N, JR3 Universal Force-Moment Sensor System, Woodland, CA), acquired by a Micro 1401 MK ii data acquisition system (Cambridge Electronic Design, Ltd., Cambridge, UK), digitized at 100Hz and shown on an oscilloscope (TDS 460, Tektronix Inc., Beaverton, OR) using a horizontal cursor as visual force feedback. Digitized force data were saved on hard disk of a personal computer.

	<b>Young</b>	<b>Healthy Elderly</b>
<b>Number</b>	20	28
<b>Age (years)</b>	22.6 ( $\pm$ 0.87 SE)	74.79 ( $\pm$ 1.37 SE)
<b>Gender (F/M)</b>	10/10	20/8

Table II. Mean values of demographic of participated individuals (SE, standard error).

For the MVC force, subjects were verbally encouraged to produce the maximal EF force for 5-7 s, with a ~45 s rest between trials (a total of 5 MVC trials). Subsequently, sub-maximal EF forces at 20, 50 and 80% of the maximal EF force were calculated based on the greatest force among the 5 trials. Over five trials of MVC EF, (in Newtons, N)  $Force_{Ave}$  (mean force) and  $Force_{MAX}$  (maximum force) for each subject were defined.

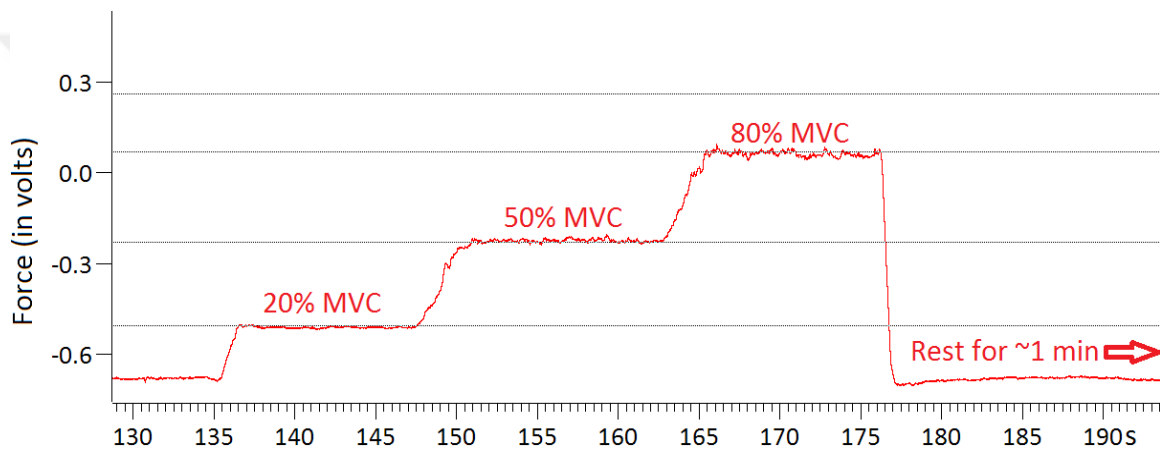


Figure 2. An example representation of submaximal EF force targets. Target lines were drawn to depict their relativity to MVC EF (100%, the top line). The actual recording had 3 submaximal force levels randomized and tested separately.

Force production at each submaximal level was accomplished by setting a target on the oscilloscope screen (e.g., 20% maximal EF force) and then the subjects attempted to match the target by exerting EF force and maintain the force on the target as steadily as possible for 10 s (Figure 2). Three trials were performed at each of the three submaximal force levels and contractions at the three force levels were randomized. Approximately 1 minute rest was provided between trials. At the end of the experiment, subjects were asked to perform an MVC again to determine if previous motor activities had induced fatigue. The subjects were asked to avoid eye

blinks, teeth biting, tensing facial and neck muscles, and head movements during each contraction. The experiment lasted less than 60 min (Figure 3).

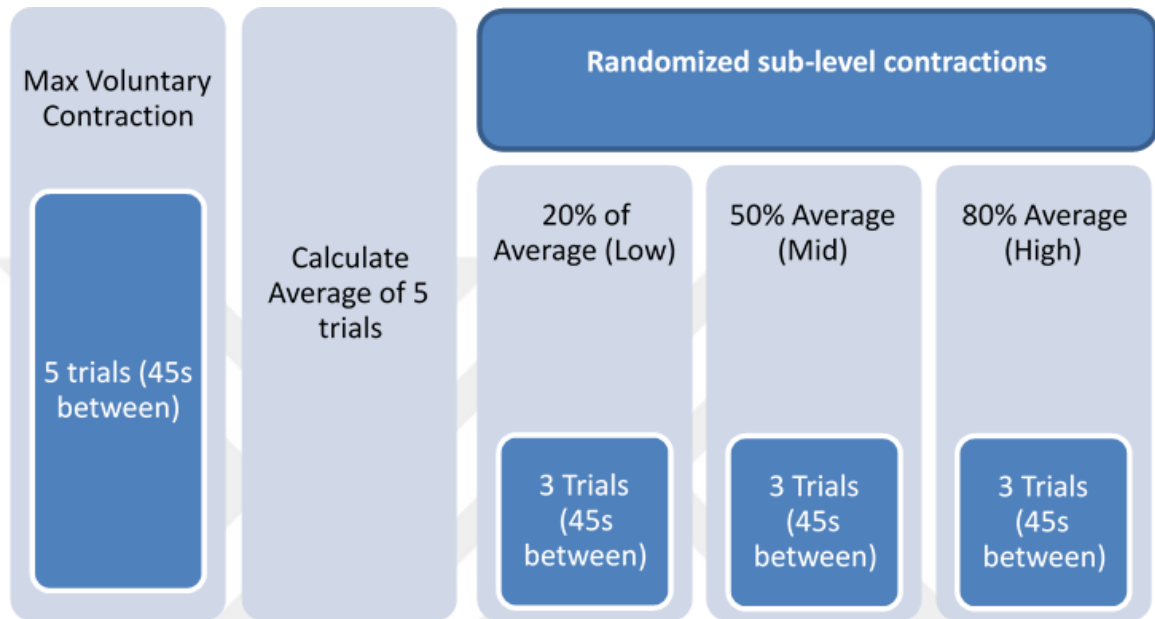


Figure 3. A flowchart representation of the Elbow Flexion (EF) task. After 5 trials of voluntary EF to identify the subjects' maximum voluntary contraction, 5 trials were average to get their "mean". It was then used to calculate their 20%, 50% and 80% of their maximum force.

### 2.2.3 EMG

Bipolar electrodes (Ag-AgCl, 8-mm recording diameter, In Vivo Metric, Healdsburg, CA) were placed on skin overlying belly of the biceps brachii (BB), brachioradialis (BR) and triceps brachii (TB) muscles, with an inter-electrode placement of ~3 cm. A reference electrode was placed over the acromion process of the shoulder. The muscle areas touching the electrodes were cleaned using abrasive gel (Nuprep ECG and EEG abrasive skin prepping gel, D.O. Weaver & Co., Aurora, CO). A more rigorous cleaning has been done with elderly group, due to their higher skin impedance (Hagemann et al. 1985). Conductive gel (SignaGel, Parker

Laboratories, Fairfield, NJ) was applied to connect to the recording surface of the electrodes.

EMG data for all MVC and sub-maximal level contractions were amplified ( $\times 1000$ ), band-pass filtered (3-500 Hz bandwidth), digitized at a sampling rate of 1000 Hz using the Micro 1401 system, and saved on hard disk of the PC. Voluntary EMG signals generated in the elbow flexors, correspondingly, during trials of MVC EF were full-wave rectified. EMG results were noted for a 1-s period (at the time of maximal force during a trial). Over five trials, (in millivolts, mV)  $EMG_{Ave}$  (mean EMG) and  $EMG_{MAX}$  (maximum EMG) were defined.

#### **2.2.4 EEG**

Scalp EEG signals were recorded continuously during the MVC and sub-maximal-level contractions using a 128-channel dense array EEG data acquisition system (Electrical Geodesics, Inc. Eugene, OR, USA), along with the force and EMG signals. EEG electrodes were arranged in a dense hat-like net and connected freely by strings. The net was put on the head after it was immersed in the electrolyte solution (the connecting media between the scalp and electrode), consisted of one liter of distilled water added with 1.5 teaspoons of potassium chloride and a few drops of baby shampoo (EGI System 200 Technical Manual). After the required alignment of the net on the head, each electrode was ensured to touch the scalp perpendicularly allowing the sponge-type electrode heads the highest connection.

The EEG data recording did not start until the impedance for the whole net was below 10,000 ohms. Additionally, 4 auxiliary channels were used to record Data of

BB, TB and BR EMG and EF Force to allow synchronization of the EEG and EMG signals for EEG-EMG coherence analysis (See Chapter 3). EEG signals were amplified (x20000), band-pass filtered (0.1 -100 Hz), sampled at 250 Hz, and recorded on hard disk of the PC. Overall experimental setup is illustrated in Figure 4.

### **2.2.5 EEG Power Analysis**

Power spectrum of EEG was calculated using Welch's method (Welch 1967; Kilner et al. 2000), using 1-second (250 data points) Hamming window with 50% overlap. Welch's method is a non-parametric power spectral density (PSD) estimation method which uses averaging to estimate power at different frequencies. It uses windows to divide time series into overlapping subsequences and then averaging the periodogram of each subsequence by discrete to estimate spectral density. The window size manages the trade-off between variance and bias of the resulting PSD. If a large window size is chosen, the bias is small but the PSD has a coarse and fuzzy whereas a small window size has higher bias in estimating the magnitude. For EEG signals, a %50 overlapping window is usually chosen in the literature (Polat and Güneş 2007). EEG data was pre-filtered using a 50 Hz Butterworth low-pass filter as the voluntary muscle contractions tend to happen below 40 Hz. Out of the 128 channels of EEG electrodes over scalp, focus was given to the electrodes over the right primary sensorimotor area contralateral to the left elbow flexion movement. A power spectrum (expressed as  $\mu V^2$ ) was calculated using the power for each of the following EEG frequency bands as outlined in Table I. Relative power of each band as a percentage of the total power was calculated.

Preliminary data analysis has been conducted in BESA EEG review and analysis program (MEGIS Software, Gräfelfing Germany) while further analysis was done in MATLAB (The MathWorks, Natick, MA.).

### 2.2.6 Statistical Analysis

A one-way repeated measures ANOVA, ordinary linear regression, t-test and F-test were adopted for EEG power comparisons between the trials, force levels, sensorimotor areas and groups. IBM SPSS Statistics 21.0 (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) was used for statistical analysis. Statistical figures have been created with Sigmaplot (Systat Software, San Jose, CA) software.

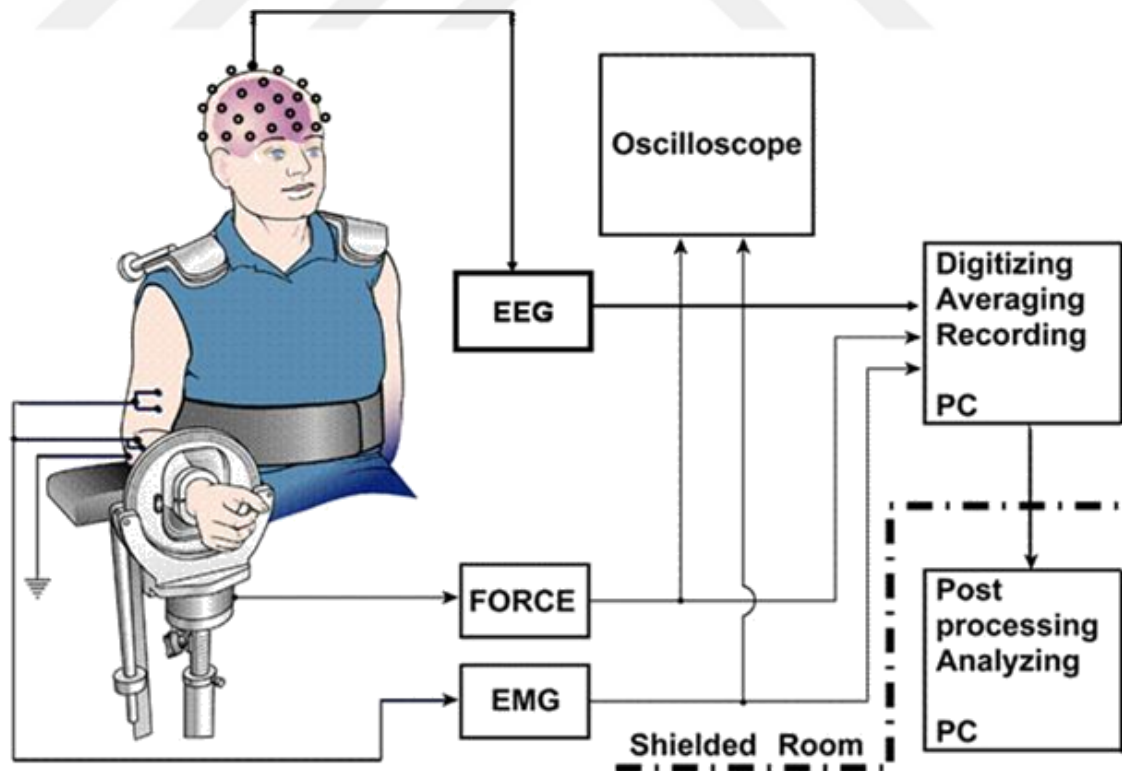


Figure 4. Experimental setup for elbow flexion task. Subjects were asked to do a voluntary elbow flexion task against a force transducer around the wrist, while EEG, EMG and Force have been collected.

