THE RELATIONSHIP BETWEEN GRIP STRENGTH, REACTION TIME, AND CEREBRAL WHITE MATTER INTEGRITY IN THE ANTERIOR INTERNAL CAPSULE OF HEALTHY OLDER ADULTS

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ABSTRACT

KARLA GRAVITT: The Relationship between Grip Strength, Reaction Time, and Cerebral White Matter Integrity in the Anterior Internal Capsule of Healthy Older Adults
(Under the direction of Dr. Bonita Marks)

This study investigated the relationship between grip strength, reaction time, and cerebral white matter integrity (CWMI) in the anterior internal capsule (AIC) of healthy older adults. Gender and hemispheric influences were also explored. Fifteen subjects (8 males, 7 females; 66.2 ± 5.8 years old) completed dynamic grip strength and reaction time testing (recognition and combined) on the dominant hand. Magnetic resonance imaging with diffusion tensor imaging determined CWMI in the AIC via computation of fractional anisotropy (FA) values. A simple regression revealed a positive correlation between grip strength and FA values in the left AIC ($r = 0.577$; $r^2 = 0.33$, $p = 0.039$). A positive correlation between combined reaction time and FA values was found in the right AIC ($r = 0.688$; $r^2 = 0.47$, $p = 0.037$). No significant gender relationships were noted. The potential hemispheric influence of fitness on CWMI should be further explored.

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LIST OF ABBREVIATIONS

BDI	Beck Depression Inventory
BMI	Body Mass Index
CWMI	Cerebral white matter integrity
DTI	Diffuser tensor imaging
FA	Fractional anisotropy
IC	Internal capsule
MRI	Magnetic resonance imaging
RRT	Recognition reaction time
CMBRT	Combined reaction time
TICS	Telephone Interview for Cognitive Status

CHAPTER ONE

Introduction

As healthcare improves and the baby boomers grow older, the number of adults over the age of 65 will increase drastically in the upcoming years. In 2000, the 65 and older population made up about 12% of the US population but by 2050, individual's age 65 or older will make up 26% of the US population (Bureau, 2000). One of the major concerns among the growing older population is the physical and mental decline (Black, Greenough, Anderson, & Isaacs, 1987; Spirduso, Francis, & MacRea, 2005) associated with aging. Although research demonstrates a link between a healthy body and a healthy mind, more research is needed to explore the mechanisms of this relationship (Colcombe & Kramer, 2003; Etnier, Nowell, Landers, & Sibley, 2006; Marks et al., 2008; Marks et al., 2007).

Research shows that various fitness parameters such as balance, 6-min walk performance, flexibility, grip strength and reaction time are correlated with parameters that are used to estimate functional decline. Older adults who score lower on tests of fitness score low on measures of functional decline. Of these fitness parameters, reductions in grip strength and reaction time have been most associated with functional decline (Judge, Schechtman, & Cress, 1996; Lord & Menz, 2002; Proctor et al., 2006; Rantanen et al., 1999). In an eight year longitudinal study of older adults, Proctor et al. (2006) found that grip strength was negatively associated with proximity from death.

Improved fitness parameters are associated with reductions in functional decline (Liu-Ambrose et al., 2004; Schlicht, Camaione, & Owen, 2001; Suzuki, Kim, Yoshida, & Ishizaki, 2004). In addition, strength training interventions improved proprioception, balance and reaction time (Liu-Ambrose et al., 2004).

Although the literature supports a relationship between improved fitness parameters and reduced functional decline, the mechanisms for the relationship are complex. One mechanism linking reductions in fitness parameters with functional decline may be cerebral white matter integrity in older adults. The cerebral white matter of the brain is made up of nerve cell axons connecting the cell bodies of the gray matter to each other. This allows transport of messages to different areas of gray matter in the brain. Nerve cell axons cross over at the junction of the medulla & spinal cord. Lesions above this point produce contralateral responses (opposite side) where as lesions below this point produce ipsolateral responses (same sided problem) (*Principles of Physiology*). Decreases in cerebral white matter integrity and plaques are associated with diseases such as Alzheimer and Multiple Sclerosis (Assaf & Pasternak, 2008).

Several studies by Marks et al. (Marks et al., 2008; Marks et al., 2007) demonstrated significant positive associations between regional cerebral white matter integrity (e.g. uncinate fasciculus, cingulum) and aerobic fitness. Other studies have shown a hemispheric relationship between impaired motor function and decreases in cerebral white matter integrity (Lindberg et al., 2007; Marks et al., 2008). In one study, higher maximum isometric grip strength in stroke patients was associated with higher cerebral white matter integrity in the left corticofugal tracts of the cerebral peduncle (Lindberg et al., 2007). Another study showed faster choice reaction times were associated with higher cerebral white matter integrity in the internal capsule of older adults (Madden, Whiting, Huettel, White, MacFall, & Provenzale, 2004). These studies suggest a positive association between fitness variables and cerebral white matter integrity.

Statement of the Problem

Decreases in muscle mass and therefore strength due to ageing may lead to functional decline, falls, and physical disability. Decreases in reaction time are also common in the older population and predictive of functional decline. Improved fitness parameters such as grip strength and reaction time are associated with improved functional performance and independence but the mechanisms for this relationship are not fully understood. Some studies suggest that fitness performance has a positive association with measurements of brain health as measured by white matter integrity (Lindberg et al., 2007; Madden et al., 2004; Sullivan et al., 2001). The objectives of this study were to better understand the mechanisms linking brain health to fitness by exploring the relationship between grip strength, reaction time, and cerebral white matter integrity in a small sample of healthy older adults. No studies have shown a direct relationship between reaction time, dynamic grip strength, and cerebral white matter integrity in the anterior region of the internal capsule in the older adult. In addition, no studies have examined gender or hemispheric differences in this relationship. **Therefore, the primary purpose of this study was to determine relationships between dynamic grip strength, reaction time, and cerebral white matter integrity measured by fractional anisotropy in the anterior region of the internal capsule in healthy older adults. A secondary purpose was to explore potential hemispheric and gender differences.**

The following research questions were investigated:

Research Questions

Research Question One: Is there a relationship between dynamic grip strength, reaction time, and cerebral white matter integrity in the anterior region (left side versus right side versus total = both sides combined) of the internal capsule in healthy older adults?

Ho_1: There is no relationship between dynamic grip strength, reaction time, and cerebral white matter integrity in the anterior region (left side versus right side versus total = both sides combined) of the internal capsule in healthy older adults.

Research Question Two: Is there a gender difference between the relationships of dynamic grip strength, reaction time, and cerebral white matter integrity in the anterior region (left side versus right side versus total = both sides combined) of the internal capsule in healthy older adults?

$Ho_{2:}$ There is no gender difference between the relationship of dynamic grip strength, reaction time, and cerebral white matter integrity in the anterior region (left side versus right side versus total = both sides combined) of the internal capsule in healthy older adults.

Definition of Terms and Abbreviations:

Cerebral White Matter Integrity (CWMI): the portion of the brain that is made up of nerve cell axons connecting the cell bodies of the gray matter to each other. This allows relaying of messages to different areas of gray matter in the brain.

Choice Reaction Time: A reaction time test involving two or more stimuli that each requires a specific motor response (Donders, 1969).

Combined Reaction Time (CMBRT): A reaction time test involving two stimuli, one that requires subjects to respond by moving their finger from one location to another and one that requires refraining from a motor response (Donders, 1969).

Diffusion Tensor Imaging (DTI): A magnetic resonance imaging (MRI) technique used to measure cerebral white matter integrity by detecting diffusion of water in tissue (Basser & Pierpaoli, 1996; Le Bihan et al., 2001).

Dynamic Grip Strength: A measurement of grip or forearm strength accessed with a hand dynamometer while moving thru a 90° range of motion. Dynamic grip strength has been hypothesized to be a more accurate measure of how individuals functionally grasp objects than static grip strength (LaStayo & Hartzel, 1999).

Fractional Anisotropy (FA): A measure of the directional diffusivity of water by compiling several DTI images. This results in a value between 0 (low cerebral white matter integrity) and 1 (high cerebral white matter integrity), allowing cerebral white matter integrity to be compared between individuals (Madden, Whiting, Huettel, White, MacFall, & Provenzale, 2004; Shimony et al., 1999).

Functional Decline: a decrease in measures of physical fitness (strength, power, flexibility, and endurance), functional performance (the ability to carry out activities of daily living), and functional independence (carrying out these activities operating on at least minimum levels of physical cognitive and mental health) (Ferrucci et al., 2004; Ravaglia et al., 2008; Spirduso et al., 2005).

Internal capsule (IC): White matter region of the brain found between the thalamus, caudate nucleus and lenticular nucleus of the brain. The fibers of the IC run anterior to posterior, top to bottom and right to left. These fibers carry information from the spinal cord to higher brain areas and from the motor cortex to the spine. Therefore, it is responsible for connecting higher brain areas to the brainstem and spinal cord. The internal capsule is divided into an anterior, posterior, and retrolenticular limb. This study is investigating relationships solely related to the anterior region of the internal capsule.

Magnetic Resonance Imagine (MRI): An imaging technique that differentiates internal structures of the body using magnetic signals (Taylor & Bushell, 1985).

Recognition Reaction Time (RRT) : A reaction time test involving two stimuli, one that requires a motor response and one that requires refraining from a response (Donders, 1969; Sternberg, 1969).

Simple Reaction Time: The amount of time elapsed between presentation of one stimuli and the motor response (Donders, 1969; Kohfeld, 1971).

Static Grip Strength: A measurement of grip or forearm strength accessed with a hand dynamometer with the wrist in a standardized static position. Hand grip strength has been correlated with overall strength and functional ability in the older adult (Skelton, Greig, Davies, & Young, 1994).

Delimitations:

This study was delimited to males and post-menopausal females between the ages of 60 and 80 years. Subjects were physically healthy, without clinical depression as measured by the Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), and had no significant cognitive impairment as measured by the Telephone Interview for Cognitive Status (TICS) (Brandt, Spencer, & Folstein, 1998). No subjects had any of the following conditions: cardiac pacemaker, insulin pump, catheters, or any non-removable metallic items that would present a hazard for magnetic resonance imaging (MRI) testing. The subjects' physical activity ranged from high (participation in a sport or other aerobic activity for at least 3 hours/week for the past 10 years) to relatively sedentary (no more than 90 minutes of aerobic activity weekly for the past 10 years).

Limitations:

Limitations of this study included potential inaccuracies in measurements of handgrip strength or reaction time. To reduce grip strength measurement inaccuracy, musculoskeletal problems of the hand, wrist and forearm were noted. All subjects participated in three measurement trials, with the highest strength measure attained used for data analysis. Even so, if any of the subjects did not report arthritis or other ailments of their hand or forearm, the handgrip test may not accurately portray their overall strength. Attention distraction can negatively impact reaction time testing. To minimize this potential limitation, the subjects were tested in a quiet private lab with restricted access to only the subject and investigators. Furthermore, they were allowed one practice trial plus two timed trials which would counter any one-time distractions. Lastly, the small sample size and minimal diversity of our subjects limits the generalizability of our results to the population.

