# NEURAL CORRELATES OF AEROBIC FITNESS AND AGING: A CROSS-SECTIONAL INVESTIGATION USING FMRI, DTI AND TMS

By

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To my wife and family, whose love and care made this possible

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| | |
|---|---|
| ACSM | American College of Sports Medicine |
| AUC | Area Under Curve |
| BA | Brodmann's Area |
| BRU | Button Response Unit |
| BOLD | Blood Oxygenated Level Dependent |
| cSP | Contralateral Silent Period |
| EMG | Electromyograph |
| FA | Fractional Anisotropy |
| FDI | First Dorsal Interosseous |
| FDR | False Discovery Rate |
| fMRI | Functional Magnetic Resonance Imaging |
| HAROLD | Hemispheric Asymmetry Reduction in Older Adults |
| HRF | Hemodynamic Response Function |
| HTC | Hierarchical Task Complexity Hypothesis |
| lHI | Paired-pulse Interhemispheric Inhibition |
| iSP | Ipsilateral Silent Period |
| lM1 | Left Primary Motor Cortex |
| LMT | Lowest Motor Threshold |
| M1 | Primary Motor Cortex |
| M1S1 | Primary Sensorimotor Cortex |
| MD | Mean Diffusivity |
| MEP | Motor Evoked Potential |
| MET | Metabolic Equivalent of Task |
| MNI152 | Montreal Neurological Institute 152-Brain Average Template |

| | |
|---|---|
| MS | Multiple Sclerosis |
| MSO | Maximum Stimulator Output |
| MVC | Maximum Voluntary Contraction |
| PASA | Posterior Anterior Shift in Aging |
| pMC | Premotor Cortex |
| rM1 | Right Primary Motor Cortex |
| rTMS | Repetitive Transcranial Magnetic Stimulation |
| SMA | Supplementary Motor Area |
| TBSS | Tract Based Spatial Statistics |
| TCT | Trancallosal Conduction Time |
| TE | Time of Echo |
| TMS | Transcranial Magnetic Stimulation |
| TR | Time of Repetition |
| TT | Talairach Tournoux |
| $VO_2Max$ | Maximum Volume of Oxygen Consumption |

Abstract of Dissertation Presented to the Graduate School
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Aerobic exercise has been offered as a buffer against aging related decline in humans. Recently, evidence has indicated that chronological aging has been associated with decreases in measures of interhemispheric suppression during unimanual movements, but that such decreases may be mitigated by long-term aerobic fitness. The present research compared differences in measures of suppression of ipsilateral (right) primary motor cortex activity using functional magnetic resonance imaging (FMRI) and transcranial magnetic stimulation (TMS) during right hand finger movements. Participants groups were comprised of 14 sedentary older adults, 14 aerobically active older adults, and14 younger adults. All participants were right handed and reportedly healthy. Younger adults show the largest measures of ipsilateral primary motor cortex suppression as compared to older groups during both TMS (duration of ipsilateral silent period) and fMRI (magnitude of negative BOLD response). Aerobically active older adults show intermediate levels of interhemispheric suppression as compared to younger and sedentary older adults. Diffusion tensor imaging analysis did not reveal group differences associated with white matter density at motor crossing areas of the corpus callosum. These findings indicate that engagement in regular

aerobic exercise may mitigate declines in suppression of the activity in ipsilateral primary motor cortex characteristic of sedentary aging.

# CHAPTER 1
# INTRODUCTION

## Overview

Recent neuroimaging research has begun to differentiate between biological and chronological aging. Chronological aging is immutable and refers to the age of the individual in calendar years. Biological aging describes a person's physiological state in comparison to average healthy individuals across age range. For example, a person aged 60 years chronologically may exhibit some characteristics of physiology typically associated with the average healthy 30-year old, but others may express physiological traits characteristic of the average 80-year old. In geriatric terms, biological age exceeding chronological age might be considered using a "frailty" index which associates older biological age with increases in both physical and cognitive ailments. A higher frailty rating has been associated with a higher incidence in motor disorders such as Parkinson’s disease (Powell, 2008; Fisher et al., 2008), essential tremor (Louis et al., 2008), tardive dyskinesia, and some forms of dystonia (Go et al., 2009).