## 2.3 Results

### 2.3.1 Strength

For the maximum voluntary elbow flexion contractions, compared with young participants, elderly volunteers were significantly weaker with regards to  $\text{Force}_{\text{Ave}}$  ( $116.76 \pm 12.44$  N vs.  $93.4 \pm 6.11$  N;  $t_{0.05, 46} = 2.07$ ,  $p = 0.037$ ) (Figure 5, **panel a**) and  $\text{Force}_{\text{MAX}}$  ( $130.01 \pm 12.97$  N vs.  $102.21 \pm 6.56$  N;  $t_{0.05, 46} = 2.07$ ,  $p = 0.02$ ) (Figure 6, **panels A and B**) in left elbow flexion. Values for  $\text{EMG}_{\text{Ave}}$  ( $0.65 \pm 0.11$  mV vs.  $0.43 \pm 0.05$  mV;  $t_{0.05, 46} = 2.1$ ,  $p = 0.02$ ) (Figure 5, **panel b**) and  $\text{EMG}_{\text{MAX}}$  ( $0.78 \pm 0.12$  mV vs.  $0.52 \pm 0.05$  mV;  $t_{0.05, 46} = 2.09$ ,  $p = 0.021$ ) (Figure 6, **panels A and B**) for left biceps brachii (BB) were again lower in the elderly versus young group.

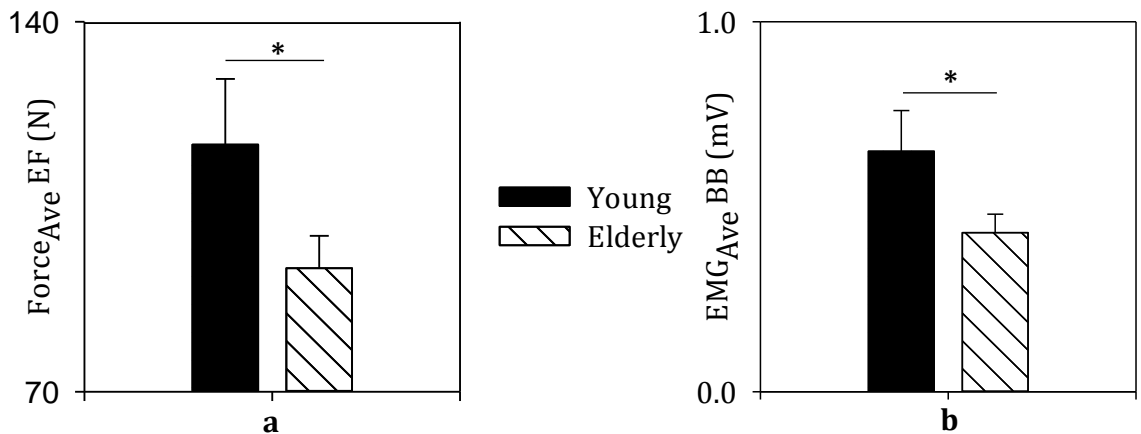


Figure 5. Average Force and Biceps Brachii (BB) EMG for young versus elderly during EF task. Panels 5a and 5b depict significantly ( $*p < 0.05$ ) lower average force ( $\text{Force}_{\text{Ave}}$ ) and average activation of BB ( $\text{EMG}_{\text{Ave}}$ ) during maximum voluntary elbow flexion.

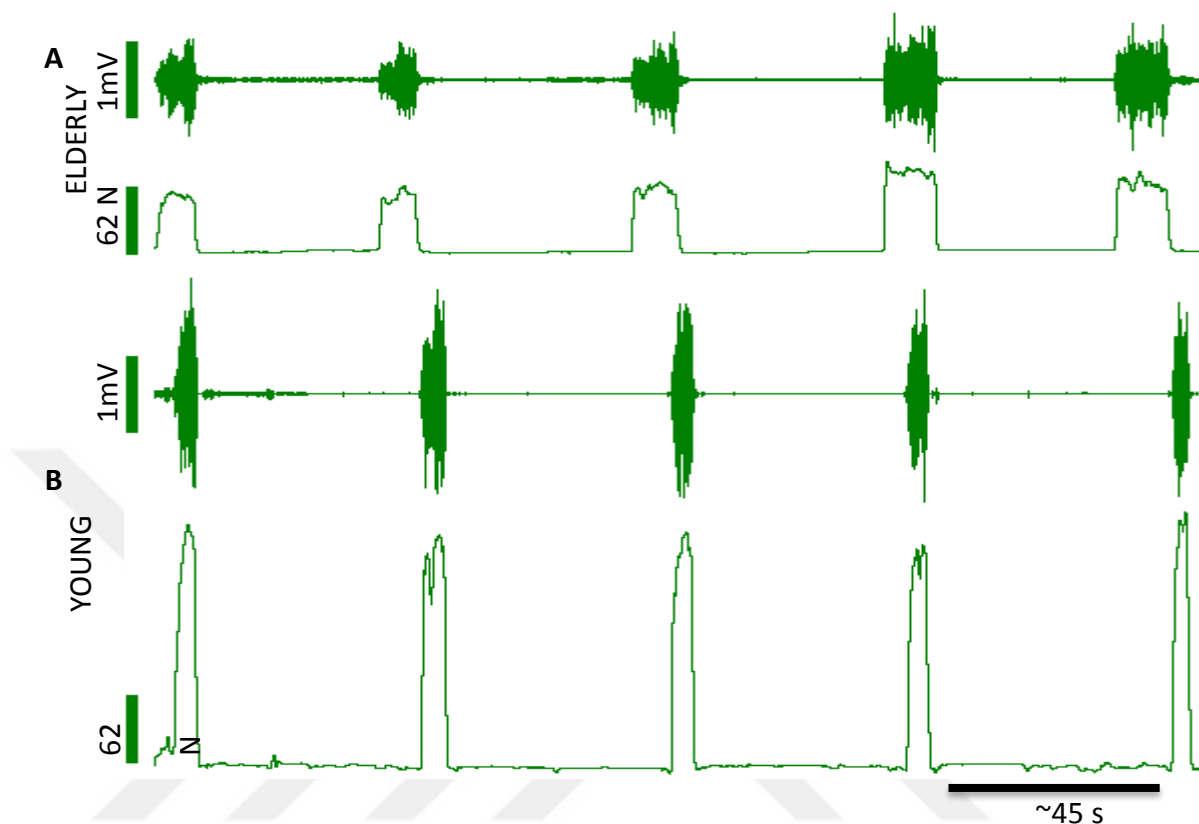


Figure 6. Representative examples indicating strength differences between young and elderly participants for maximum voluntary left elbow flexion. Representative examples from one elderly (Panel A) and one young subject (Panel B) illustrating five traces each for EMG signals (top traces, expressed in millivolts, mV) and Force (bottom traces, in Newtons, N) generated during maximum voluntary elbow flexion.

### 2.3.2 EEG Spectral Analysis

Power spectrum analysis from EEG collected over contralateral (right) primary sensorimotor area indicated, the total power output from cortical oscillations for the left isometric elbow flexion task, elderly and young subjects did not show significant differences in the sub-maximal MVC levels except for the high force exert (for MVC 80%,  $525.3 \pm 156.3 \mu V^2$  vs.  $175.39 \pm 31.62 \mu V^2$ ;  $t_{0.05, 46} = 2.22$   $p = 0.015$ ) (Figure 7).

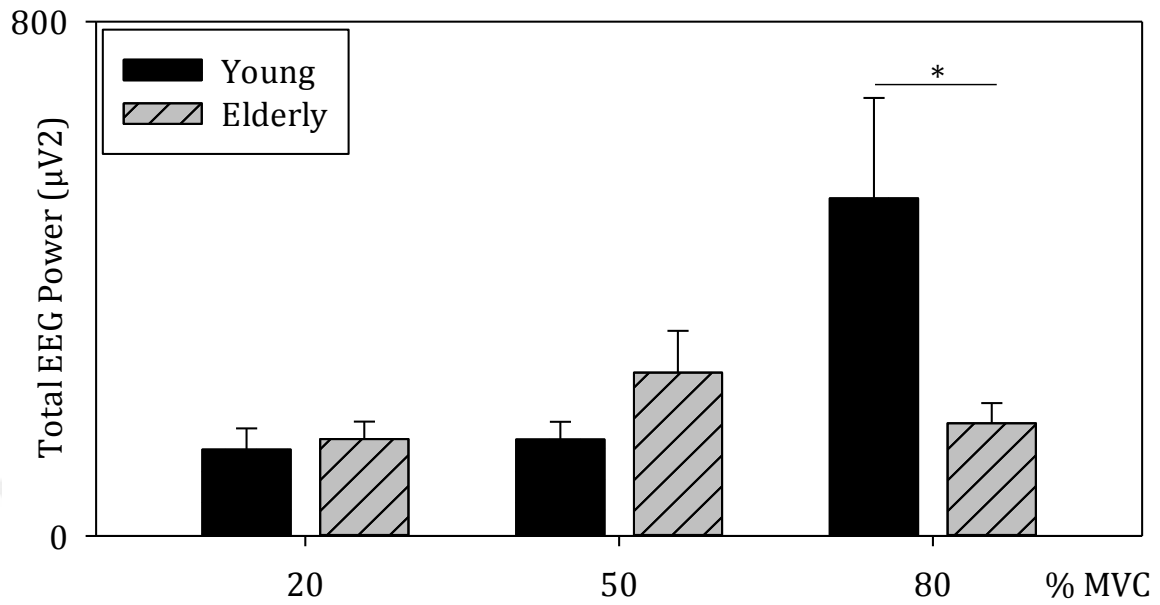


Figure 7. Total EEG power output (in  $\mu V^2$ ) for low (20%), medium (50%) and high (80%) force levels showed significant difference between both groups for only high force exert ( $525.3 \pm 156.3 \mu V^2$  vs.  $175.39 \pm 31.62 \mu V^2$ ,  $p = 0.015$ )

By classifying individual brain bands (Table I) to show how particular frequency intervals contributed to the overall EEG power, both absolute and relative EEG power magnitudes for each band were calculated. Absolute magnitudes were significantly lower in elderly for alpha ( $44.93 \pm 18.34 \mu V^2$  vs.  $17.36 \pm 2.59 \mu V^2$   $p = 0.05$ ) and gamma bands ( $201.72 \pm 116.37 \mu V^2$  vs.  $29.89 \pm 4.95 \mu V^2$   $p = 0.047$ ) (Figure 8, **lower panel**) in left elbow flexion. On the other hand, relative EEG power as the percentage of the total power, showed highly significant differences in beta band, with elderly showing higher relative beta band activity for both low ( $22.9 \pm 2.5 \%$  vs.  $34.6 \pm 2.6 \%$   $p = 0.004$ ) and medium ( $21.1 \pm 2.6 \%$  vs.  $29.8 \pm 2.3 \%$   $p =$