Assumptions:

1. Researchers used the correct techniques and protocols when collecting data.
2. Subjects performance on the grip strength and reaction time tests were an accurate representation of their capabilities.

Significance of the Study:

Functional decline is a major concern among the growing older population resulting in enormous health care costs and death. Improvements in scores on grip strength and reaction time are associated with decreased functional decline; however, the mechanisms linking fitness parameters to functional decline are complex. MRI studies have used DTI to show that grip strength and reaction time scores may be linked to the cerebral white matter integrity in certain regions of interest. This study further elucidates the relationship between dynamic grip strength, reaction time, and cerebral white matter integrity in the anterior internal capsule.

CHAPTER TWO

Literature Review

Introduction

Decreases in muscle mass and therefore strength due to ageing may lead to increases in functional decline, falls, physical disability (Spirduso et al., 2005), and increased health care costs (Alemayehu & Warner, 2004; Buraeu, 2000; Martini, Garrett, Lindquist, & Isham, 2007). Fortunately, many studies have shown that improvements in fitness are successful at reducing functional decline in this population (Barnett, Smith, Lord, Williams, & Baumand, 2003; Cyarto, Moorhead, & Brown, 2004; Ferrucci et al., 2004; Suzuki et al., 2004). Two common measures of fitness often cited in the literature include measures of grip strength and reaction time (Kallman, Plato, & Tobin, 1990; Rantanen et al., 1999).

The mechanisms linking decreases in fitness to functional decline are currently being explored. Studies have shown a relationship between cerebral white matter integrity with healthy ageing (Pfefferbaum & Sullivan, 2003), aerobic fitness (Marks et al., 2008; Marks et al., 2007), grip strength (Lindberg et al., 2007), and reaction time (Lindberg et al., 2007; Madden et al., 2004; Tuch et al., 2005).

The area of the brain often associated with motor control and attention is the anterior portion of the internal capsule (Zaborszky, Pang, Somogyi, Nadasdy, & Kallo, 1999). A few studies have shown a correlation between a decline in cerebral white matter integrity and slower reaction time in older adults (Madden et al., 2004; Tuch et al., 2005). However, the relationship between measures of strength, reaction time, and white matter integrity concurrently has not been examined. Therefore, the purpose of this study was to determine if a relationship existed between grip strength, reaction time and cerebral white matter integrity in the anterior (left, right and both sides combined) internal capsule. A secondary aim was to explore potential gender and hemispheric differences in these relationships.

Functional Decline in the Elderly

Successful aging implies ageing without declines in fitness, functional performance, or functional independence. Fitness includes measures of strength, power, flexibility, and endurance. Functional performance is defined as the ability to carry out activities of daily living. Functional independence is defined as carrying out these activities operating on at least minimum levels of physical cognitive and mental health (Ferrucci et al., 2004; Ravaglia et al., 2008; Spirduso et al., 2005). As individuals age, there is often a significant decline in fitness and functional performance. These declines may include decreases in flexibility, cardiovascular and pulmonary function, muscular strength and power, balance posture and locomotion, reaction time, and cognitive function (Spirduso et al., 2005).

In order to understand how fitness and brain health among the older population are linked, researchers have examined how neurobiological changes may lead to functional decline. It has been shown that cerebral white matter integrity is diminished in older populations. Pfefferbaum et al. (2005) looked at the areas of cerebral white matter deterioration through DTI in 10 healthy younger and 10 healthy older adults. He found that the older adults had lower cerebral white matter integrity in the anterior regions of the brain compared to younger subjects while no significant differences were found in posterior regions (Pfefferbaum, Adalsteinsson, & Sullivan, 2005). The frontal lobe is crucial for executive functioning such as problem solving, memory and dual tasking. Deteriorations in cerebral white matter integrity in the frontal lobe are seen in subjects scoring low on tests of cognitive function (Gouw et al., 2006; Grieve, Williams, Paul, Clark, & Gordon, 2007). Lesions in cerebral white matter of the frontal lobe are also seen in older adults who have dementia and Alzheimer Disease (Gold, Giannakopoulos, Herrmann, Bouras, & Kovari, 2007).

Functional decline in the elderly is a major public health concern. In 1990, the American Medical Association urged the medical and research community to be aware of the potential impact the growing older population would have on future medical costs and the demands for medical care. In fact, they stated that preparing for this problem should be the medical community's most important task of the 1990's and 21st century (American Medical Association white paper on elderly health report of the council on scientific affairs, 1990).

The financial cost of the growing aging population suffering from functional decline is enormous. Martini et al. (2007) compiled data from Health Partner Health Plan administrative data, the US Census Bureau population projections 2000-2050, and the Medical Expenditure Planning Survey's annual 2001 health care per capita costs to determine the future financial impact of the baby boomer generation. They found that cross-sectional data from 2002-2003 projects that total per capita costs due to ageing will increase by 18% by the year 2050 (Martini et al., 2007). Likewise, Alemayehu & Warner (2004) found that US per capita health care costs will increase by 20% between 2000 and 2030 due to aging.

Indeed, from a health and financial standpoint, research examining the mechanisms of functional decline in the elderly is needed. Although we know ageing results in both functional and cerebral white matter integrity declines, the link between these declines is still not completely understood. By better understanding this relationship, perhaps the financial burden and functional decline of the aging population can be decreased.

Measuring Functional Decline

Identification of reasons for functional decline in the older adult is vital in order to improve quality of life and decrease health costs. Many studies have identified ways to successfully measure physical impairment and reductions in function. Judge et al. (1996)

provides a conceptual framework to explain how functional decline in the elderly may lead to disability. Their meta-analyses, based upon a cross-sectional data base from six separate sites (FISCIT Trials), reported strong positive associations between fitness measures (e.g., grip strength) and instrumental activities of daily living (IADLs, e.g. shopping, money management) (Judge et al., 1996) . Brach et al. (2002) looked at 83 community dwelling older men with a mean age of 75.5 years. They used a stepwise linear regression to determine the relationship between physical impairment and disability with activities of daily living (ADL's). It was found that 68.2 % of all the variance in ADL's was accounted for by impairments in function such as mobility/fall risk, coordination (modified gait abnormality rating scale), fitness (modified sitting step test) and flexibility (ankle range of motion) (Brach & VanSwearingen, 2002).

Sachdev et al. (2007) examined the relationship between cerebral white matter integrity and functional decline. Sachdev found impairments in cerebral white matter integrity was associated with a number of physical disabilities and poor motor function including grip strength and reaction time in the older adult (Sachdev, Wen, Christensen, & Jorm, 2005). These correlations were significant in the frontal and parietal regions. Studies have also shown correlations between declines in reaction time and decreases in cerebral white matter integrity (Madden et al., 2004) suggesting deterioration of cerebral white matter is associated with decreases in task attention control. Researchers have also found positive relationships between grip strength and cerebral white matter integrity emphasizing the importance of cerebral white matter integrity for maintenance of upper body strength (Lindberg et al., 2007). This data suggests declines in fitness such as grip strength and reaction time may be associated with declines in cerebral white matter integrity in the anterior brain.

Grip Strength as a Measure of Functional Decline

Grip strength has been shown to be a valid field measurement of body strength in the older population. Normative data for grip strength has been established in the older population (Desrosiers, Bravo, Hebert, & Dutil, 1995). Kallman et al. (1990) looked at grip strength measures in the younger (20-40 years old) and older adult (40-100 years old) and found grip strength to be highly correlated with muscle mass ($r = 0.60$, $p < 0.0001$). It was also found that grip strength declined at an accelerated (nonlinear) rate between 40-65 years of age (Kallman et al., 1990). Rantanen et al. (1999) found that midlife impairments in grip strength is a predictor of disability in the older adults (Rantanen et al., 1999).

Anstey et al. (1997) examined test-retest reliabilities for grip strength. They examined 50 women between the ages of 60-86 and found grip strength of both the right and left hand to have a high test-retest reliability (right hand, $r = 0.81$, left hand, $r = 0.84$) (Anstey, Smith, & Lord, 1997).

Grip strength using a hand dynamometer has a special significance in research in geriatric research because isokinetic dynamometers, such as those used to test hand grip strength, are recommended over one repetition max strength tests in order to reduce injury and establish more objective testing criteria (Pollock et al., 1991; M. Rogers, N. Rogers, Takeshima, & Islam, 2003; Rosler, Conley, Howald, Gerber, & Hoppeler, 1986). Stalenhoef et al. (2002) visited the homes of 300 community dwelling individuals over the age of 70 to evaluate their physical and mental health, strength, mobility, balance and gait. Handgrip strength was found to be a predictor of future falls (odds ratio 3.1) (Stalenhoef, Diederiks, Knottnerus, Kester, & Crebolder, 2002).

Grip strength in midlife has been shown to predict functional decline and disability in old age. Rantanen (1999) performed a 25 year cohort study on 3,218 middle age men between the ages of 45-68. They compared midlife hand grip strength measured using a dynamometer to walking speed, sit to stand performance and self-reported disability 25 years later. They found a significant positive correlation between the hand grip strength of middle age men and their functional performance measures and self-reported disability outcomes 25 years later (Rantanen et al., 1999).

Measurements of grip strength are often used in common functional assessments and disability tests (Ishizaki, Watanabe, Suzuki, Shibata, & Haga, 2000; Judge et al., 1996; Proctor et al., 2006). In a study by Ishizaki et al. (2000) risk factors for decline in basic ADL's and IADL's was assessed in a group of 583 Japanese men and women over the age of 65. Assessment of functional status was measured using the Tokyo Metropolitan Institute of Gerontology (TMIG) Index of Competence. This index assessed activities of daily living such as subject's proficiency at using public transportation, ability to pay bills; time spent reading books or newspapers and visits made to friends. Fitness decline predictors included body mass index (BMI) and grip strength. A stepwise multiple regression analysis revealed low hand grip strength was a predictor of functional decline in ADL's (odds ratio 0.91) and IADL's (odds ratio 0.9) during a three year follow up (Ishizaki et al., 2000).

In another study by Judge et al. (1996), dynamic grip strength was related to deficits in activities of daily living in community dwelling older adults between the ages of 65-85. In their FISCIT Trials meta-analysis, grip strength was used as a predictor variable for functional decline. The study reported that the positive association between hand grip strength and instrumental activities of daily living scores was highly significant ($p = 0.074$) (Judge et al., 1996).

Proctor et al. (2006) found that grip strength was a particularly useful indication of physical fitness in the oldest-old. He looked at 579 Swedish twins age 79-95 over eight years to determine changes in function. The researchers found that initial grip strength and rate of change in grip strength rather than weight, age, repeated chair stand and peak expiratory flow rate had the strongest prediction of death (Proctor et al., 2006).