Identification of markers of biological age is a challenge for researchers and clinicians in the motor aging domain. Recent neuroimaging studies in the motor domain have begun to show distinctive patterns of activity associated with older and younger adults that potentially could be used as markers of biological age. These activity patterns relate to interhemispheric communication during unimanual motor activity and have been described by neuroimaging techniques including functional magnetic resonance imaging (fMRI) (McGregor et al., 2009; Talelli et al., 2008a) and transcranial magnetic stimulation (TMS) (Sale & Semmler, 2005; Peinemann et al., 2001). Using these imaging modalities, we now have putative markers to discern biologically older from biologically younger adults using patterns in their motor neurophysiology.

Research into biological aging is not just the identification of an individual's current state, but also for finding intervention to retard or even reverse the progression of biological age. One such intervention that has been proposed is aerobic exercise, which has shown some promise in the mitigation of aging-related declines in brain structure. The use of structural neuroimaging techniques, particularly anatomic MRI and diffusion tensor imaging (DTI) has provided valuable information about the potentially beneficial effect exercise has on structural neuroanatomy. For example, exercise has been associated with increases in overall brain volume (Colcombe et al., 2006), increases in volume of the hippocampus (Erickson et al., 2009), and increased density of gray matter (Colcombe et al., 2003). DTI research has indicated that aerobic fitness level may contribute to increased density in brain white matter, as well. A recent study by Marks et al., 2007 reported a positive correlation between white matter density measures from DTI (fractional anisotropy) and level of cardiovascular fitness (self-report) on a sample of older adults.

Recent evidence has shown that age-related changes in patterns of cortical activity, not just structure, may be altered in individuals with a history of significant aerobic exercise. In a recent study (McGregor et al., 2009), older and younger adults engaged in a unimanual learned sequence execution task during functional magnetic resonance imaging (fMRI). Results show highly stereotypic patterns of activity that differed between young and older adults with a single exception in the elderly group. This individual was a highly trained aerobic athlete whose patterns of cortical activity were characteristic of the younger samples. TMS has also shown that aerobic exercise may increase levels of intracortical primary motor cortex (M1) inhibition.

TMS is a technique in which a strong magnetic flux density (~1 Tesla) can be transiently introduced in to part of the brain of a living and behaving person. The changing magnetic field induced electrical current sin the conductive brain tissue, which in turn evoke neural activity. Magnetic field strength declines rapidly with distance deep from the skin surface the geometry of the magnetic lines of force relative to the oriented dielectric properties in the tissues act to limit the volume of brain tissue supporting the activity induced instantaneously by the TMS pulse. When the lateral primary motor cortex is stimulated with a single TMS pulse then muscles in the contralateral upper extremity can visibly twitch. Electromyograph (EMG) recording of the evoked muscle potential provides a more sensitive measure of the evoked muscle potentials than such qualitative visual observation. Of particular interest in the present context, EMG reveals a characteristic suppression of EMG in muscles of the opposite upper extremity (the hand ipsilateral to the cortical TMS pulse), an observation termed the “ipsilateral silent period. This suppression of EMG is related to decreases in amplitude of magnetic evoked potentials during paired pulse stimulation deemed interhemispheric inhibition.

fMRI is a technique in which a strong magnetic flux density (~3 Tesla in the present case) permeates the brain in a relative sustained an spatially more homogeneous manner than in TMS. The presence of this permeating magnetic field determines the radio frequency of resonance of hydrogen protons in water. Scanner controlled distortions of this magnetic field by gradients allows this resonance to be spatially encoded. Participant controlled distortions of the magnetic field are usually small but time locked to behaviors. Head motion creates artifacts and neural activity correlated in to time to a task creates magnetic susceptibility changes. Magnetic susceptibility differs between oxygenated and deoxygenated hemoglobin. At a place in

the brain where neural activity demands support form oxidative metabolism the relative concentrations of oxy vs. deoxygenated hemoglobin change. This particular susceptibility change is small (less than $1.5 \times 10^{-6}$) but the event physiologically induces a disproportionally large hemodynamic response in which increase perfusion by new blood dominates the magnetic susceptibility of the active brain region. fMRI based on the Blood Oxygenated Level Dependent (BOLD) contrast has limits: 1) being driven by oxidative metabolic demand it cannot inherently discriminate between excitatory and inhibitory effect on local neural activity, 2) it has a protracted time course, and 3) it is vulnerable to artifacts even partially locked in time to the task because the magnetic signals of BOLD contrast are quite small.