0.024) force levels (

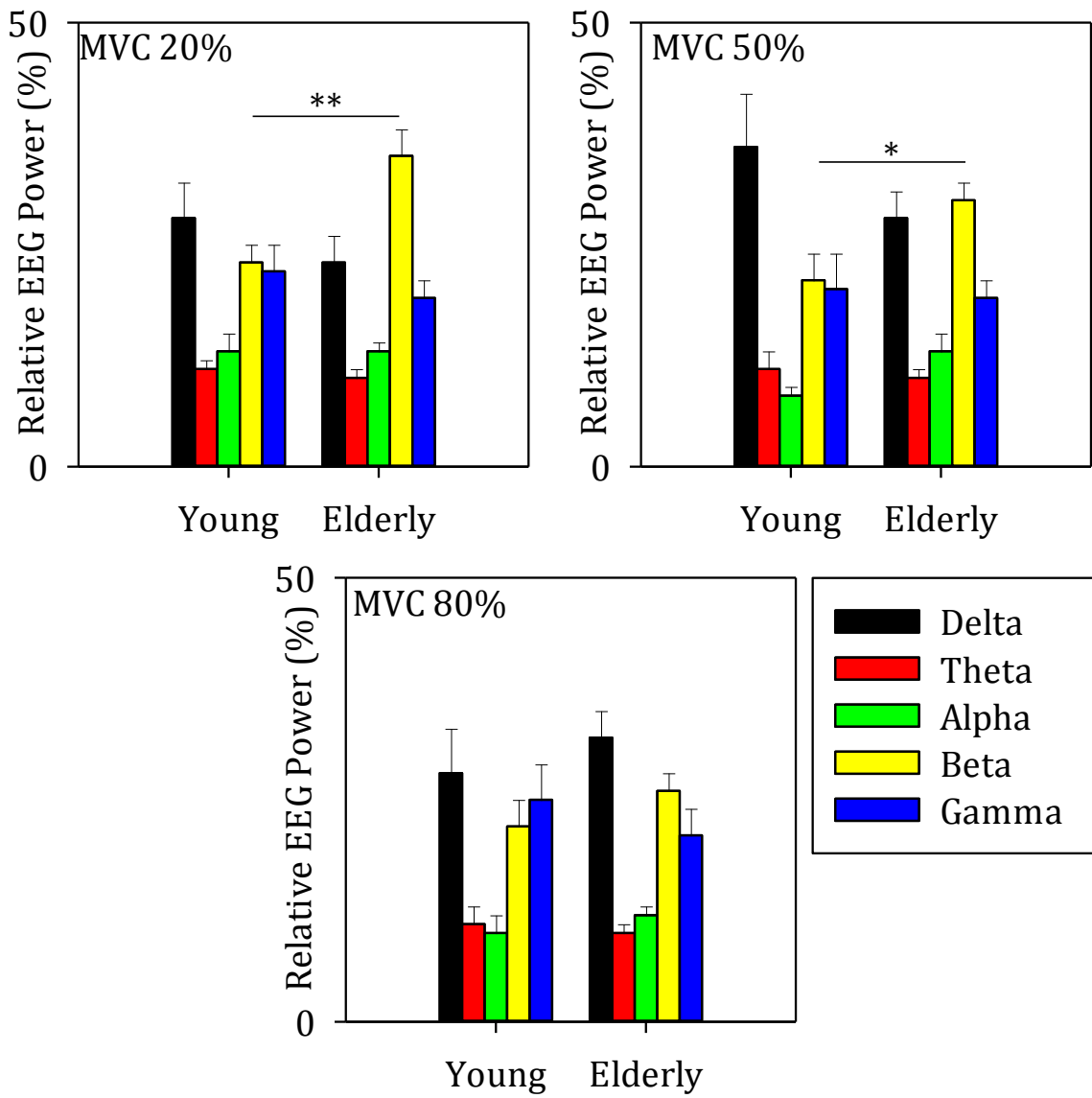


Figure 9).

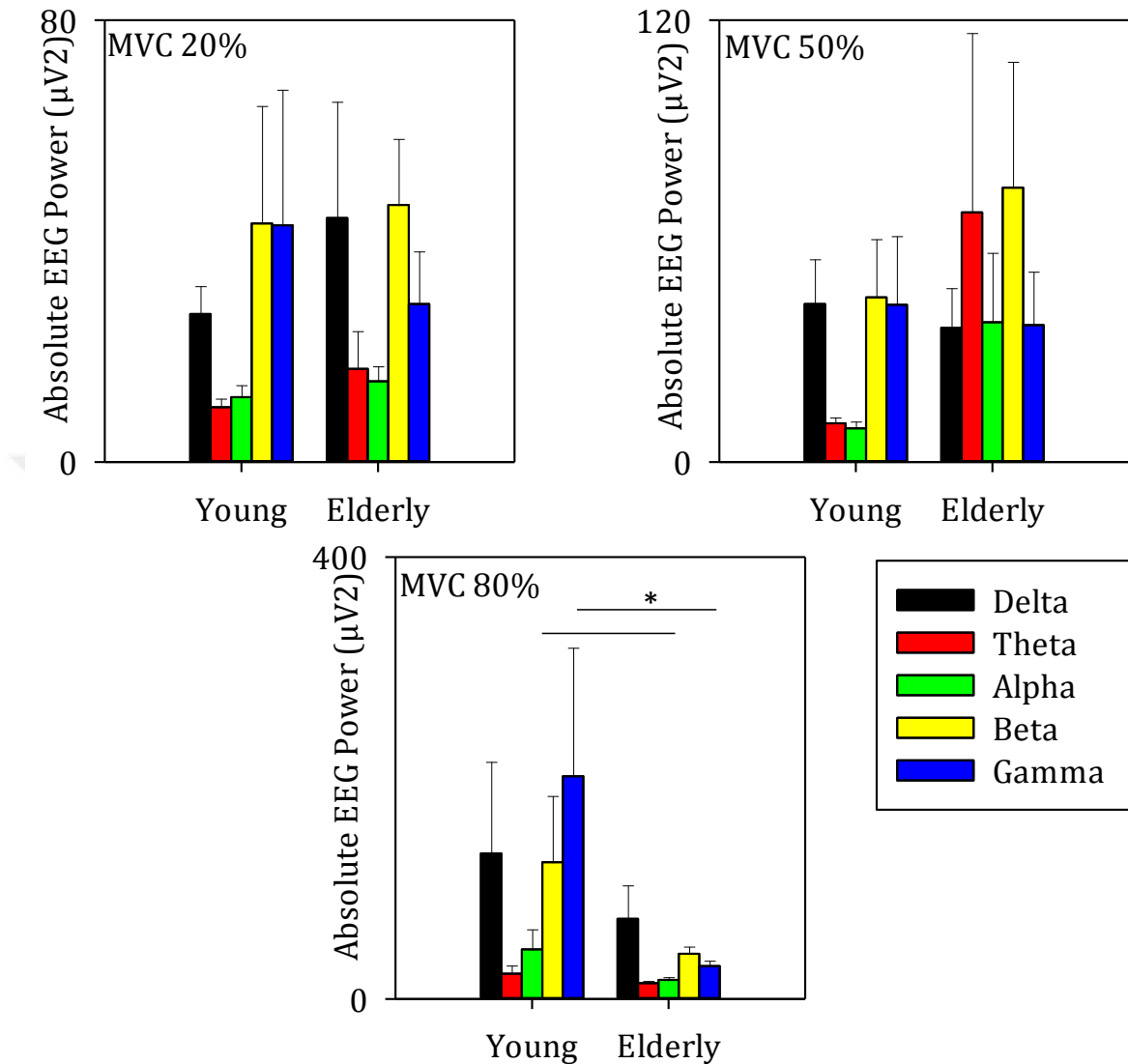


Figure 8. Absolute EEG Power, calculated from sub-maximal voluntary contractions showed no significant differences except 80% of maximum voluntary force, where both alpha and gamma bands showed significantly ( $*p < 0.05$ ) lowered EEG power for elderly.

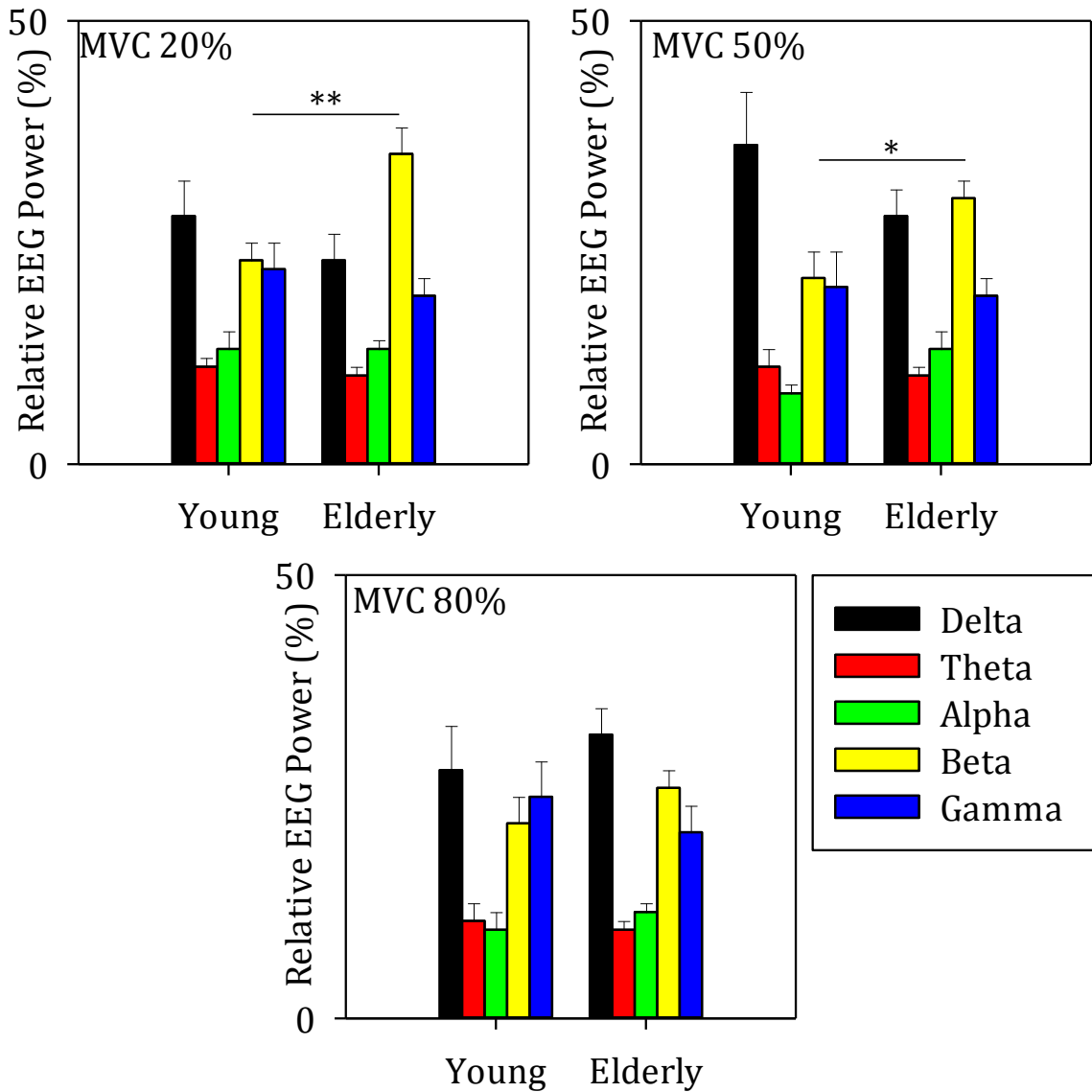


Figure 9. Relative EEG Power, calculated from sub-maximal voluntary contractions showed significant differences for both low and medium force levels in beta band, with elderly having highly significant elevation (\*\* $p < 0.01$ ) at MVC 20% and significant elevation (\* $p \leq 0.05$ ) at 50% MVC during elbow flexion task.

In order to check if any particular brain band had a correlation with exerted force levels, a simple vector representation showing the “trend” was calculated. For absolute EEG power, young subjects had all brain bands positively correlated with the exerted force (up from 50% to 80% MVC), whereas elderly showed positive

correlation only in the Delta band in the place of faster brain bands (Figure 10). For relative EEG power, young subjects had their Alpha, Beta and Gamma power decreased, which compensated by Delta power increase for medium (50% MVC), whereas high force showed the exact opposite. Elderly had their Delta band increase positively correlated with higher force output, in the expense of lowered faster brain bands, except for the 80% MVC in Gamma band. Theta band for both groups did not show any changes for different levels of force (Figure 11).