Very few studies have examined the relationship between grip strength and neurobiology. Of the studies that have shown a relationship between grip strength and cerebral white matter integrity (Lindberg et al., 2007; Sachdev et al., 2005), none have examined potential gender differences. This study helps establish a mechanistic link between the internal capsule and strength using grip strength as a simple field measurement.

Reaction Time as a Measure of Functional Decline

Along with grip strength, reaction time is also commonly used as a marker of functional decline in the elderly. A decline in reaction time is one of the most visible changes of the aging population (Spirduso et al., 2005). In fact, older individual's reaction time is about 25% slower than younger subjects (Amrhein, Stelmach, & Goggin, 1991).

Kane et al. (1986) was one of the first researchers to use computerized systems to examine associations between reaction time and functional decline in the elderly. In his study, software with three different reaction time tests was used. In the first simple reaction time test, subjects had to push a button as quickly as possible in response to a "Go" sign. In the second recognition reaction time test, subjects had to either respond by tapping a key or refrain from responding to squares of two different colors. In the final choice reaction time test, subjects had to press one button in response to one shape and a different button in response to a second shape. In order to validate the test, a series of neuropsychological tests were completed after the computerized testing. The researchers found an 82% concordance rate between grip strength and neuropsychological tests. This was one of the first studies to show that computerized software was tolerated by older subjects and a valid surrogate measure of functional decline (Kane et al., 1986).

Many researchers have found a relationship between reaction time and fitness. Anstey et al. (2005) examined how choice reaction time is related to functional decline. The researchers found that simple and choice reaction time was more closely related to strength (as measured by grip strength) than either physical or mental health (Anstey, Dear, Christensen, & Jorm, 2005). Other researchers have found a positive relationship between faster reaction times, 6 mile walk times and sit-to-stand performances in older adults (Lord & Menz, 2002; Lord, Murray, Chapman, Munro, & Tiedemann, 2002).

Although there is substantial evidence that reaction time and grip strength are associated with a variety of measures of function decline, there have been no studies evaluating the associations between these variables concurrently and cerebral white matter integrity. Our study will add a new dimension to the literature base by examining the relationships between both these variables and cerebral white matter integrity.

Mechanisms Linking Decreases in Functional Decline and Fitness

Although research shows a positive relationship between fitness parameters and decreases in functional decline, the mechanisms for this relationship are complex. The majority of research has focused on aerobic fitness. In a 2003 study, Colcombe et al. compared high-resolution magnetic resonance imaging scans from 55 adults over the age of 55 and VO_2max scores. By using MRI imaging and a voxel-based morphometric (VBM) technique, this study was the first to show a relationship between aerobic fitness and cognitive decline (Colcombe et al., 2003). In 2004, Colcombe et al. examined highly functioning older adults to determine a relationship between cortical plasticity and both cardiovascular fitness and resistance training using a randomized control test. For this study, subjects were divided into either an aerobic training intervention or a stretching and toning control group where they met three times per week for six months. Cross-sectional study revealed that those who participated in the aerobic training group had greater cortical activation in several brain areas compared to the stretching and toning group. Likewise, the subjects who took part in the aerobic intervention experienced higher activation in areas of the brain responsible for intentional control (Colcombe et al., 2004).

Marks et al. (2007) examined the relationship between estimated aerobic fitness and cerebral white matter integrity in 13 younger (mean, SD = 24 ± 3 years old) and 15 older (mean, SD = 69.6 ± 4.7 years old) adults. The researchers estimated VO_2 max scores from a validated fitness regression equation using gender, age, body mass index (BMI), and a physical activity rating score (Jackson et al., 1990). MRI was used to derive fractional anisotropy values from DTI images in order to estimate white matter integrity. Significant positive associations were found between cerebral white matter integrity within specific brain regions (e.g. uncinate fasciculus, cingulum) and aerobic fitness (Marks et al., 2007). In a follow up study, Marks et al. (2008) determined that the relationship between cerebral white matter integrity and aerobic fitness were primarily evident in the anterior and medial segments of the cingulum on the left side of the brain in older adults.

Although several studies have shown a relationship between cardiovascular fitness and cerebral white matter integrity, very few studies have examined potential relationships between strength and cerebral white matter integrity. Limited research suggests that the combined effects of aerobic and strength training can improve cognitive performance. In a meta-analysis of 18 different studies by Colcombe (2004), subjects participating in a strength and aerobic training program scored higher on tests of cognition than an aerobic group alone.

Very few studies have looked at grip strength and cerebral white matter integrity in the older adult (Lindberg et al., 2007; Madden et al., 2004). Lindberg et al. (2007) examined cerebral white matter integrity in seven hemiplegic stroke patients between the ages of 40-71 years old. Fractional anisotropy values were obtained from the DTI images. The researchers used the Grippit™ to access maximum isometric grip strength. The Grippit™ is a portable instrument with an elliptical handle and electronic force transducers that measures subjects static grip strength every half second (Lagerstrom & Nordgren, 1998). Maximum grip strength in these patients was positively correlated with cerebral white matter integrity in the corticofugal tracts of the brain suggesting maintenance of cerebral white matter in this area is necessary to maintain upper limb strength (Lindberg et al., 2007).

There have also been a few studies that have examined reaction time and cerebral white matter integrity. Bucur et al. (2007) examined nine healthy older women between the ages of

63 -78 years of age to determine the relationship between episodic memory retrieval, choice reaction time and cerebral white matter integrity. Her research group found declines in cerebral white matter integrity in the pericallosal frontal region and in the genu of the corpus callosum were associated with decreases in choice reaction time and episodic memory retrieval ($r = -0.613$, $p < .01$) (Bucur et al., 2007). Madden et al. (2004) looked at 19 younger adults (mean = 21 years old) and 19 older adults (mean = 65 years old) to determine the relationship between cerebral white matter integrity and choice reaction time. Cerebral white matter integrity was estimated by fractional anisotropy values obtained through DTI imaging. Choice reaction time was measured through visual target detection of an oddball and target object. In the younger adult, there was a negative correlation between reaction time and white matter integrity in the splenium region of the brain. The same relationship existed for older adults but in the anterior internal capsule rather than the splenium (Madden et. al, 2004).

In summary, research suggests a relationship between fitness and cerebral white matter integrity but little research exists investigating the relationship between strength and cerebral white matter integrity. Also, many of the studies have not looked at possible gender effects in a healthy older population. Our study examined both grip strength and reaction time in healthy older men and women.

Important Role of the Internal Capsule to Fitness

Many studies on the internal capsule have focused on diseases such as schizophrenia, Parkinson’s disease, multiple sclerosis, or strokes that result in motor impairments (Brickman et al., 2006; Lee et al., 2000; Pendlebury, Lee, Blamire, Styles, & Matthews, 2000). Pendlebury et al. (2000) compared indexes representing demyelization and axonal injury loss in the internal capsule of both multiple sclerosis patients and patients suffering motor impairment from an ischemic stroke. They found that in stroke patients, demylination and axonal injury loss in the internal capsule were both associated with motor deficit scores (Pendlebury et al., 2000).

Brickman et al. (2006) examined schizophrenic patients who were categorized as either "good-outcome" or "poor-outcome" based on self-care deficits. They found that the "poor-outcome" patients had significantly smaller areas of white matter in the anterior limb of the internal capsule. "Good-outcome" patient's white matter density did not differ from healthy controls (Brickman et al., 2006).

The internal capsule is often the focus of brain density studies that evaluate motor impairments in older subjects. In a study by Lundgren et al. (1982), 53 patients with hemi-paralyses due to a stroke were examined to determine a relationship between the site of brain lesions and motor function. The researchers found that lesions in the internal capsule were significantly associated with impairments in self-care and activities of daily living (Lundgren, Flodstrom, Sjogren, Liljequist, & Fugl-Meyer, 1982).

The internal capsule contains the deepest axons of the motor pathway, transmitting information between the spinal cord and the motor cortex. These motor pathways, which originate in the motor cortex, cross-over between the spinal cord and medulla of the brain eighty five percent of the time. This suggests a contralateralization effect may exist where motor control areas in the left hemisphere may control motor movements on the right side of the body and vice versa (*Principles of Physiology*). The internal capsule lies above this junction so we may expect a contra-lateral response. However, everyday movement requires the left and right side of the body to work in unison, suggesting the left areas of motor control in the brain may control movement on both sides of the body (Sabate, Gonzalez, & Rodriguez, 2004). Studies on patient's with diseases marked by motor impairments such as Turner Syndrome, Huntington Disease, and patients recovering from a stroke all show damage in the left hemisphere (Holzapfel, Barnea-Goraly, Eckert, Kesler, & Reis, 2006; Gavazzi et al., 2007; Sabate et al., 2004). In addition, both Marks et al. (2008) and Lindberg et al., (2004) found an association between fitness and cerebral white matter integrity in brain regions in the left hemisphere in older adults.

There is a general decline in the cerebral white matter integrity in the anterior brain of disease free older adults as well (Pfefferbaum et al., 2005). However, research also shows that the brain is malleable and the amount of cerebral white matter declines can be influenced by environmental variables such as exercise (Black et al., 1987; Colcombe et al., 2003; Marks et al., 2008; Marks et al., 2007). Some researchers have shown gender differences in the cerebral white matter integrity in the healthy older adult. Hsu et al (2004) found that females had higher cerebral white matter integrity in the anterior internal capsule than males.

Madden et al. (2004) examined reaction time and cerebral matter integrity of the internal capsule in younger and older healthy subjects. He found that younger subject's with slower choice reaction time had lower fractional anisotropy values in the splenium ($r^2 = 0.1$, $p < 0.01$) while older subject's showed the same relationship but in the anterior limb of the internal capsule ($r^2 = 0.11$, $p < 0.01$) (Madden et al., 2004).

These studies emphasize the important role of the anterior region of the internal capsule for fitness in the older adult. Research shows that even though declines in the cerebral white matter integrity are typical in a healthy aging population, variances exist from person to person. By examining reaction time, grip strength and hemispheric cerebral white matter integrity in both men and women, we add further data on the association between fitness and brain structure of the healthy older adult.

Summary and Conclusions

The relationship between cerebral white matter integrity in the anterior internal capsule and fitness in the older adult has not been comprehensively examined. A few studies have shown a relationship between grip strength and reaction time and cerebral white matter integrity in the anterior internal capsule. However, to our knowledge, no studies have examined grip strength and reaction time's relationship with cerebral white matter integrity in the anterior internal capsule concurrently in the healthy older adult and none have investigated gender or hemispheric influences.

Both grip strength and reaction time are associated with functional decline in the elderly. As our older population grows, decreases in muscle strength and physical function lead to injuries and economic costs. The mechanisms linking improved fitness parameters and improved cerebral white matter integrity are not fully understood. By examining the relationship between grip strength and reaction time with cerebral white matter integrity in the anterior internal capsule, we may be able to better understand the mechanisms linking brain structure to fitness.