The term “inhibition” is common parlance in TMS literature to describe of decreased electromyography (EMG) output from a muscle when the cortex is stimulated with TMS pulse(s). Studies reporting decreases in fMRI activity in cortex ipsilateral to unimanual movements also have used the term “inhibition” (Riecker et al., 2006; Manson et al., 2006; Manson et al., 2008; Lenzi et al., 2007). However, this term is somewhat imprecise in its mechanistic inference of a decreased activity by inhibitory neurotransmitter as the proximate cause, an inference that cannot be directly demonstrated by either TMS or fMRI. Because transcallosal fibers in the corpus callosum are almost entirely glutamatergic with excitatory post-synaptic effects, ipsilateral “inhibition” outcomes must involve a secondary inhibitory connection. The suppressive effect on ipsilateral cortex likely derives from locally projecting inhibitory interneurons with short axons or axonal collaterals, the density of whose connections is known to decrease as individuals age. Moreover, to exhibit a decrease in BOLD signal from fMRI, the involvement of a tertiary neuron target would be necessitated. In light of

the current uncertainty in the physiology of interhemispheric communication, the term “suppression” will be used in the current thesis to refer to decreases in ipsilateral primary motor cortex BOLD activity, whereas use of the term “inhibition” will be restricted to TMS measures, as is common in the related literature.

To test the hypothesis that regular aerobic exercise changes interhemispheric communication dynamics within the motor system, the present research used fMRI and TMS to compare patterns of cortical motor activity across elderly adults who were either aerobically active or sedentary. A group of younger adults was also included in the current investigation. It was hypothesized that older adults who engage in regular bouts of aerobic exercise would exhibit patterns of interhemispheric activity similar to those shown in the younger group. An additional measure, diffusion tensor imaging (DTI), was taken to compare correlates of white matter integrity, the variation of which could potentially explain the predicted fitness-related differences in patterns of cortical activity. It was hypothesized that posterior areas of the corpus callosum, in which crossing fibers of the primary motor cortex reside, would show higher levels of fractional anisotropy (FA) in younger and aerobically active elderly adults as compared to sedentary elderly adults. Higher FA is interpreted in clinical DTI as evidence of greater integrity of white matter.

## Aging Related Changes in Interhemispheric Communication

During unimanual hand movements, the brain's right and left primary motor areas (M1) are thought to be in constant communication via the corpus callosum (Meyer et al., 1998; Reddy et al., 2000), though the exact nature and conduits of this interhemispheric transfer is as yet unclear. Volitional unimanual hand movement will almost invariably result in increased metabolic activity in the primary motor cortex contralateral to the

moving hand (Rao et al., 1993). However, the involvement of the ipsilateral cortex during such movements may vary according to one's biological age. In younger adults, increasing evidence from fMRI indicates that the ipsilateral primary motor cortex exhibits a suppression of activity, denoted by the presence of a negative BOLD signal, below the level of resting baseline conditions (Kastrup et al., 2008; Stefanovic et al., 2004; McGregor et al., 2009; Stefanovic et al., 2005; Newton et al., 2005; Aramaki et al., 2006; Allison et al., 2000; Hamzei et al., 2002; Hanajima et al., 2003). However, during similar movements in sedentary older adults, the ipsilateral cortex appears to be recruited (correlates of metabolic activity appear to increase in magnitude), a change indexed by fMRI by the presence of a positive BOLD signal in ipsilateral sensorimotor cortex (Riecker et al., 2006; McGregor et al., 2009; Hlushchuk & Hari, 2006).

The use of fMRI in the description of interhemispheric patterns of communication is a relatively recent development in the investigation of the human neural motor system. Since almost immediately after its inception (Barker et al., 1985), the “gold standard” technique for motor systems inquiry and the investigation of interhemispheric inhibition has been the use of transcranial magnetic stimulation (TMS). In younger adults, TMS has also revealed that unimanual movements are associated with increases in inhibition of the ipsilateral cortex (Muellbacher et al., 2000; Giovannelli et al., 2008). Aging-related studies of interhemispheric communication have employed TMS and, similar to findings from fMRI, have reported that aging may indeed be associated with a loss of interhemispheric inhibition. For example, using a paired-pulse TMS paradigm, Peinemann et al., (2001) tested differences between age groups (total N=26) on levels of interhemispheric inhibition (IHI) and found age to be associated with

decreases in IHI. This finding has been recently replicated by other paired-pulse TMS research involving larger sample sizes (Talelli et al., 2008a; Talelli et al., 2008b).