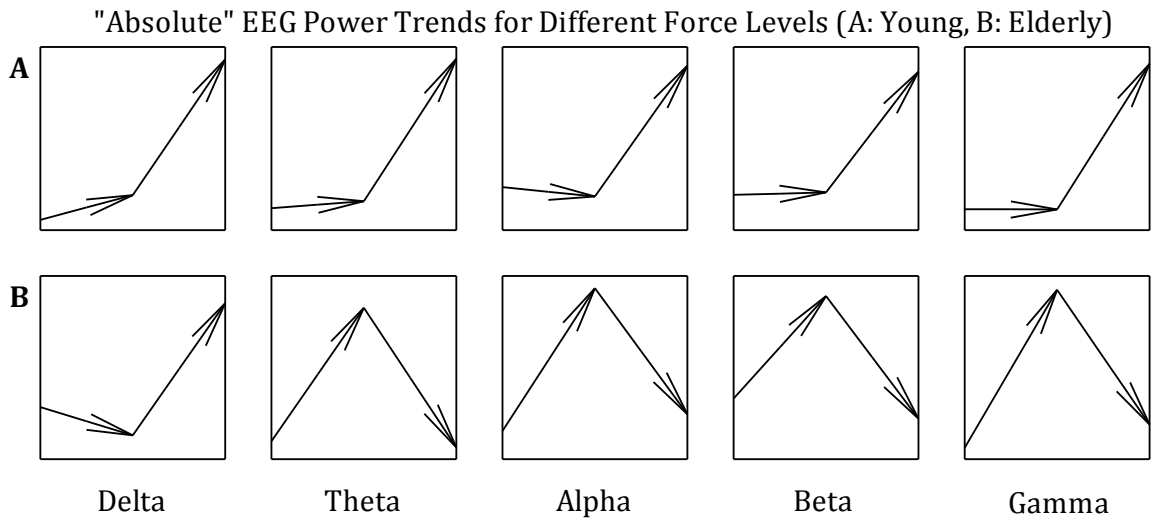


Figure 10. Representation vectors for absolute EEG power trending for different force levels. In each panel, first vector shows the change from 20% to 50% MVC, and the second vector shows from 50% to 80% MVC. Young subjects had all brain bands positively correlated with the exerted force going up from 50% to 80% of their maximum, whereas elderly showed positive correlation only in the Delta band in the place of faster brain bands.

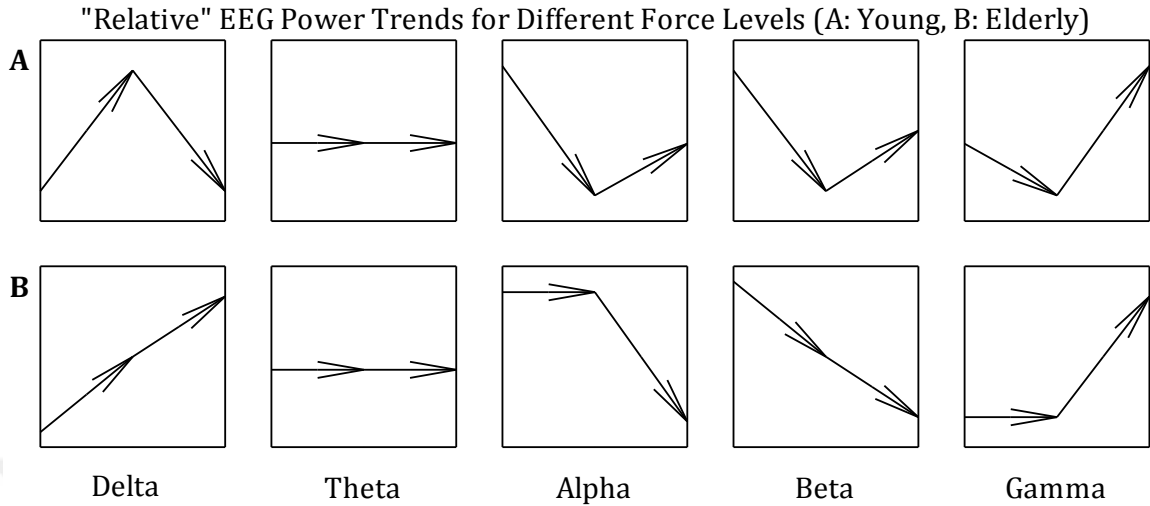


Figure 11. Representation vectors for relative EEG power trending for different force levels. In each panel, first vector shows the change from 20% to 50% MVC, and the second vector shows from 50% to 80% MVC. Young subjects had their Alpha, Beta and Gamma power decreased, which compensated by Delta power increase for medium (50% MVC), whereas high force showed the exact opposite. Elderly had their Delta band increase positively correlated with higher force output, in the expense of lowered faster brain bands, except for the 80% MVC in Gamma band. Theta band for both groups did not show any changes for different levels of force.

## 2.4 Discussion

This study investigated a direct young-elderly cortical oscillatory power changes with different (low, medium, and high) levels of exerted force, during a voluntary motor action. The study had the following major findings: (i) Elderly individuals were weaker for proximal (elbow flexion) muscle groups. (ii) Elderly individuals had lowered total EEG power output for higher force demanding task. (iii) Relative EEG power in Beta band significantly elevated for elderly group. These findings suggest that, there may be significantly different age-related cortical reorganization happening, which systematically shifts between EEG power frequencies.

Elderly group having significantly lower strength for voluntary elbow flexion task, assumes that muscle atrophy (Narici et al. 2003) as well as other central nervous systems such as lack of voluntary activation levels of the (flexor) muscles might directly affect the force output (Yue et al. 1999). Jakobi and Rice presented that elbow flexion and elbow extension MVC's are significantly impaired in elderly, which correlates with the findings here (Jakobi and Rice 2002).

Absolute EEG power levels for both groups did not differ significantly, except for the high (80% MVC) demanding task. This is similar what Kamp et al. found on less demanding tasks and Stackhouse et al. found while subjects were challenged with more demanding flexion tasks (Kamp et al. 2011; Stackhouse et al. 2001). The present study did not allow for participants to get fatigued, as the contractions last no longer than 10 seconds with around 1 minute of rest time between, but fatiguing might cause this difference became even larger for higher demanding tasks (Stackhouse et al. 2001). This may be attributed that elderly had impaired central activation for such demanding tasks.

Previously, it was demonstrated that in healthy young people not only is there a linear relationship between the amplitude of motor activity-related cortical potential (on EEG) and voluntary activation of upper limb muscles (Siemionow et al. 2000). The absolute EEG power results showed similar patterns for the young, but such correlation could not be found for elderly (Figure 10). This result was highly correlated with the total EEG power output between two groups. For young, no significant difference in EEG power output found when they were asked to increase their force output from 20% to 50% MVC, but there was significant difference for all

brain bands when the exerted force levels were going up from 50% to 80% MVC. Elderly, on the other hand showed positive correlation in Delta band only, while the power levels on other bands were not correlated. EEG power correlation in Delta band might suggest that age-related cortical reorganization happening in the elderly for demanding task. It was previously shown that slower EEG power bands having the highest magnitudes (Bayram et al. 2010). This shift in the oscillatory signal to the slower frequencies revisits previous studies, where lower frequencies having the highest magnitude might be used to compensate for the stronger descending signal (Brown 2000; Lim et al. 2011; Gola et al. 2012). Slowing of oscillatory activity has generally been linked to progressive motor-unit loss associated with healthy aging (Brown et al. 1988; Doherty et al. 1993).

Relative EEG power estimation showed the most significant difference between groups for low (20% MVC) and medium (50% MVC) force output, in the Beta band. Witte et al. had similar results with elderly having greatly significantly ( $p < 0.01$ ) high Beta band activity for low force output (Witte et al. 2007). This study extended this finding with significant difference also in the Beta band for medium force output.

Figure 11 shows young subjects had their Alpha, Beta and Gamma power decreased, which compensated by Delta power increase for medium (50%), whereas high force showed the exact opposite. This also correlates with Ho et al. showing Alpha and Beta decreased for less force demanding tasks (Ho et al. 2012). In line with absolute EEG power levels, elderly had their Delta band positively correlated with higher force output, in the expense of faster brain bands. A small increase in Gamma band for the 80% MVC could be negligible and might be due to the constant focus on the

screen to match their sub-maximal target levels, which Muller et al. showed Gamma band increase with visual stimuli (Muller 2000). Relative EEG power in Theta band for both groups did not show any changes with different levels of force, which usually associated with navigation and learning (Buzsaki 2005) and had similar results with previous research (Ho et al. 2012).

## **2.5 Conclusion**

The relationship between EEG-recorded cortical waves and frequency modulation of upper limb muscles has been explored at different levels of voluntary effort. Total EEG power output for high demanding tasks showed that aging had weakened cortical oscillations that caused unable to maintain necessary descending command. This impairment might be a potential mechanism associated with aging related muscle weakness. On the other hand, highly elevated Beta band EEG power spectra for low demanding tasks might be a good predictor for predicting early aging.

## **CHAPTER III**

### **WEAKENING OF CORTICOMUSCULAR COUPLING IN AGING**

#### **3.1 Introduction**

Aging comes with neuromuscular and musculoskeletal system degeneration thus has a direct effect on motor performance and quality of daily lives. Numerous studies have reported evidence of age-related structural and functional degenerations in the central nervous and muscular systems that contribute to motor function impairment. While the most commonly implicated mechanism involves muscle atrophy (Doherty 2003; Faulkner et al. 2007), following death of spinal motor neurons (Faulkner et al. 2007), peripheral degeneration only partially explain aging-related weakness (Doherty 2003; Young et al. 1985). Changes within the central nervous system, both microscopic and macroscopic, exaggerate the deficit. Degenerative processes include reduction in gray matter volume (Good et al. 2001), fewer motor cortical neurons (Henderson et al. 1980), decrease in synaptic density (Haug and Eggers 1991), loss of white matter integrity (Davis et al. 2009; Lindberg

et al. 2010), lowered neurotransmitter levels (Gu 2002) and greater variability in motor unit behavior (Laidlaw et al. 2000).

Techniques that generate real-time information of central-peripheral communication in motor control may best address this question. Functional coupling is such method. Functional coupling between the brain and muscle can be estimated by calculating coherence in frequency domain between brain and muscle signals. This coherent measure has been suggested to solve the “binding” problem, acting as a mechanism to link information related to the same function but processed in different neural populations (Salenius et al. 1997; Thiele and Stoner 2003). Coherence between Electroencephalography (EEG) and Electromyography (EMG) signals at particular frequency bands has been reported by many studies (Baker et al. 1997; Gross et al. 2000; Yang et al. 2011) to demonstrate functional coupling between the brain and muscle. It has been previously shown that the level of brain-muscle or corticomuscular coherence (CMC) increases with the level of EMG (Kilner et al. 2000), indicating a dependence of muscle output on strength of brain-muscle functional coupling or CMC.

Aging related effects on functional coupling have been explored preliminarily. Few recent studies have attempted to investigate CMC in aging. Kamp et al. (Kamp et al. 2011) showed slowed and shifted CMC in people with more advanced ages compared with young individuals but they did this only on force level, thus could not determine if the level of force is dependent on strength of CMC. Others (James et al. 2008) compared CMC among subjects in ages from infancy to elderly and reported prominent differences during motor development in children. Although

CMC changes with aging, a direct comparison of young and elderly is missing. Moreover, it is unknown if a positive relationship between the CMC and muscle output is maintained in the elderly. Addressing these questions will help understand whether changes in functional coupling across increasing muscle output may partly explain muscle weakness in elderly.

Therefore, the purposes of this study were (1) to estimate strength of CMC in elderly by calculating EEG-EMG coherence during voluntary motor performance and compare the CMC values between elderly and young participants, and (2) determine the relationship between the CMC and voluntary muscle force by determining the CMC at three force levels, and make comparisons on the CMC values and relationship between the two groups. Findings of this research are likely to contribute to a better understanding of neural mechanisms underlying motor function deficit, especially weakness in aging and its possible recovery following training the neuromuscular system.

## **3.2 Methods**

### **3.2.1 Subjects**

Please refer to Chapter 2, section 2.2.1 “Subjects” for details.

### **3.2.2 Data Collection**

Please refer to Chapter 2, sections 2.2.2 “Elbow Flexion (EF) Strength and Submaximal EF Contractions”, 2.2.3 “EMG” and 2.2.4 “EEG” for data collection details.