CHAPTER THREE

Methodology

This was a secondary analysis from the main study entitled, "Role of recreational sport participation on cerebral white matter integrity in older adults". The study was approved by the Committee on the Protection of the Rights of Human Subjects at the University of North Carolina at Chapel Hill (P.I.: Bonita L. Marks, PhD, Bio-Medical IRB #: 05-3151), funded by UNC Biomedical Research Imaging Center (BRIC). Research supports a link between declines in cerebral white matter integrity and motor impairments; however, few studies have examined the relationship between fitness parameters and cerebral white matter integrity in healthy older adults. The purpose of this study was to determine if a relationship existed between dynamic grip strength, reaction time, and cerebral white matter integrity in the anterior internal capsule of older adults.

Subjects

We screened 120 community-dwelling older adults in the Raleigh-Durham-Chapel Hill area. Nineteen healthy older adults completed the study however only 16 completed the MRI procedure. Of these 16, one was prospectively excluded due to poor imaging results. Thus this study reports on the MRI data of eight males and seven female subjects. The participants were between the ages of 60-76 years of age.

All subjects signed an informed consent prior to testing. At the conclusion of each of the appointments, the subjects received $20 after filling out a payment disbursement form. Testing was completed within a four-week period from their initial appointment.

Subjects were excluded from the study if they had any of the following:

- Diagnosed depression or significant cognitive impairment detected using the Beck Depression Inventory (BDI) (Beck et al., 1961).
- Contraindication to an MRI screen such as inability to perform an MRI because of pacemakers, claustrophobia, metallic implant or cochlear implant.
- Orthopedic, metabolic, or cardiopulmonary limitations that would limit their ability to participate in a " maximal" treadmill test or MRI scan.

Instrumentation

The following instruments from the main study were included in this study: Telephone prescreening, physical exam, medical history questionnaire, Beck Depression Inventory (BDI), Telephone Interview for Cognitive Status Screening (TICS), grip strength hand dynamometer, Moart Reaction Time apparatus and the MRI evaluation for cerebral white matter integrity.

Questionnaires.

Telephone Prescreening. In order to determine if subjects met the study's inclusion/exclusion criteria, a 15 minute telephone interview was administered to all subjects. The interview queried their physical activity history, current medical status and any contraindications for neuroimaging (I looked this up and no hyphen). The screening was designed to ensure subjects were healthy and available subjects had a wide range of physical activity histories.

Medical History Questionnaire. This form provided detailed health information, sociological demographics, and physical history information.

Beck Depression Inventory (BDI). The BDI is a short self-assessment questionnaire that was used for estimating depression. A standard score of < 15 (using a scale of 0-63) was the end point for inclusion of subjects with regards to clinical depression. The test has shown an internal consistency of 0.85 in a number of populations (Beck et al., 1961).

24-Hour History Form. This was used to ensure subject was mentally and physically rested for the testing session.

Telephone Interview for Cognitive Status Screening (TICS). The TICS is used as a cognitive screening test to differentiate between healthy and mildly cognitive impaired subjects. This test is a shortened version of the Folstein Mini-Mental State Exam (MMSE) (Folstein, Folstein, & McHugh, 1975), which is not as sensitive in detecting mild cognitive impairment in community dwelling older adults. The TICS consists of 11 questions and takes less than 10 minutes to administer. Although this test was originally developed as a phone-screening tool, it can also be conducted in the standard personal interview format (Brandt et al., 1998).

Performance Measurements

Anthropometric Measurements: Height, weight and BMI were recorded for each subject.

Hand Grip Strength: Handgrip has been shown to be a reliable indicator of physical function in the elderly (Rantanen et al., 1999). A Jamar handgrip dynamometer (Lafayette Instruments, Brooklyn, NY) was used to assess handgrip strength in the dominant and non-dominant hand of each subject.

Reaction Time: Reaction time has been shown to be a reliable indicator of physical function in the elderly (Jordan & Rabbitt, 1977). We measured reaction time using the MoART Reaction Time System (Lafayette Instruments, Lafayette, IN). A visual light stimulus with an auditory signal was utilized as the basis for the test. Two different tests were performed; the first test measured recognition reaction time and the second test measured combined reaction time.

Cerebral white matter Integrity Assessment: MRI and DTI have been used to reliably estimate white matter integrity in the brain (Basser & Pierpaoli, 1996; Le Bihan et al., 2001). In this study, DTI images were acquired using a 3.0 Tesla MRI unit (Allegra, Sieman Medical

Systems). A maximum gradient strength of 40 mT/m and a maximum slew rate of 40 mT/m/sec was used. A spin echo diffusion tensor weighted sequences were used to acquire the MRI images. Twenty one directional images repeated 4 times were acquired at an isotropic resolution of 2x2x2mm. The imaging data was used to formulate fractional anisotropy values. Fractional anisotropy is a valid way to compare white matter integrity between subjects (Madden et al., 2004; Shimony et al., 1999) and was used to evaluate cerebral white matter integrity in this study. Fractional anisotropy scores range from zero to one, with scores approaching one representing higher cerebral white matter integrity.

Procedures

Subjects who met the initial 15-minute telephone pre-screening questionnaire requirements, were booked for their first appointment. The consent form and medical history questionnaire were mailed to qualifying subjects to review before the initial appointment.

Appointment One: Medical Exam and Functional Testing.

For their first appointment, subjects reported to the Exercise Science Teaching Laboratory in the Fetzer Gym Building at the University of North Carolina, Chapel Hill. The primary investigator reviewed the consent form and procedures with the subject. Once the subject understood the purpose of the study and their involvement, subjects signed the consent form. After consent was given, the investigator screened the subjects for depression using the BDI. A 24 hour history form was administered to determine if the subjects were mentally and physically rested for the remainder of the assessment, the 24 hour history form was administered. The TICS cognitive screening test was administered to screen for mild cognitive impairment.

Before any testing began, the completed medical history questionnaire and the BDI were reviewed by a physician (board certified in both Emergency Medicine and Internal Medicine). A 15 minute physical examination that included vision screening (using a standard eye chart) and a standard ear test for hearing (presenting various noises to each ear) followed. Subjects were also asked if they were color-blind. The purpose of the physical examination was to screen for any contraindications to any of the testing procedures as detailed on the consent form. If no contraindications were found, the subject was approved to continue on with the study test procedures. All performance screenings were administered by a trained research assistant.

Dynamic Hand Grip Strength. Maximum hand grip strength was determined using a hand grip dynamometer on both the left and right hands. Subjects indicated hand dominance and whether any medical condition existed that might impair their performance on this test. The dynamometer was adjusted to each subject's hand size. The subject started with his/her elbow bent at a 90 degree angle. When instructed, the subject exerted a maximal gripping effort for 2-3 seconds while lowering his/her arm to full extension. The test was repeated 2 times on each hand with a brief rest period between trials. Left and right hands were tested in an alternating fashion. The highest score obtained per dominant hand was used.

Appointment Two: Reaction Time Testing

Grip strength and reaction time testing were completed on separate days to ensure the subjects were well rested. At least 48 hours passed between appointment days.

Reaction Time. A visual light stimulus was utilized as the basis for the test. There was also an auditory stimulus to signal the start of the test as well as a yellow 'holding' or pause color between testing phases. A total of two different tests were performed. Each test was first performed for three trials on the right hand followed by three trials on the left hand. Before each test, subjects performed a practice trail with their right hand.

a. **Recognition Reaction Time**: In this test, the subject placed their finger over a button and either responded to the presence of a green light by tapping the button as quickly as possible or refrained from responding to the presence of a red light.

b. Combined Reaction Time: In this test the subject held down a button on the bottom of the keypad and had to respond depending on whether a red or green light appeared. If a green light appeared the subject had to reach up and tap a button on the top of the keypad but if a red light appeared, the subject continue to press the bottom button.

Appointment Three: MRI Testing.

For their third and final appointment, subjects reported to the Biomedical Research Imaging Center (BRIC) at the University of North Carolina, Chapel Hill. Another 24-hour history form was administered in order to assure that subject was mentally and physically rested for the MRI scan. As with the cognitive tests, all the subjects had at least 48 hours rest between test appointments.

An MRI technician reviewed the procedures for the test with the subject, answered any questions, and reviewed the MRI screening form for any MRI screening contraindications. The subject lied face up on a platform in front of the MRI scanner while the technician positioned the subject's head appropriately. A soft cushion stabilized the head to prevent motion artifact during the scanning procedure. Headphones were worn by the subject to muffle the standard MRI noises as well as to enable communication between the subjects and MRI technician. When correct positioning was ensured and the subject was ready, the platform slowly moved into the scanner up to the person's chest. The MRI-DTI scan was completed in approximately 30 minutes.

Research Design and Statistical Analysis

This study was a retrospective correlational study. The independent controlled variables were dynamic grip strength, reaction time, and gender. The dependent variable was cerebral white matter integrity in the anterior region of the internal capsule as measured by fractional anisotropy values.

Descriptive statistics (means, standard deviations) were used to summarize the personal characteristics of the subjects (age, height, weight, BDI, TICS, reaction time, and grip strength). The data was analyzed using SPSS statistical software package (SPSS Inc., SPSS 17.0 for Microsoft Windows XP). Statistical significance was set a priori at $p < 0.05$ for all analyses. The following analyses were used to test specific research questions and corresponding null hypotheses:

Research Question One: Is there a relationship between dynamic grip strength, reaction time, and cerebral white matter integrity in the anterior region of the internal capsule (left side versus right side versus total = both sides combined) in healthy older adults?

Ho_1: There is no relationship between dynamic grip strength, reaction time, and cerebral white matter integrity in the anterior region of the internal capsule (left side versus right side versus total = both sides combined) in healthy older adults.

Statistical Analysis: A simple regression was used to determine the strength of the relationship between dynamic grip strength, reaction time and cerebral white matter integrity as measured by fractional anisotropy in the anterior region of the internal capsule.

Research Question Two: Is there a gender difference between the relationship of dynamic grip strength, reaction time, and cerebral white matter in the anterior region of the internal capsule (left side versus right side versus total = both sides combined) in healthy older adults?

$Ho_{2:}$ There is no gender difference between the relationship of dynamic grip strength, reaction time and cerebral white matter integrity in the anterior region of the internal capsule (left side versus right side versus total = both sides combined) in healthy older adults.

Statistical Analysis: A simple regression was used to determine the strength of the relationship between dynamic grip strength, reaction time, and cerebral white matter as measured by fractional anisotropy values in the anterior region of the internal capsule in males and females.

Chapter Four

RESULTS

Subjects

Nineteen older adults completed functional assessments; however, only 16 completed the MRI procedure. Of these 16, one was prospectively excluded due to poor imaging results. Thus this study reports on the MRI data of 15 subjects, eight males and seven females. Two of the remaining 15 subject's (1 male, 1 female) grip strength data was prospectively excluded due to reported shoulder pain at the time of testing and carpal tunnel syndrome. One male subject's reaction time values was prospectively excluded because his recognition reaction time score was over three interquartile (checked, no hyphen) ratios from the mean (individual score = 1385, group mean, SD = 505.4 ± 261) and he was unable to properly perform the combined reaction time test (see Figure 1). Another female did not have combined reaction time data due to a technical error with the reaction time trial.