### 3.2.3 EEG – EMG coherence

The EEG and EMG data with artifacts related to electrical stimulation was visually inspected and carefully excluded for the corticomuscular coherence analysis. Sampling rate of 3 muscles was reduced to 250 Hz to match EEG recording's sampling frequency. In each stage, autospectrum and cross-spectrum of the EEG and rectified EMG were calculated with a 256-point fast Fourier transform with Hamming window. It has been shown that rectification of the EMG alters EMG power spectrum but does not change EEG-EMG coherence; further, the rectification makes the coherence peaks more clear (Yao et al. 2007). A simple coherence calculation between EEG channels and the EMG of each of the two elbow flexor muscles was computed as follows (Rosenberg et al. 1989). Assume that there are two signals  $l$  ( $l = 1, 2$ ), and  $F_{i,l}(f)$  are the 256 points FFT derived from signal  $l$  over the  $l$ th 256-point section; then the cross-spectrum is:

$$X_{12}(f) = \frac{1}{L} \sum_{l=1}^L F_{1,l}(f) F_{2,l}^*(f)$$

where \* denotes complex conjugate. The auto-spectrum of one signal is:

$$A_i(f) = \frac{1}{L} \sum_{l=1}^L F_{i,l}(f) F_{i,l}^*(f)$$

Thus the coherence is given by

**Eq. 1**

$$C_{12}(f) = \frac{|X_{12}(f)|^2}{A_1(f)A_2(f)}$$

The significance of the coherence measurement was estimated. According to the null hypothesis that the two signals were independent, coherence above  $Z$  was considered significant at  $P < \alpha$ , where

**Eq. 2**

$$Z = 1 - \alpha^{1/(L-1)}$$

A non-overlapping moving window size of 0.5 s was used for coherence analysis and coherence was considered significant when the value was over 95% confidence level. After computing coherence of all the EEG channels with EMG of each of the two flexor muscles, coherence maps were generated to demonstrate which channels on the scalp at which frequency exhibit significant coherence with a given muscle. Due to the volume of information, especially the large number of EEG channels, the coherence values of EEG channels overlying primary sensorimotor function-related brain regions with each of the three muscles (BB, BR or TB) were grouped into five scalp areas for statistical comparisons (ten electrodes in each scalp area): left, right, frontal, central and parietal. For this research, coherence was calculated between EEG collected over the right primary sensorimotor area and EMG of each of three muscles **Error! Reference source not found.** (Figure 12).

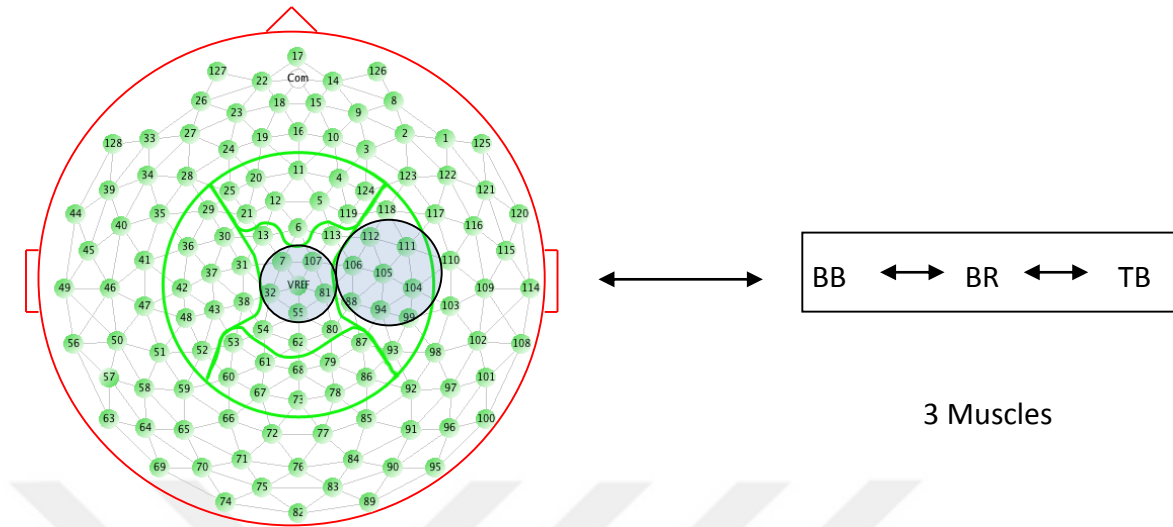


Figure 12. The EEG-EMG coherence, EEG areas and selected muscles.

### 3.2.4 Statistical Analysis

A repeated-measures 2-way ANOVA, ordinary linear regression, t-test and F-test were adopted for coherence comparisons between the trials, force levels, sensorimotor areas and muscles using IBM SPSS Statistics 21.0 (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) Statistical figures have been created with Sigmaplot (Systat Software, San Jose, CA) software. In addition to analyzing amplitude of the coherence that above the significance level (95% confidence), the number of frequency bins reached the significance level was also quantified and analyzed. Since the frequency resolution was about 1 Hz, each 1-Hz step from 15 to 35 Hz consisted of one bin. The elbow flexion force, force variation (SD), and EMG of the relevant muscles were compared using paired t-tests. All figures have been created with Sigmaplot (Systat Software, San Jose, CA) software.

### 3.3 Results

#### 3.3.1 Corticomuscular Coherence

Corticomuscular coherence is defined as the neural connection quality between the brain and the muscles, by evaluating EEG and EMG data. Robust corticomuscular coherence at Beta (20-30 Hz) band was observed between EEG acquired at right side of M1 location and EMG of BB muscle in a majority of young subjects. However, no such significant EEG-EMG coherence was present in the elderly group (Figure 13). The coherence was stronger for both groups at higher EF force levels with the highest coherence value occurring at 80% MVC level. Figure 14 shows group results indicate (i) corticomuscular coherence was weaker in the elderly and (ii) the level of the coherence was proportional to the exerted force.

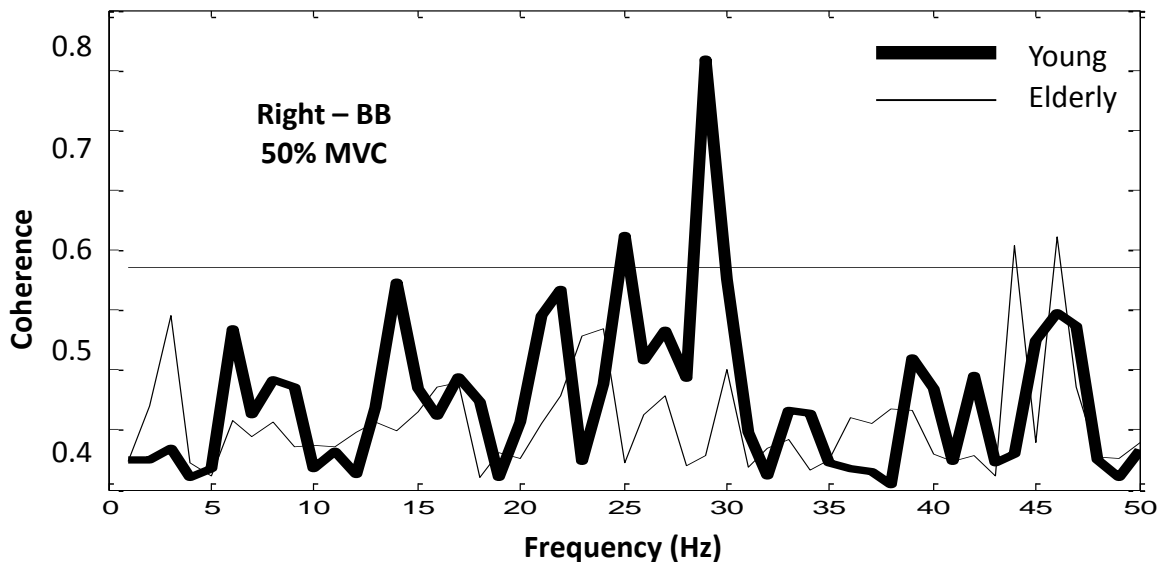


Figure 13. A coherence spectra map showing one subject from each group. Young has higher coherence between right side over the right sensorimotor area and BB muscle throughout the beta band (15-35Hz) with the highest coherence occurring at 28Hz. Elderly subject has the highest coherence at 24.5Hz, in the beta band.

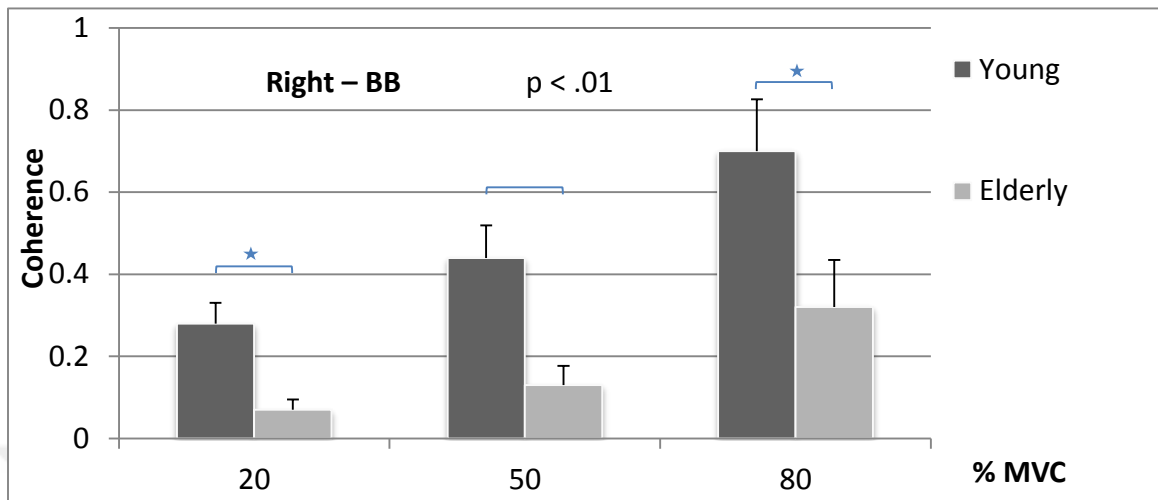


Figure 14. Coherence for both groups for different exerted force levels between right side over the right sensorimotor area and BB muscle throughout the beta band (15-35Hz. Level of coherence was proportional to the exerted force for both groups.

Figure 15, shows z-normalized coherence maps based on the selected EEG channels with EMG of the BB, BR and TB muscles (first, second and third columns, respectively) for elderly (first row) and young (second row) subjects at the beta band (15-35 Hz). The scale bar on the left shows color-coded normalized coherence values. The figure shows that young subjects have higher coherence levels compared to elderly on every muscle for MVC. The strongest MVC coherence with both flexor muscles can be seen in right-parietal area for elderly, which is shifted more parietally compared to young group's spatial maps.

Corticomuscular coupling versus force for BB muscle at 80% MVC shows strong linear association for both groups (Figure 16). Strong positive correlation between EEG-EMG coherence and force suggests the force output is highly dependent on corticomuscular coupling.

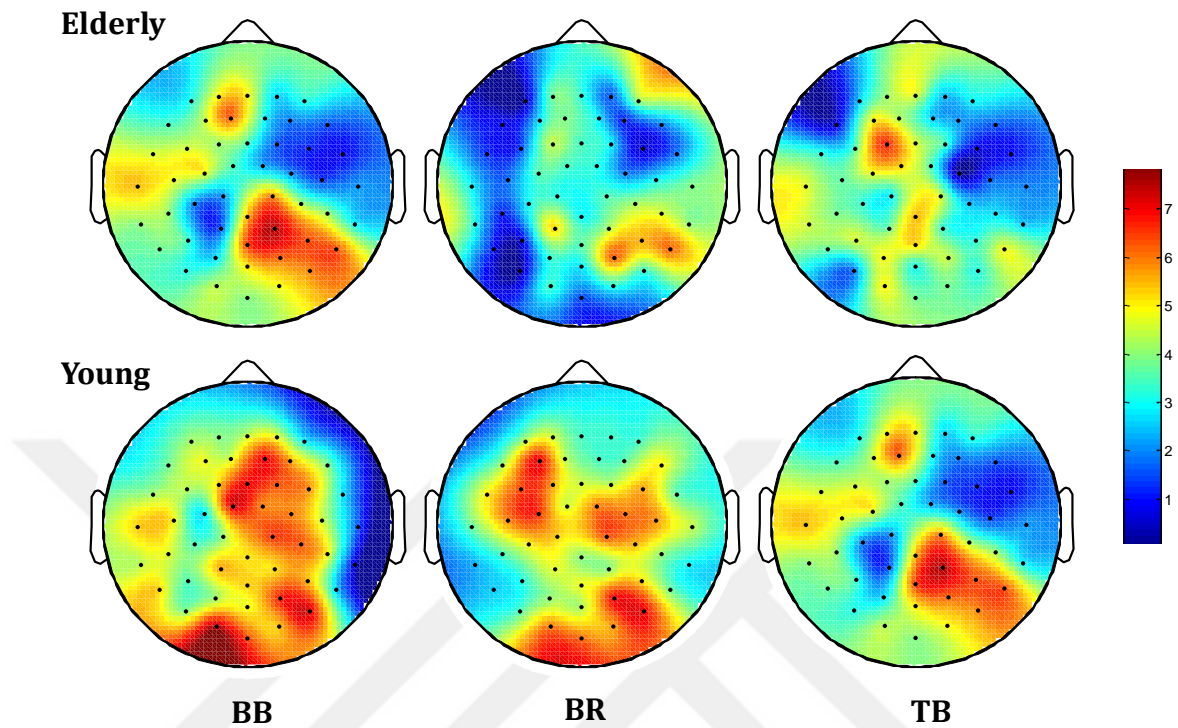


Figure 15. Z-normalized EEG-EMG coherence maps for both groups, 3 muscles show young subjects have higher coherence levels compared to elderly on every muscle for MVC. The strongest MVC coherence with both flexor muscles can be seen in right-parietal area for elderly, which is shifted more parietally compared to young group's spatial maps. Blue is weak and red is high coherence.