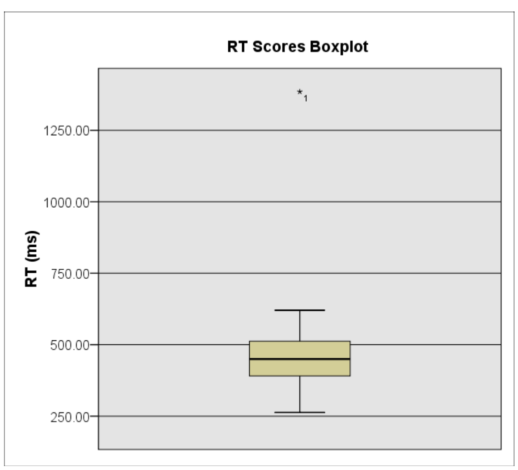

Figure 1. Boxplot showing the excluded outlier reaction time (RT) score. The boundaries of the box are Tukey's hinges. The median is identified by a line inside the box. The length of the box is the interquartile range (IQR) computed from Tukey's hinges. Values more than three IQR's from the end of a box are labeled as extreme, denoted with an asterisk (*).

All subjects were college educated with a bachelor's degree or higher. Subject's ethnic breakdown was as follows: 12 Caucasian, 1 Asian, 1 Caucasian-Native American and 1 mixed origins.

Subject Characteristics

The means, standard deviations and ranges for the subject's characteristics are listed in Table 1. All of the subjects were independent community dwelling and free from depression according to their BDI scores. All subjects were right handed except one. All grip strength and reaction time data reported are scores from the subject's dominant hand.

Variable	**n**	**Mean ± SD**	**Range**
Age	15	66.2 ± 5.8	60 – 76
BMI	15	26.2 ± 4.1	19.7 - 35.4
TICS	15	34.9 ± 2.5	31 – 40
BDI	15	3.0 ± 3.1	0 – 13

Table 1. Subject Characteristics where BMI = body mass index score; TICS = Telephone Interview for Cognitive Status; BDI = Beck Depression Inventory

Relationship between grip strength, reaction time, and cerebral white matter integrity

The null hypothesis for Research Question One stated there is no relationship between dynamic grip strength, reaction time, and cerebral white matter integrity in the anterior region of the internal capsule (left side versus right side versus total = both sides combined) in healthy older adults. A simple regression was used to test the strength of the relationship between grip strength, reaction time, and fractional anisotropy in the anterior internal capsule. Table 2 shows the mean, standard deviation, and range for grip strength and reaction time scores of the dominant hand.

Variable	n	Mean ± SD	Range
Grip Strength (kg)	13	28.5 ± 7.5	18.2 - 41.8
RRT	14	442.6 ± 98.0	263 - 620.5
CMBRT	13	961.1 ± 300.7	576 - 1536.7

Table 2. The mean, standard deviation and range of the subject's grip strength, recognition reaction time (RRT) and combined reaction time (CMBRT) scores.

Figure 2 shows no significant correlation between grip strength and fractional anisotropy values in the "total" anterior internal capsule region, right and left sides combined ($r = 0.286$ and $r^2 = 0.082$; $p = 0.343$). However, when the left and right sides of the brain were analyzed separately, the left side exhibited a positive moderate association between fractional anisotropy and grip strength ($r = 0.577$ and $r^2 = 0.322$; $p = 0.039$) whereas no association was found on the right side of the brain. These hemispheric relationships can be seen in Figures 3 and 4.

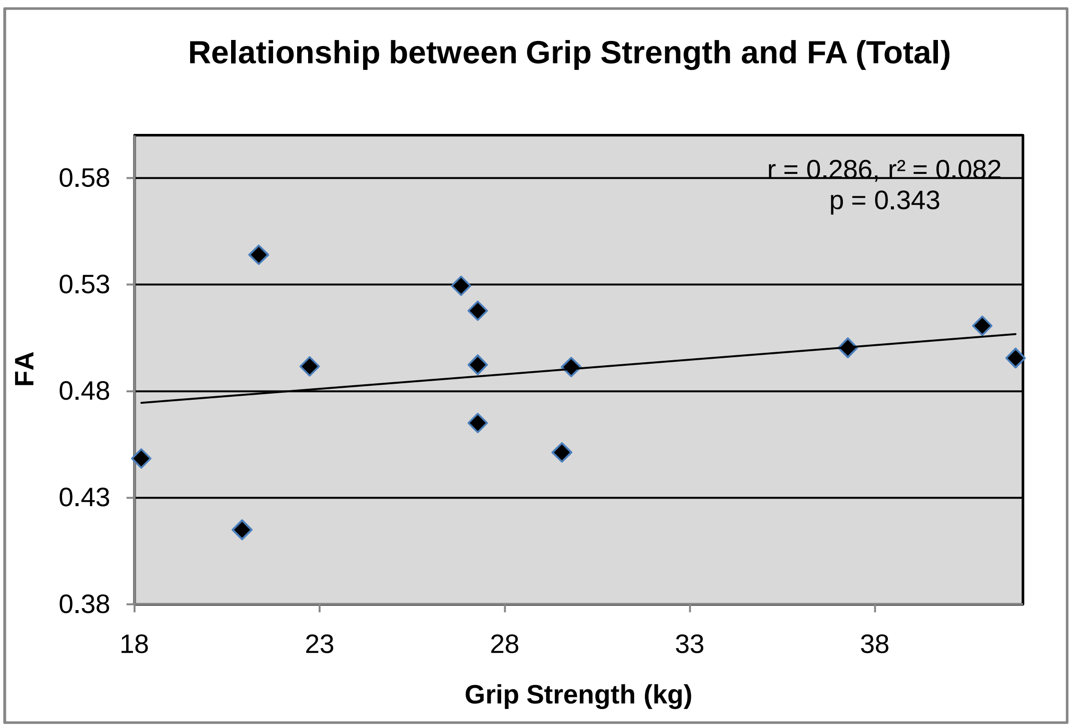

Figure 2. Scatter plot depicting the relationship between grip strength and fractional anisotropy (FA) values in the total anterior internal capsule with line of best fit.

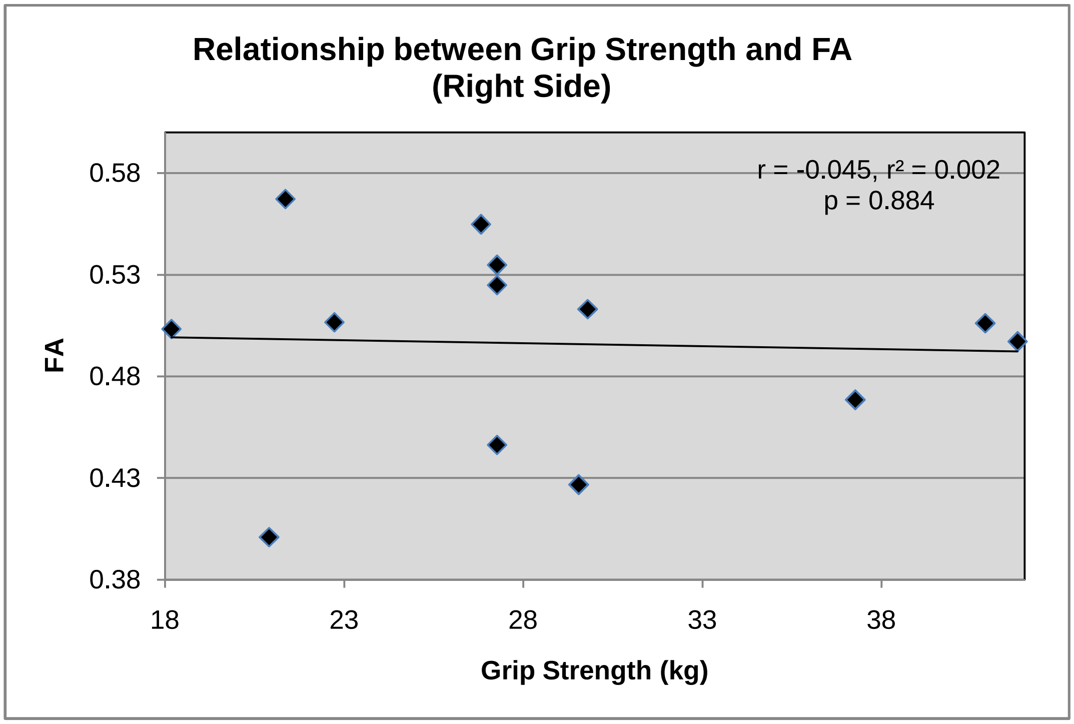

Figure 3. Scatter plot depicting the relationship between grip strength and fractional anisotropy (FA) values in the right anterior internal capsule with line of best fit. Title fixed

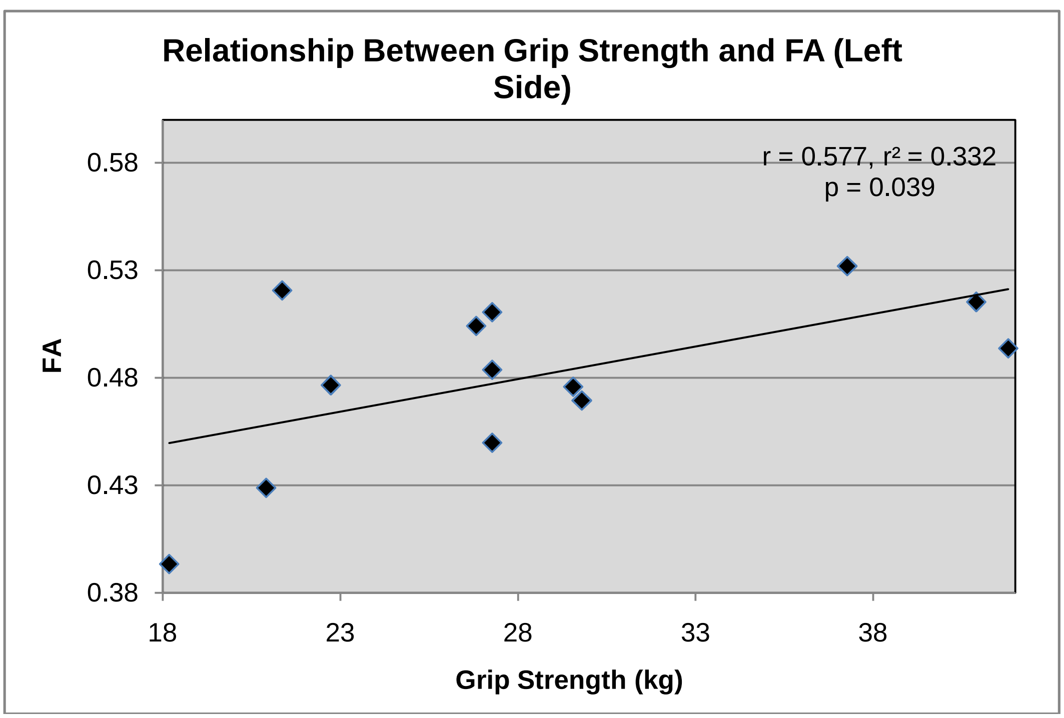

Figure 4. Scatter plot depicting the relationship between grip strength and fractional anisotropy (FA) values in the left anterior internal capsule with line of best fit.

As with grip strength, no significant relationship was found between recognition reaction time ($r = -0.061$ and $r^2 = 0.004$; $p = 0.835$) and fractional anisotropy values in the total anterior internal capsule, right and left sides combined (see Figure 5). However, contrary to grip strength, when hemispheric differences were explored, no significant relationships were found between recognition reaction time and fractional anisotropy values in either side of the brain (see Figures 6 and 7).

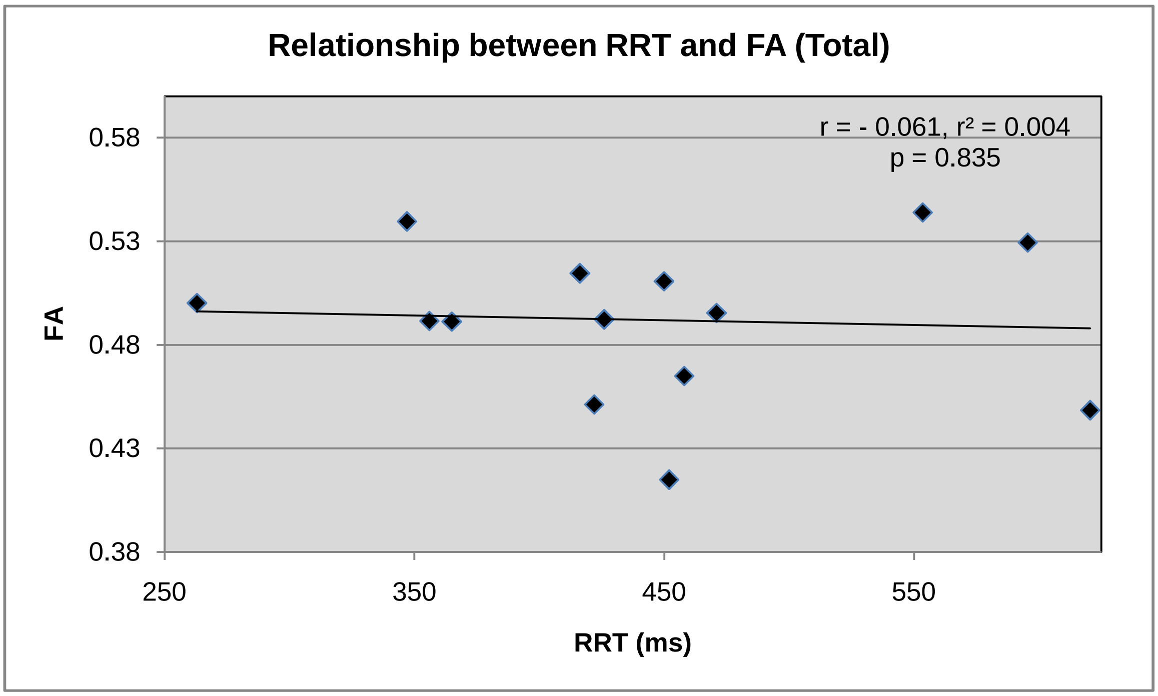

Figure 5. Scatter plot depicting the relationship between recognition reaction time (RRT) and fractional anisotropy (FA) values in the anterior internal capsule with line of best-fit. Increasing RRT (ms) value indicates *slower* reaction time.

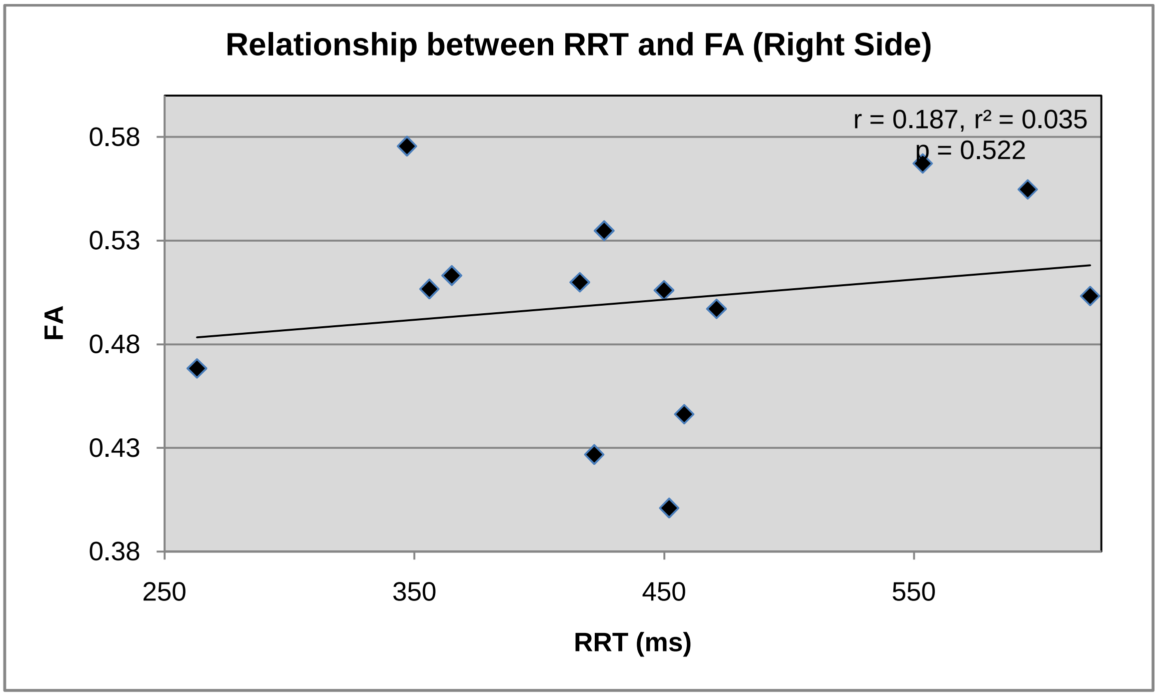

Figure 6. Scatter plot depicting the relationship between recognition reaction time (RRT) and fractional anisotropy (FA) values in the right anterior internal capsule with line of best-fit. Increasing RRT (ms) value indicates *slower* reaction time.

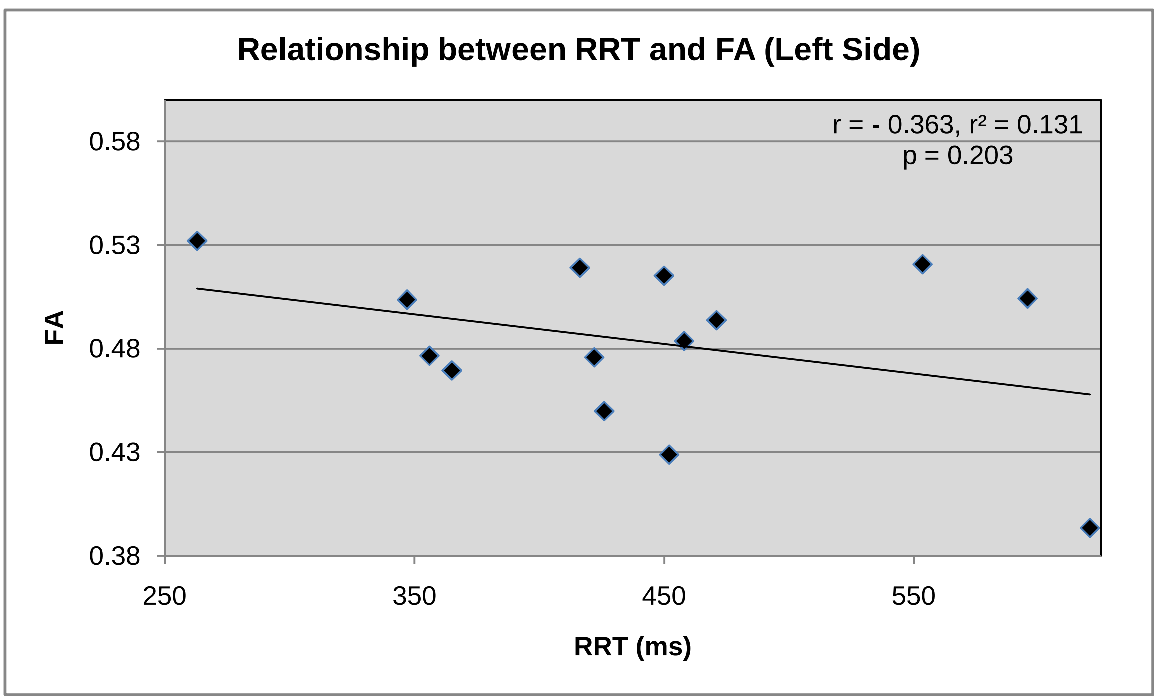

Figure 7. Scatter plot depicting the relationship between recognition reaction time (RRT) and fractional anisotropy (FA) values in the left anterior internal capsule with line of best-fit. Increasing RRT (ms) value indicates *slower* reaction time.

Although no significant relationship was found between combined reaction time and fractional anisotropy values in the total anterior internal capsule ($r = 0.455$ and $r^2 = 0.207$; $p = 0.118$), when analyzed by hemisphere, a significant positive relationship was found between combined reaction time and fractional anisotropy values in the right side of the brain but not the left. These results can be seen in Figures 8-10.