### 3.4 Discussion

This study is the first to investigate direct young-elderly functional coupling changes with different (low, medium, and high) levels of exerted force. The study had the following major findings: (i) the CMC was significantly lower in the elderly compared to young subjects at all force levels examined and for all three (BB, BR and TB) muscles evaluated. (ii) There was a proportional relationship between the CMC and force with stronger force being associated with higher levels of CMC for both groups.

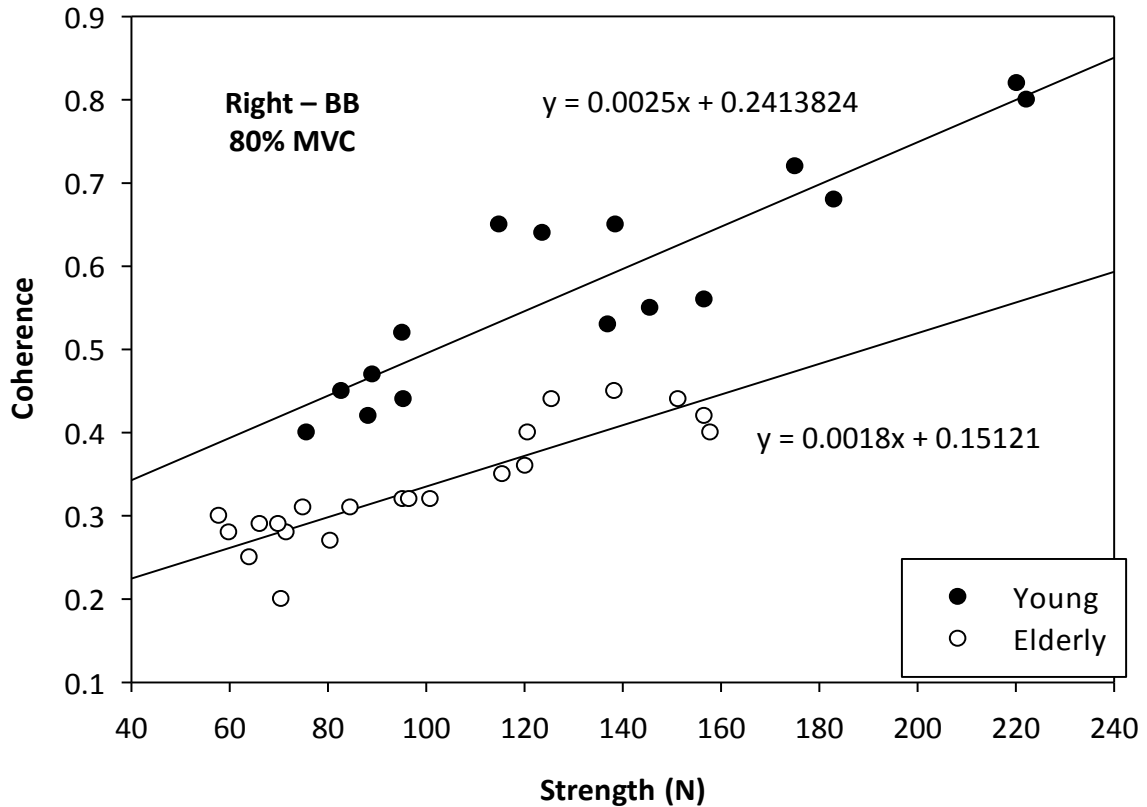


Figure 16. Coherence versus Strength for both groups. Although the CMC is lower in the elderly as well as strength output, strong Strength – CMC positive relationship suggests, force output is (near) linearly correlated with CMC for both groups.

Corticomuscular coherence was significantly smaller in elderly patients suggests the weakened or impaired corticomuscular binding. This impairment could potentially be one of mechanisms contributing to age-related muscle weakness, loss of motor skills and coordination. Findings about force-coherence levels also revisits Kilner et al. (Kilner et al. 2000), which states the level of EEG-EMG coherence increases with the level of EMG.

The findings also correlate with earlier studies that beta-band oscillations play the leading role for isometric voluntary upper-limb movements in healthy subjects (Conway et al. 1995; Brown et al. 1998; Doppelmayr et al. 1998; Neubauer et al.

2004; Omlor et al. 2011), but also slowed/shifted with age (Kamp et al. 2011). It should be noted that aging comes with muscle atrophy which also changes muscle structure and fiber type composition. By age, muscles get 25-35% smaller and have significantly more fat and connective tissue than limb muscles compared to young. More importantly, fiber type composition of elderly people reveals that type 2 (fast-twitch) fibers are affected but type 1 (slow-twitch) fibers are mostly intact (Lexell 1995). This atrophy causes reduction mainly in both number and size of type 2 muscle fibers, which may have an address the slowed/shifted CMC with aging.

Comparing elderly findings with stroke patients, whereas beta-band coherence reported to be not differentiated (Fang et al. 2009) between age-matched patients and controls, it is safe to assume that stroke has a different type of deficiency effect on CMC.

CMC for both the BB and BR muscles were significantly higher than CMC of TB muscle. This is expected as for a typical EF movement, BB and BR are agonists, whereas TB is the antagonist muscle to elbow flexion, controlling the fine tuning (braking) by working against but also in tandem. CMC differences between groups were getting higher for BB muscle, compared to other muscles. This is also expected as BB is the main contributor for to EF task (Levin et al. 2000).

High positive correlation between beta band CMC and different levels of EF force output for both groups suggests correlates with earlier findings (Chakarov et al. 2009). It may also suggest that the impairment in the elderly is occurring more cortically, not more peripherally as the muscle reacts to the descending cortical signals similar to in young population.

There were some limitations to this study. EEG and EMG signals, mostly for elderly subjects, were noisy. This may be due to increased skin impedance in aging. Precautions were taken to minimize the noise during data collection: The subjects were required sit comfortably but quiet, not biting, leaning forward, moving head or body, avoiding excess eye blinking or teeth biting when contracting. They were also encouraged to do their best and concentrate on the task. Practice runs were performed, especially for different levels of MVC EF, until they were fully certain of the task. At the post processing stage, about 15% of total trials were excluded, which included observable artifacts.

### **3.5 Conclusion**

Functional corticomuscular coupling and coupling between synergist muscles during voluntary elbow flexion are impaired in elderly. This impairment could potentially be one of mechanisms contributing to age-related muscle weakness, loss of motor skills and coordination. High positive correlation between EEG-EMG coherence and force suggests that the coherence can serve as a predictor of muscle strength in aging.

## **CHAPTER IV**

### **NEUROPHYSIOLOGIC MARKERS OF AGING-RELATED WEAKNESS**

#### **4.1 Introduction**

The study described by the last chapter found that although both young and elderly demonstrate a linear relationship between CMC and elbow flexion force, the level of the CMC is significantly lower in elderly, indicating perhaps weakened descending command or reduced ability by these individuals to voluntarily activate the muscles. The level of descending command can be influenced by motor cortex excitability, inter or intra hemispheric inhibition, or intra hemispheric facilitation to the motor cortex projecting to the performing muscle. Therefore, the major goal of the study presented by chapter IV is to determine if these factors are changed in the elderly population using Transcranial magnetic stimulation (TMS), a standard non-invasive method to test brain-to-muscle coupling in rest state (using TMS and EMG).

TMS is a technique widely used to study excitability of human brain, such as primary motor cortex (M1) and interacting inhibitory and excitatory effects on the M1 by other cortical areas in the motor control network. TMS uses electromagnetic induction through an induction coil by changing its magnetic field thus creating an

electric current which then causes depolarization in the neurons (Theodore 2002). Since it is non-invasive and has minimal discomfort to the subject, it is one of the most influential new methods to explore intra- and inter-cortical excitability/connectivity, or corticomuscular functional connectivity.

A number of TMS parameters can be defined for different outcomes. When TMS is delivered to certain motor cortex regions in the brain, Motor Evoked Potentials (MEP) can be recorded from a muscle or muscles as special form of surface EMG as a result of activating the M1 neurons controlling the muscle(s) by the TMS. Since MEP amplitude is correlated with motor excitability and electromagnetic output from the TMS delivery equipment can be increased or decreased, the MEP response from the muscle is changed accordingly, thus TMS offers a quantitative way to detect induced muscle activity. On the other hand, MEPs should be standardized among subjects, as every person has different motor excitability (Pitcher et al. 2003). Motor threshold (MT) is defined as ~50mV peak-to-peak MEP amplitude required for evoked muscle response which is obtained at a given stimulus intensity (Kammer et al. 2001). MT is calculated as resting or active motor threshold (RMT and AMT, respectively) which shows the calculated intrinsic or extrinsic excitability based on the subject's state of contraction (Rossini et al. 1991; Ziemann et al. 1996). When a sub-threshold conditioning pulse precedes a supra-threshold test pulse at short interval (1-5ms) at a same location, the evoked muscle response from the test pulse is inhibited, a phenomenon termed as intra-cortical inhibition (ICI), while when it precedes at longer intervals (7-15ms), the response from the test pulse is facilitated, a phenomenon called intra-cortical facilitation (ICF) (Ziemann et al. 1996). While ICI

is generally believed to be mediated by GABA<sub>A</sub>ergic receptors (Florian et al. 2008), ICF is based on N-Methyl-D-Aspartate (NMDA) receptors and glutamatergic interneurons (Ziemann 2004). Since the inhibitory and excitatory interneurons are connected with the M1, activating these neurons by the conditioning pulse preceding the test pulse would allow us to see the level of inhibition or facilitation and the difference in the level between elderly and young populations.

The significance of degenerative processes within the central nervous system has long been established in aging (Semmler et al. 2006). Yet the role of M1 has received limited attention with regards to age-related loss in muscle strength. One of the reasons may be that traditionally M1 is viewed as being critical for skill rather than muscle strength (Remple et al. 2001).

There are conflicting reports as if M1 relates to loss of muscle strength with aging. For instance, corticospinal control was shown to get impaired by aging (McGinley et al. 2010; Sale and Semmler 2005; Peinemann et al. 2001; Pitcher et al. 2003), conversely, there is also findings suggesting that it may not change (Oliviero et al. 2006; Talelli et al. 2008b). Regarding intra-cortical physiology, similarly, some (Oliviero et al. 2006) claimed that advancing age has little effect on ICI, while others report a reduction (Peinemann et al. 2001; Marneweck et al. 2011). There is also no common findings as if inter-hemispheric interactions remain unchanged (Hinder et al. 2010) or become less inhibitory (Talelli et al. 2008b) with aging.

It still remains unknown what age-related adaptations in M1 underlie age-related muscle weakness in the literature. By defining what specific markers, like an

increase or a decrease in corticospinal, intra-cortical and inter-hemispheric outcomes may predict elderly muscle strength.

The purpose of Chapter IV was to define correlates of proximal muscle strength in M1, studied using TMS, in elderly versus younger participants. Strength of left elbow flexors (with the focus on the main flexor, biceps brachii (BB) was measured during maximal voluntary isometric contraction. Its representation in contralateral M1 was examined with TMS; excitability is defined at the corticospinal, intra-cortical and inter-hemispheric levels. Specifically, corticospinal excitability was noted as intensity of TMS required to evoke pre-defined minimal and maximal responses in BB. Inhibition and facilitation of the maximal evoked response was measured as ICI and ICF using paired-pulse TMS. Transcallosal interactions were measured as inter-hemispheric inhibition (IHI); IHI was calculated as attenuation of maximal evoked response in BB when a preceding conditioning pulse was applied to the opposite M1.