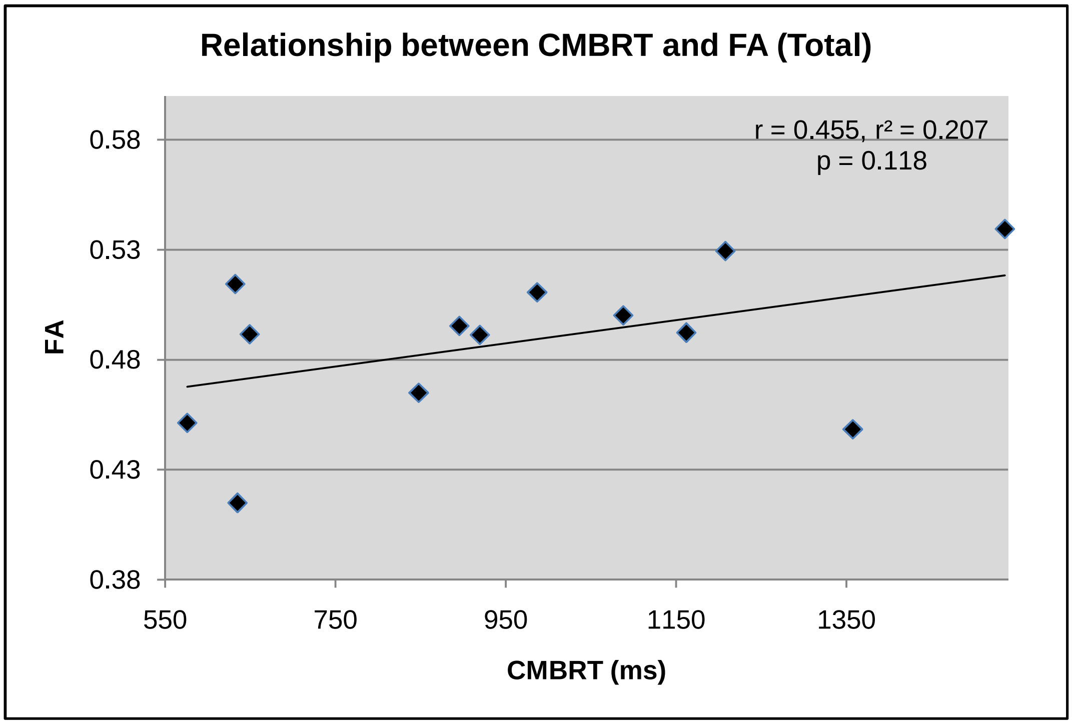

Figure 8. Scatter plot depicting the relationship between combined reaction time (CMBRT) and fractional anisotropy (FA) values in the total anterior internal capsule with line of best fit. Increasing CMBRT (ms) value indicates *slower* reaction time.

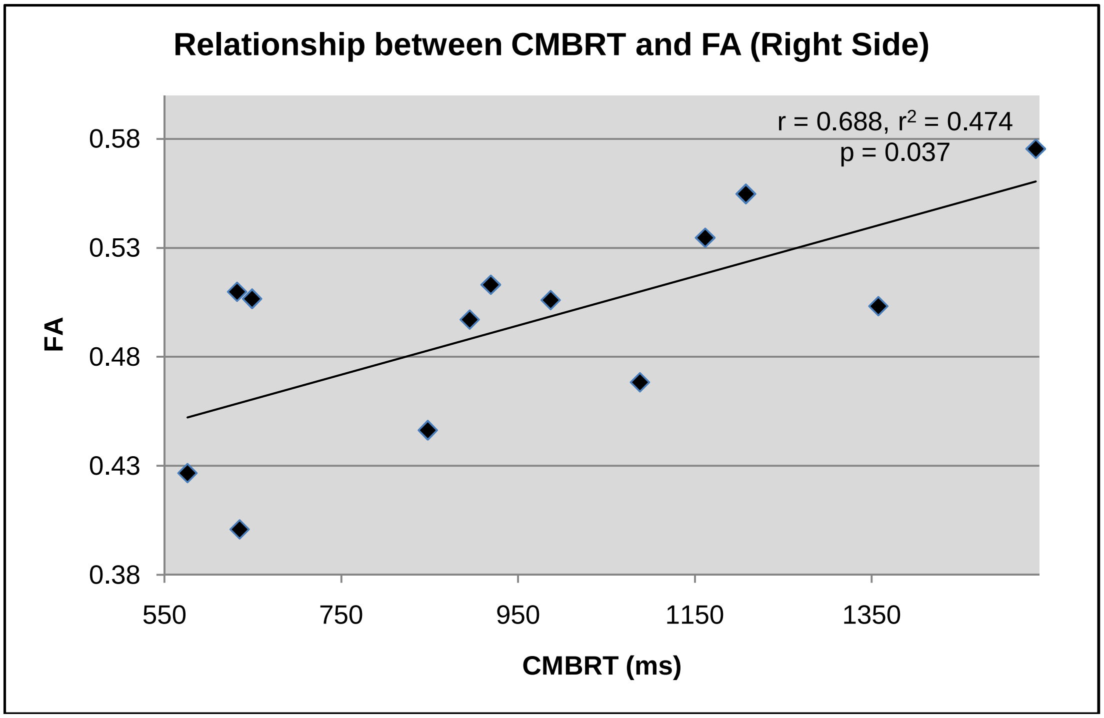

Figure 9. Scatter plot depicting the relationship between combined reaction time (CMBRT) and fractional anisotropy (FA) values in the right anterior internal capsule with line of best fit. Increasing CMBRT (ms) value indicates *slower* reaction time.

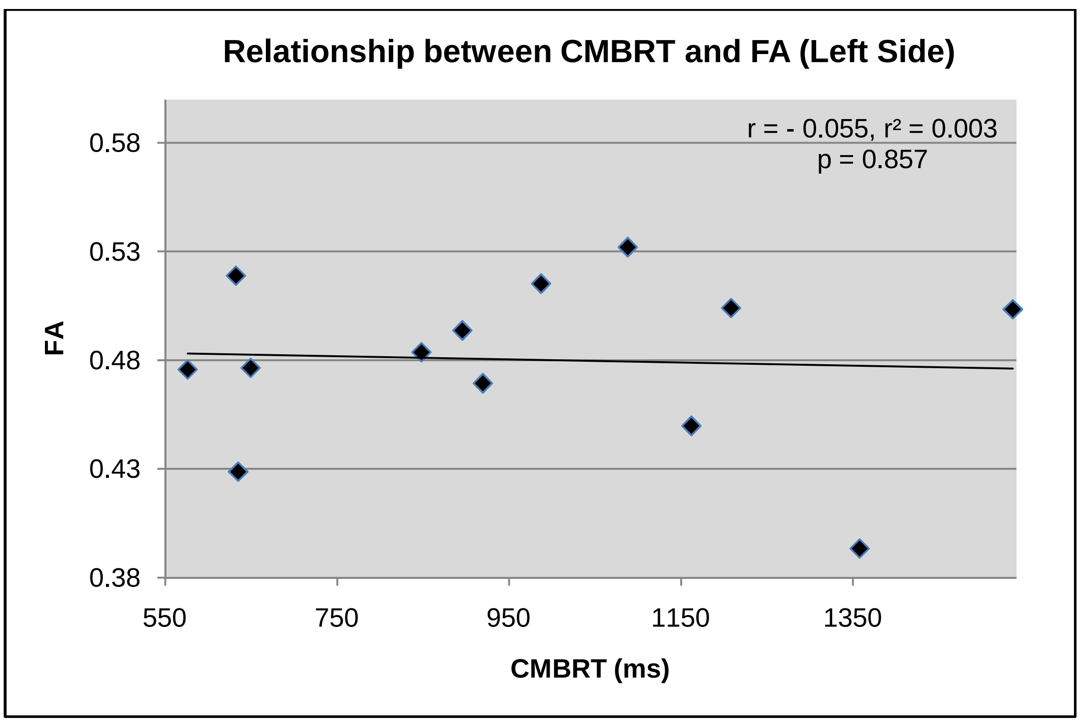

Figure 10. Scatter plot depicting the relationship between combined reaction time (CMBRT) and fractional anisotropy (FA) values in the right anterior internal capsule with line of best fit. Increasing CMBRT (ms) value indicates *slower* reaction time.

<u>Gender difference in the relationships between grip strength, reaction time, and cerebral white matter integrity</u>

The null hypothesis for Research Question Two stated there is no gender difference in the relationships between reaction time, grip strength, and cerebral white matter integrity in the anterior region of the internal capsule (left side versus right side versus both sides combined) of healthy older adults. A simple correlation was used to determine the strength of the relationship in both males and females. <u>Table 3</u> shows that mean grip strength was significantly greater for males ($t[11] = 3.092$; $p < 0.05$) but reaction time ($t[12] = -0.284$; $p > 0.05$) and combined reaction time ($t[11] = -0.318$; $p > 0.05$) were similar between males and females. In addition, no significant differences in fractional anisotropy scores were found between males and females in the total ($t[13] = 0.878$; $p < 0.05$), right ($t[13] = 0.036$; $p < 0.05$), or left ($t[13] = 1.744$; $p < 0.05$) anterior internal capsule.

	n	Males	N	Females
Grip Strength	7	32.9 ± 6.76*	6	23.4 ± 4.3
RRT	7	434.8 ± 97.9	7	450.3 ± 105.3
CMBRT	7	935.5 ± 249.7	6	990.9 ± 374.3
FA Right	8	0.503 ± 0.04	8	0.502 ±0.062
FA Left	8	0.500 ± 0.026	8	0.468 ± 0.044
FA Total	8	0.468 ± 0.044	8	0.485 ± 0.047

<u>Table 3.</u> Mean ± SD of the subject's grip strength, recognition reaction time (RRT) and combined reaction time (CMBRT) and fractional anisotropy (FA) values in males and females. *p < 0.05

No gender specific relationships were found between recognition reaction time, combined reaction time or grip strength and fractional anisotropy values in the total, right or left anterior internal capsule when subjects were divided by gender. The statistical results of the simple correlations are summarized in <u>Tables 4-6</u>.

	Pearson r	$\mathbf{r^2}$	**p - value**
Right IC			
Males	-0.307	0.095	0.502
Females	-0.030	0.001	0.955
Left IC			
Males	0.439	0.193	0.324
Females	0.457	0.209	0.362
Total IC			
Males	-0.026	0.001	0.956
Females	0.212	0.045	0.687

Table 4. Statistical results of the relationship between **grip strength and fractional anisotropy** divided by region of the anterior internal capsule in males (n = 7) versus females (n = 6).

	Pearson r	$\mathbf{r^2}$	**p -value**
Right IC			
Males	0.591	0.349	0.162
Females	- 0.067	0.004	0.887
Left IC			
Males	- 0.268	0.072	0.561
Females	- 0.427	0.182	0.339
Total IC			
Males	0.353	0.125	0.437
Females	- 0.243	0.059	0.599

Table 5. Statistical results of the relationship between **recognition reaction time and fractional anisotropy** values divided by region of the anterior internal capsule in males (n = 7) versus females (n = 7).

	Pearson r	**r^2**	**p-value**
Right IC			
Males	0.659	0.434	0.107
Females	0.728	0.531	0.101
Left IC			
Males	- 0.033	0.001	0.944
Females	0.009	0.000	0.986
Total IC			
Males	0.546	0.299	0.204
Females	0.518	0.268	0.293

Table 6. Statistical results of the relationship between **combined reaction time and fractional anisotropy** values divided by region of the anterior internal capsule in males (n = 7) versus females (n = 6).

Chapter Five

DISCUSSION

The primary purpose of the present study was to investigate the relationship between dominant grip strength, reaction time, and cerebral white matter integrity in the anterior internal capsule in healthy older adults. A secondary goal was to explore potential gender differences in these relationships. A significant positive correlation was found between grip strength and cerebral white matter integrity (as measured by fractional anisotropy) in the left side of the anterior internal capsule for predominately right handed individuals. Furthermore, a significant positive correlation was found between combined reaction time and cerebral white matter integrity indices in the right anterior internal capsule. No other significant relationships were uncovered. The following discussion examines the above mentioned results followed by a review of the limitations of the study.