TMS measures of corticospinal, intra-cortical as well as inter-hemispheric excitability to predict age-related differences in strength of elbow flexors because these mechanisms interact to define motor output of M1 (Daskalakis et al. 2002; Udupa et al. 2010; Chen 2004). Since their adaptations are witnessed with aging (Talelli et al. 2008b; Sale and Semmler 2005; Peinemann et al. 2001; Oliviero et al. 2006; Marneweck et al. 2011; Kossev et al. 2002; Hinder et al. 2010) and with strength training-related gains (Weier et al. 2012; Griffin and Cafarelli 2007; Beck et al. 2007; Lee et al. 2009; Kidgell and Pearce 2010; Goodwill et al. 2012), in theory, aging-related effects on strength might similarly be manifested at these levels. By

highlighting the relation between adaptations in M1 to age-related strength, the present study serves to broaden the scope of M1's role, traditionally viewed as being critical for dexterity (Remple et al. 2001; Jensen et al. 2005).

## **4.2 Methods**

### **4.2.1 Subjects**

Please refer to Chapter 2, section 2.2.1 "Subjects" for details.

### **4.2.2 Data Collection**

TMS was applied using figure-of-eight coils (70 mm) connected to one or two Magstim devices (200<sup>2</sup> and Bistim device, Magstim Co., Dyfed, UK). The coil was placed tangential to the scalp with the handle oriented backwards and laterally at 45° from the midsagittal axis (Figure 17-A). Positioning of the coil was guided by a frameless stereotaxy (Brainsight, Rogue Research Inc, Montreal, Canada) that defined the online relationship between the position of the subject's head, the coil and the cortical target and updated this information with high spatial resolution (Figure 17-B). Surface electrodes (Ag-AgCl, 8 mm diameter) were placed on the skin overlying the left and right BB to record TMS-evoked muscle responses. EMG responses were amplified, band-pass filtered (10 Hz-2 KHz), digitized (4 kHz; PowerLab 4/25T, AD instruments, Salt Lake City, UT), and stored on a computer for offline analysis (Scope software, version 4.0.8).

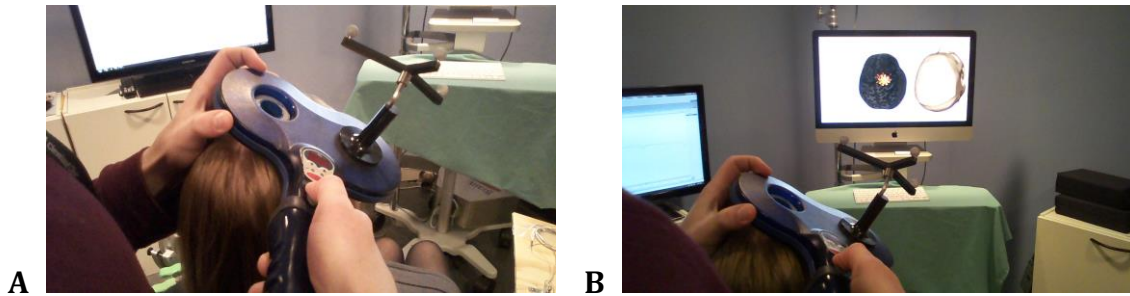


Figure 17. Panel A: TMS coil placement on the head; B: Brainsight neuronavigation system.

Using single-pulse TMS, optimal site in right M1 devoted to the left BB was identified. This site was determined based on elicitation of EMG potentials of at least  $50 \mu\text{V}$  (peak-to-peak amplitude) in three of the five trials in the resting left BB using the lowest TMS intensity (the resting motor threshold). A supra-threshold intensity of TMS, which evoked larger (0.1-0.5 mV) EMG responses in the BB reliably in three of the five trials, was also noted.

Using paired-pulse TMS, intra-cortical excitability in the right M1 was investigated. Paired stimuli were delivered, of which the first was a sub-threshold conditioning pulse (90% of resting motor threshold) and the second a supra-threshold test pulse (evoking 0.1-0.5 mV as above). Inter-pulse intervals of between 1-5 ms and 7-15 ms were selected, which generated maximal intra-cortical inhibition and facilitation, respectively.

Paired-pulse TMS, delivered to both hemispheres simultaneously, tested IHI. Pulses were delivered to the left, then right, M1 at supra-threshold intensity (evoking  $\sim 0.1\text{-}0.5$  mV EMG in the corresponding BB). By preceding the pulse delivered to the left vs. right by 12 ms, the inter-hemispheric effect exerted by the left (dominant) upon the right M1 was measured. Such an inter-hemispheric effect

between bilateral M1s is mediated by transmissions across the corpus callosum (transcallosal pathways) (Udupa et al. 2010; Ferbert et al. 1992; Irlbacher et al. 2007; Chen et al. 2003).

#### 4.2.3 TMS analysis

Outcome measures related to TMS included (i) corticospinal excitability, defined as the resting motor threshold of representation of BB muscle in right M1 (expressed as percent of maximum stimulator output [% MSO]) and supra-threshold TMS evoking a 0.1- to 0.5-mV response (expressed as percent of resting motor threshold); and (ii) ICI, ICF and IHI, expressed as a percent change in EMG response evoked from paired-pulse vs. response from the supra-threshold test TMS pulse. Specifically, the formulae are given below:

**Eq. 3**

$$\text{ICI (\%)} = 100 \times \frac{(\text{Test Pulse} - \text{Paired Pulse})}{\text{Test Pulse}} \text{ EMG response evoked}$$

**Eq. 4**

$$\text{ICF (\%)} = 100 \times \frac{(\text{Paired Pulse} - \text{Test Pulse})}{\text{Test Pulse}} \text{ EMG response evoked}$$

**Eq. 5**

$$\text{IHI (\%)} = 100 \times \frac{(\text{Test Pulse} - \text{BiHemispheric Paired Pulse})}{\text{Test Pulse}} \text{ EMG response evoked}$$

#### **4.2.4 Statistical Analyses**

Variables were compared between elderly and young subjects using one-tailed, independent-samples *t* tests, with the alpha level of significance set at 0.05. To identify predictors of strength of BB across all participants, a multiple-regression analysis using predictors such as age (young or older), intra-cortical excitability and IHI is implemented. Association between muscle strength and TMS variables was explored using bivariate Pearson's correlation. SPSS v16 (SPSS Inc., Chicago, IL) was used for statistical analysis.

### **4.3 Results**

#### **4.3.1 TMS Measures**

Comparison of corticospinal excitability between young and elderly subjects yielded no significant differences. The resting motor threshold of the right M1 for young vs. elderly groups was not different ( $66.5 \pm 3.86$  %MSO vs.  $64.82 \pm 2.52$  %MSO;  $t_{0.05, 46} = 0.39$ ,  $p = 0.7$ ). Similarly, values for supra-threshold TMS intensity in young vs. elderly were comparable ( $126.04 \pm 3.81\%$  vs.  $126.2 \pm 2.15\%$  resting motor threshold;  $t_{0.05, 46} = 0.28$ ,  $p = 0.96$ ).

ICI (Figure 18 **a**) and ICF (Figure 18 **b**) within the right M1 did not differ significantly between groups. Elderly individuals showed comparable ICI as the young ( $72.38 \pm 4.32$  vs.  $74.19 \pm 4.38\%$ ;  $t_{0.05, 43} = 0.28$ ,  $p = 0.78$ ); values of ICF appeared to be greater in the young than in elderly group but results were not significant ( $258.54 \pm 166.6$  vs.  $128.77 \pm 31.15\%$ ;  $t_{0.05, 30} = 0.92$ ,  $p = 0.36$ ) (Figure 18 **b**). Unlike intra-cortical measures, IHI demonstrated marked changes related to

aging. Compared with the young, elderly participants showed a significant degree of inter-hemispheric inhibition ( $51.52 \pm 5.55\%$  vs.  $67.83 \pm 4.74\%$ ;  $t_{0.05, 37} = 2.22$ ,  $p = 0.032$ ) (Figure 18 c).

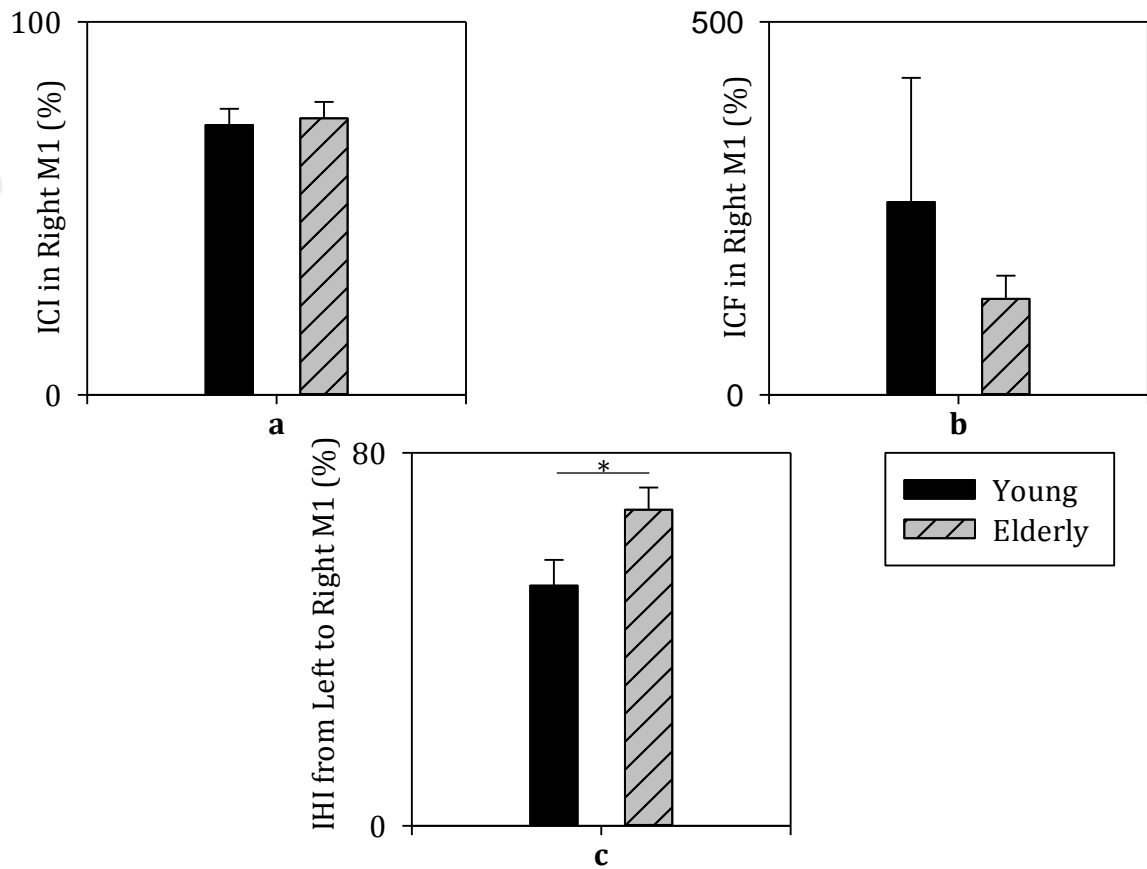


Figure 18. Differences in intra-cortical TMS measures between young and elderly participants. Panels **a** and **b** illustrates that in the right (non-dominant M1), elderly and young subjects do not differ significantly with respect to intra-cortical inhibition or intra-cortical facilitation. Panel **c** illustrates that elderly subjects show significantly greater inter-hemispheric inhibition from the left to the right M1 compared with young participants.

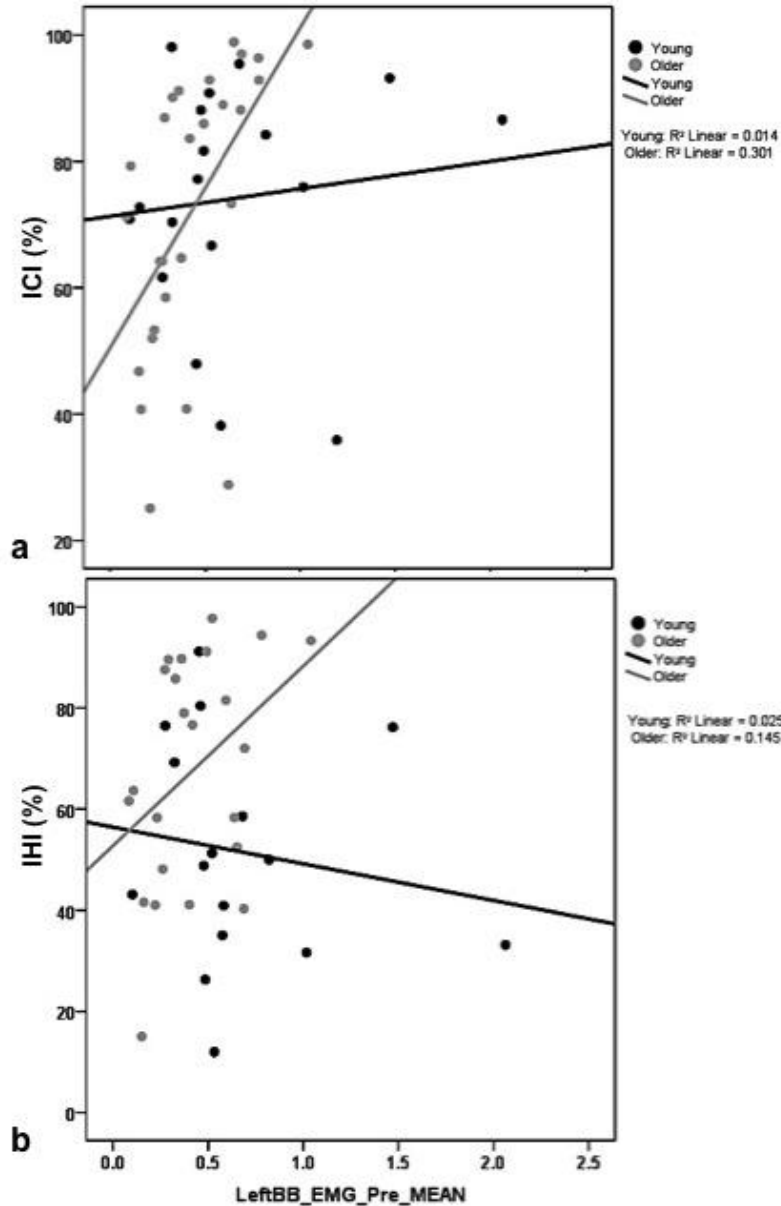


Figure 19. Association between TMS measures and strength in younger and elderly participants. Panel **a** shows the association between intra-cortical inhibition in the right M1 and mean activation of BB during MVC elbow flexion ( $EMG_{Ave}$ ); the association is moderately strong, positive and significant only for the elderly participants. Panel **b** illustrates a positive correlation between inter-hemispheric inhibition in the right M1 and  $EMG_{Ave}$  of BB; again the relation trends towards significance only in elderly participants.

#### **4.4 Discussion**

The purpose of the present study was to investigate the measures of excitability in M1 that explain age-related differences in muscle strength of elbow flexors. Inter-hemispheric inhibition exerted by opposite M1 was exaggerated in elderly versus younger subjects. Inter-hemispheric inhibition (IHI) exerted by opposite M1 of the elderly subjects was exaggerated compared to the younger subjects. Intra-cortical inhibition (ICI) was an indicator of the strength of the elbow flexors. While intra-cortical and inter-hemispheric mechanisms were indicators of elbow flexor muscle strength in elderly subjects, they were not for the young subjects. Therefore, age-related changes in M1 may provide information about the proximal muscle strength in elderly, the same prediction may not be done for the young subjects. The study elaborates the preliminary evidence that M1 may indicate the flexors strength particularly in elderly.

Intra-cortical excitability was an elbow flexors strength indicator. The relationship was obvious in elderly; who showed increased strength of elbow flexors also showed greater ICI and vice versa. Skill learning had significant impact on muscle strength, as strength training is now being considered a form of skill acquisition where new patterns of muscle recruitment are learned (Carroll et al. 2002), and comparable mechanisms of plasticity are witnessed (Kidgell and Pearce 2010). In skilled and experienced musicians, Rosenkranz et al. (Rosenkranz et al. 2007) had increased ICI; higher inhibition is considered as a braking mechanism to stop unwanted spread of activation (Rosenkranz et al. 2007) to antagonists (Hortobagyi et al. 2006) as well as co-activated muscles (Sohn and Hallett 2004),

maximizing the strength of trained muscles. Neuroimaging literature similarly discusses that as the greater force is generated, intensity of activation within M1 increases linearly (Post et al. 2009; Benwell et al. 2007); whereas, as an individual fatigues while sustaining high forces, ICI decreases and allows activation in order to spread to neighboring muscles to maintain the higher forces (Takahashi et al. 2009; Maruyama et al. 2006). Based on these findings, potentially, relatively stronger elderly may show higher ICI as a sign of the ability to focus output from flexors while the weaker ones may have reduced ICI to recruit agonists in action.

The results of the present study apparently encounter with the finding that states that ICI reduces with greater muscle activation in generating higher forces (Zoghi and Nordstrom 2007). This conflict can be explained by the different testing conditions as Zoghi and Nordstrom examined task-specific modulation of ICI by delivering paired-pulse TMS during activation of the muscle. The findings of this “task-specific” study cannot be compared with our results, where paired pulse TMS was delivered in resting state of the muscle due to differing state of cortical networks. Baseline cortical state indicates whether effects of TMS are facilitatory or inhibitory (Silvanto et al. 2008; Silvanto and Pascual-Leone 2008). ICI with a paired pulse paradigm delivered in resting state based on previous work in aging adults (Peinemann et al. 2001; Oliviero et al. 2006; Marneweck et al. 2011; Wassermann 2002) is chosen. Additionally, Zoghi and Nordstrom’s procedure of task-specific ICI could be investigated in elderly in order to verify whether variation in intra-cortical excitability with higher forces is altered in aging.

Normally, during rest, both hemispheres utilize common inhibitory influence upon one another, which is called IHI and is believed to be conducted via transcallosal connections (Chen 2004). In resting state, IHI is exaggerated in elderly. Our finding matches the results of Talelli et al. (Talelli et al. 2008a; Talelli et al. 2008b) who have shown that IHI exerted by the contralateral upon the ipsilateral M1 is insufficient in elderly during unilateral movement, due to the lack of adequate activity in contralateral M1 to prevent the opposing M1 in unilateral movement because of the significantly high IHI exerted by the opposing M1. In order to confirm these findings in elderly, inhibition in both directions, contralateral to ipsilateral and vice versa, and during rest and unilateral movement should be examined. In addition, the influence of aging-related changes on inter-hemispheric interactions, such as stroke, should be understood, as excessive IHI from unaffected to affected M1, is one of the biggest factors which cause poor motor control in stroke (Taub et al. 2003). However, the present study suggests that the influence of age should be carefully considered in interpreting IHI in stroke.

The finding that adaptations in M1 were highly related to strength of elbow flexors in elderly rather than younger subjects is captivating. Although training of strength in young individuals is associated with adaptations in corticospinal and intra-cortical properties in the M1 (Griffin and Cafarelli 2007; Beck et al. 2007; Lee et al. 2009; Kidgell and Pearce 2010; Goodwill et al. 2012), this study suggests that maintenance of strength may not be highly related to central mechanisms in the M1 in the young individuals. In fact, peripheral adaptations at the level of muscle (Chilibeck et al. 1998), neuromuscular activation (Andersen et al. 2005) or spinal

motor excitability (Taube et al. 2007) can be one of the predictors of strength in the young. On the other hand, in the elderly, due to the progressive neuronal death at all levels of the neuraxis (Doherty 2003; Henderson et al. 1980; Kapur et al. 2010), the M1 may begin to adapt to help counteract degenerative changes. For instance, weaker individuals, who have lowered ICI, may represent a compensatory strategy that may help elderly recruit all synergists in generating force. This study presented the findings suggesting that M1 adapts quickly in cases of neural damage, due to spinal cord injury (Saturno et al. 2008) or peripheral nerve damage (Sanes et al. 1988).

#### **4.5 Conclusions**

The present study highlights the neurophysiologic substrates in the motor cortex that are associated with strength loss of elbow flexors occurring in aging. Weaker elderly show higher intra-cortical excitability reflecting an adaptation that perhaps helps spread activation to adjacent synergists in generation of higher forces, while stronger elderly show reduced intra-cortical excitability, signifying their ability to inhibit diffuse, irrelevant activity and focus output from a muscle. Inter-hemispheric inhibition is exaggerated in elderly that may explain their deficient control in movement. That younger individuals did not show association between mechanisms in the M1 and the strength of elbow flexors muscle indicates that maintenance of strength in young age may not involve M1; with aging though, M1 may adapt to counteract weakness occurring due to progressive neuronal death along the neuraxis.

## **CHAPTER V**

### **CONCLUSIONS AND FUTURE WORK**

This dissertation includes two major parts. The first part reports findings of two studies that examined how aging affects power and functional neuromuscular coupling for voluntary motor action tasks. The aims of the two studies were:

1. To quantify EEG oscillation changes in the frequency domain during voluntary elbow flexion task in healthy elderly individuals compared to young controls (Chapter 2).
2. To identify functional corticomuscular coupling impairment in elderly subjects during the same task. (Chapter 3).

Results indicate that cortical signal oscillations vary systematically with muscle output. The oscillatory changes may represent modulations of the cortical control signals for weaker or greater descending command for lower or higher muscle output. The findings of this study may offer the possibility of using the EEG frequency power as an objective parameter for monitoring how the aging brain is changed.

The relationship between EEG-recorded cortical waves and frequency modulation of upper limb muscles has been explored at different levels of voluntary effort. Total EEG power output for high demanding tasks showed that aging had weakened cortical oscillations that caused inability to maintain necessary descending command. This impairment might be a potential mechanism associated with aging related muscle weakness. On the other hand, highly elevated Beta band EEG power spectra for low demanding tasks might be a good predictor early aging. A significant result of this study was to further analyzed EEG power in Beta band for medium force exert and found the similar significant different between groups.

Additionally, EEG-EMG coherence, as a neuromuscular index, was calculated as a representation of strength in the brain for functional coupling during voluntary elbow flexion task. Functional corticomuscular coupling and coupling between synergist muscles during voluntary elbow flexion are impaired in elderly. This impairment could potentially be one of mechanisms contributing to age-related muscle weakness, loss of motor skills and coordination. Another significant result of the study was the high positive correlation between EEG-EMG coherence and force suggests that the coherence can serve as a predictor of muscle strength in aging.

The second part of the dissertation (Chapter 4) describes aging brain has significantly different intra-cortical excitability which may have an influence for weakened muscle output in the elderly. Future studies may help us better understand how age-related degeneration in the motor cortex affects inferences drawn from geriatric adults who present with neurological conditions as stroke.

The studies here tested the proximal muscle group (biceps brachii, brachioradialis and triceps brachii) whose importance for the daily lives activities can be listed such as lifting heavy objects and carrying them. A more distal muscle groups, such as muscles in hand may be evaluated in the future which may reveal differences for fine motor skills.

Finding a predictor of aging for motor actions is crucial. Therefore, many directions of future work based on the findings of this study can be evaluated, including whether weakening of strength output in aging mainly peripheral (muscle to brain) or cortical (brain to muscle) in aging. If the weakening is mainly cortical, the idea of rectification of the impaired descending command may help to regain lost strength in aging. Since weight training is not feasible for elderly people, a motor training paradigm which uses the markers found in this study, may accomplish such task. Therefore this research will contribute to a better understanding of neural mechanisms underlying voluntary movement deficit in aging and its recovery following training the neuromuscular system.

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**APPENDICES**

## APPENDIX A

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## **APPENDIX B**

### **Abbreviations**

AP: Action potential  
BB: Biceps brachii  
BCI: Brain-computer interface  
BR: Brachioradialis  
CMC: Corticomuscular coupling  
EEG: Electroencephalography  
EF: Elbow flexion  
EMG: Electromyography  
FFT: Fast Fourier transform  
fMRI: Functional magnetic resonance imaging  
ICA: Independent component analysis  
ICI: Intra-cortical inhibition  
ICF: Intra-cortical facilitation  
IHI: Inter-hemispheric inhibition  
LDA: Linear discriminant analysis  
LFP: Local field potential  
M1: Primary motor cortex  
MVC: Maximal voluntary contraction  
PSD: Power spectral density  
SNR: Signal-to-noise ratio  
STFT: Short time Fourier transform  
TB: Triceps brachii  
TF: Time-frequency  
TMS: Transcranial magnetic stimulation