Relationship between Grip Strength and Cerebral White Matter Integrity

Although many studies have shown a relationship between pathologically induced brain changes and motor function (Sachdev et al., 2005; Schiemanck, Kwakkel, Post, Kappelle, & Prevo, 2008; Lee et al., 2000), few have focused on the healthy older adult without motor deficits. In our study, a significant positive correlation was found between grip strength and fractional anisotropy scores in the left hemisphere of the internal capsule. This suggests that increased grip strength is associated with greater cerebral white matter integrity and may be hemispheric-specific.

Our finding is substantiated by results of earlier MRI clinical studies by Lindburg et al. (2007) as well as a recent study by Marks et al. (2008). Lindberg (2007) reported findings from seven right handed hemiplegic stroke patients between the ages of 40-71 with damage to their left corticofugal tract. He found a positive correlation between fractional anisotropy values in the left cerebral peduncle and grip strength, suggesting greater grip strength was associated with greater cerebral white matter integrity in the corticofugal tract on the left side of the brain (Lindberg et al., 2007). Lastly, Marks et al. (2008) also found a positive relationship between aerobic exercise and cerebral white matter integrity for the cingulum on the left side of the brain in healthy older adults, further substantiating the hemispheric influence of exercise on brain structure.

The hemispheric-specific findings in our study as well as the studies above may be due to a contralateralization effect – namely that right side motor dominance (in this case right-handedness) impacts brain structures on the left side of the brain. The internal capsule contains the deepest axons of the motor pathway, transmitting information between the spinal cord and the motor cortex. These motor pathways, which originate in the motor cortex, connect to the contralateral cells of the brainstem and spinal cord (Sabate, Gonzalez, & Rodriguez, 2004). Eighty-five percent of the time this crossover happens at the junction of the medulla & spinal cord (pyramidal decussation point). Lesions above this point produce contralateral responses (opposite side) where as lesions below this point produce ipsilateral responses (same sided problem) (*Principles of physiology*). The internal capsule lies above this junction so we may expect a contralateral response. Since all but one of our subjects were right hand dominant, according to motor movement research and the contralateralization effect (Sabate et al., 2004), we would expect to see a relationship in the left hemisphere as opposed to the right.

As detailed in Chapter Two, exercise neuroscience research is reporting positive relationships between physical fitness and brain integrity. Cross-sectional studies by Marks et al. (Marks et al., 2008; Marks et al., 2007) as well as cross-sectional and intervention studies by Colcombe et al. (Colcombe et al., 2003; Colcombe et al., 2004; Colcombe et al., 2006) showed that greater aerobic fitness resulted in greater cerebral white matter integrity, greater cortical brain activation and cortical volume. However, few studies have focused on determining if a link exists between strength and brain health. Studies by Colcombe et al. show that the brain benefited from aerobics and strength training combined but not strength and toning exercises alone (Colcombe, Kramer, McAuley, Erickson, & Scalf, 2004; Colcombe et al., 2006; Kramer et al., 2003). Yet our cross-sectional grip strength study results suggest otherwise as do other studies which demonstrated that grip strength is reflective of overall health and lower grip strength is associated with both abnormalities in the brain as well as functional declines (Ishizaki et al., 2000; Lindberg et al., 2007; Marks et al., 2008; Rantanen et al., 1999; Sachdev et al., 2005). In summary, the findings of Lindburg et al. (2007) corroborate our findings that indeed grip strength is related to cerebral white matter integrity in the internal capsule of healthy older adults and it may be hemispherically mediated perhaps due to dominant hand preference.

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Relationship between reaction time and cerebral white matter integrity

Although no significant correlations were found between reaction time and cerebral white matter integrity (i.e. fractional anisotropy values) in the anterior internal capsule for the whole brain, it was interesting to discover that slower combined reaction time was significantly associated with greater cerebral white matter integrity on the right side of the brain. Very few studies have examined reaction time and cerebral white matter integrity in the anterior internal capsule of the healthy older adult. As opposed to our results, Madden et al. (2004) found a negative relationship between choice reaction time and cerebral white matter integrity in the internal capsule in a healthy older adult sample. Those who took longer to respond in the choice reaction time test had lower cerebral white matter integrity in the anterior internal capsule (Madden et al., 2004).

Methodological differences could account for the difference in our findings. First, Madden's study involved functional neuroimaging (fMRI) plus DTI, with the reaction time test completed shortly before imaging, thereby providing a more precise method of assessing reaction time to real-time brain function. Our subjects participated in reaction time testing on a separate day and as such, our results are only suggestive of the cumulative effect on brain structure, but not real time influence. Second, in Madden's research in an "oddball" task was employed wherein the subject had to press a button when a target symbol was displayed (a filled circle) versus a standard symbol (a filled square) or novel photograph of every day objects. Thus, the oddball reaction time task may have relied more heavily on a visual target response than the color-coded response to a light stimulus of varying color. Our combined reaction time task required either responding or refraining from responding to a light stimulus. If a red light was displayed, subjects did not respond; if a green light was displayed, subjects moved their finger from one location to another. It was assumed, since none of the subjects were color-blind, that the subjects would associate the "red light-green light" with the conditioned response of "red light stop, green lights go". However, there was also an auditory beep signal signifying the start of the test as well as a "yellow standby color". It is possible that either the auditory signaling interfered with the visual signaling or the yellow standby color confused the subjects, and thereby inadvertently slowed down our subjects' response time. More practice trials prior to testing may have helped the subjects understand the responses required. Future studies with more subjects may help clarify the relationship between reaction time and cerebral white matter integrity in the internal capsule of the healthy older adult.

Gender differences

Some studies suggest gender differences exist in the cerebral white matter integrity of the anterior brain. For example, Colcombe and Kramer's (2003) meta-analysis concluded that females showed greater overall effects of aerobic training on cognitive performance (Colcombe & Kramer, 2003). More closely aligned with our study, Hsu et al. (2008) reported that females (mean age 50) had higher cerebral white matter integrity in the left anterior internal capsule compared to males. Both of these previous reports are contrary to our findings as we uncovered no significant differences in cerebral white matter integrity between males and females nor any relationships between gender and reaction time or grip strength on cerebral white matter integrity in the older brain. Furthermore, other studies that have examined the role of grip strength and reaction time on cerebral white matter integrity in the internal capsule have not looked at gender effects. Since we only had 7 males and 6 females in this study, a power analyses suggested we did not have enough power to detect significant gender differences (observed power for the internal capsule x gender with $p \leq 0.05$: = total internal capsule = 10%; L side = 7%; R side = 10%). Further research with more subjects would help determine if any true gender differences exist within the internal capsule with either grip strength or reaction time.

Limitations

There were four major limitations that may have impacted our study. First, it is likely the small subject number (15) limited our ability to detect significant associations. Second, although it is common practice in pilot studies to recruit subject's beginning at age 60 for "ageing" studies, it is possible that biologically this is not appropriate, especially for community dwelling healthy older adults. Ageing experts consider adults between the ages of 45-64 years "middle age" and adults between the ages of 65-74 years "young old" (Spirduso et al., 2005). Therefore, future studies should be more consistent with their aging classifications and consider recruiting adults who are at least 65 years old. Furthermore, as some studies suggest, if cerebral white matter integrity declines at a faster rate as individuals age (Pfefferbaum et al., 2005; Sullivan & Pfefferbaum, 2006), we may find different results in different age cohorts. In addition, the results of this current study may not be comparable to others, who may have used subjects of lower socio-economic/educational stratus as both have been shown to influence cognitive function, and perhaps in turn brain structure and function (Spirduso et al., 2005). Finally, analyzing the dominant hand, which in this study was in all but one case the right hand, may have biased the study and future investigations should look at both dominant and non-dominant grip strength and reaction time.

Chapter Six

SUMMARY AND CONCLUSIONS

Summary

The purpose of this thesis was to determine the relationship between grip strength, reaction time, and cerebral white matter integrity in the anterior internal capsule of the healthy older adult. Fifteen older adults (8 men, 7 women) between the ages of 60 and 76 participated in this study. Their activity levels ranged from highly active to inactive. All of the subjects were free from depression, significant cognitive impairments, or any contraindications for MRI testing. The subjects all had at least a post-secondary education.

This study found a significant positive relationship between grip strength and fractional anisotropy score in the left anterior internal capsule of the healthy older adult. A significant positive relationship was found between combined reaction time and fractional anisotropy in the right anterior internal capsule. No statistically significant relationship between recognition reaction time and fractional anisotropy was found. When subjects were analyzed by gender, no relationship between grip strength or reaction time and cerebral white matter integrity in the anterior internal capsule was found.

Conclusions

Based on the results of the current investigation, the following research questions and null hypothesis from Chapter One were addressed:

Research Question One: Is there a relationship between dynamic grip strength, reaction time, and fractional anisotropy in the anterior region of the internal capsule (left side versus right side versus total = both sides combined) in healthy older adults?

Ho_1: There is no relationship between dynamic grip strength, reaction time, and fractional anisotropy in the anterior region of the internal capsule (right side versus left side versus total = both sides combined) in healthy older adults.

*The null hypothesis **was rejected** because a significant positive relationship was found between grip strength and fractional anisotropy in the left anterior internal capsule. Furthermore, a significant positive relationship was found between combined reaction time and fractional anisotropy scores in the right hemisphere of the brain.*

Research Question Two: Is there a gender difference between the relationships of dynamic grip strength, reaction time, and fractional anisotropy in the anterior region of the internal capsule (left side versus right side versus total = both sides combined) in healthy older adults?

$Ho_{2:}$ There is no gender difference between the relationship of dynamic grip strength, reaction time, and fractional anisotropy in the anterior region of the internal capsule (right side versus left side versus total = both sides combined) in healthy older adults.

The null hypothesis **was accepted** because no significant relationships or differences were found between genders for grip strength, reaction time, and fractional anisotropy in the anterior internal capsule (right side versus left side versus both sides combined) of the healthy older adult. However, the results are limited by the power of this study.

Practical Application and Future Research

Decreases in muscle mass and therefore strength due to aging may lead to increases in functional decline, falls, physical disability, and resulting economic costs. Decreases in response time are also common in the older population and predictive of functional decline. Improved fitness parameters such as grip strength and reaction time are associated with decreases in functional decline but the mechanisms for this relationship are not fully understood. Some studies suggest that improved fitness performance is associated with improvements in measurements of brain health as measured by cerebral white matter integrity. The purpose of this study was to better understand the mechanisms linking brain health to functional health by exploring the relationship between grip strength, reaction time, and cerebral white matter integrity in a small sample of healthy older adults. It is one of the few studies that have looked at potential hemispheric influences impacting the relationship between grip strength, reaction time, and cerebral white matter integrity in the anterior internal capsule of healthy older adults. These results suggest that a contralateral relationship may exist between cerebral white matter integrity and dominant grip strength suggesting increased strength is associated with healthier brain structure in older adults. A larger, more diverse subject pool is recommended to further examine relationships between strength, reaction time, and brain structure.

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