An additional TMS technique that has been used to investigate aging related change in interhemispheric communication involves the application of a single TMS pulse to the contralateral (e.g. -left) motor cortex during unimanual muscle contraction in the ipsilateral (e.g.- left) hand. The resulting temporary depression in the muscle's electromyography (EMG) is called the ipsilateral silent period (Wasserman et al., 1993) and is generally considered to be a measure of transcallosal inhibition (Meyer et al., 1998). Using this technique, Sale and Semmler (2005) compared the ipsilateral silent period (iSP) across younger and older adults and reported that older adults evidenced a significantly shorter iSP than that of the younger group. More recently, Fujiyama et al. (2009) compared older and younger adults' ipsilateral and contralateral (left M1 stimulation during right hand muscle activity) silent periods during interlimb coordination and found that the duration of both measures was lower in older samples.

The findings from fMRI and TMS indicate that chronological age, which was used in the studies to differentiate age groups, appears to be associated with decreased inferred inhibition of the ipsilateral sensorimotor cortex during unimanual tasks. However, it is important to note that not all individuals evidence the patterns of activity described by the aforementioned group analyses. Further, perhaps the most consistent finding in aging related research is the variability of patterns of activity in older adults (D'Esposito et al., 2003). A likely contributor to the reported variability in findings related to aging adults is the conflation of biological age with chronological age.

## Biological Aging and Aerobic Exercise

Because progressive biological aging in sedentary adults is associated with declines in the neurological motor system, an important application of aging-related research is the identification of interventions that may slow, stop or even reverse the biological aging process. This goal is most pressing in adults nearing the biological sixth decade where losses tend accelerate into more pronounced deficits in motor neurophysiology (Smith et al., 1999; Castillo-Garzon et al., 2006). For example, motor disorders such as Parkinson's disease (Van Den Eeden et al., 2003), essential tremor (Louis et al., 2009), and some forms of dystonia (Powell, 2008; Go et al., 2009) all exhibit non-linear increases in incidence after the sixtieth year. One intervention that has shown promise in rehabilitative and preventative care is the regular engagement in aerobic exercise, which may alter biological age and patterns of cortical activity which may serve as a marker thereof.

Aerobic exercise is a general term given to describe extended (> 20 minutes) periods of increased physical activity evidencing increased heart rate with a resulting improvement in the body's efficiency of oxygen consumption (Cooper, 1968). Aerobic exercise is currently under investigation by a number of groups for its potential as a regimen or adjuvant for treatment in the rehabilitation of motor pathology. For example, promising findings have been reported using exercise as an adjuvant to motor rehabilitative therapy after stroke (Enzinger et al., 2009; Macko et al., 2005). In a recent study (Luft et al., 2008), stroke patients attempting locomotor rehabilitation were divided into either a control group involved in a non-aerobic stretching routine or a group engaging in treadmill based aerobic exercise program. Participants in the aerobic training group evidenced larger and more permanent gains on measures of locomotor

stability and velocity. Along with behavioral outcome measures described above, Luft et al., (2009) also acquired fMRI on stroke patients during a leg flexion task both pre and post intervention. Group comparisons of the fMRI data revealed differences in the recruitment of the cerebellum and portions of the midbrain known to be involved in the coordination of motor activity. The group concluded that the aerobic training regimen may have assisted to engage these coordinative motor circuits, which could be responsible for the sustained behavioral gains in locomotive stability and velocity evidenced by the aerobic training group.

**Aerobic Exercise and Biological Aging: Neuroimaging**

The use of neuroimaging techniques, particularly magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) has begun to provide valuable information about the positive effect exercise has on structural neuroanatomy. Exercise has been associated with increases in overall brain volume (Colcombe et al., 2006), increases in gray matter density (Colcombe et al., 2003), and may contribute to an increased density in brain white matter (Marks et al., 2007; Gordon et al., 2008).

In addition to structural imaging reports, some of the most exciting findings exploring aerobic fitness' effects on the aging brain have come from functional neuroimaging methodologies. Functional MRI has also been used to investigate differences in brain activity on tasks involving prefrontal areas between individuals of varying aerobic fitness. In a cross-sectional study, Colcombe et al., (2004) reported that participants who were aerobically fit tended to show brain activation consistent with younger adults, while sedentary older adults, who also exhibited lower memory capacity during behavioral testing, indicated patterns of over-activity in the medial prefrontal cortex. This activity was interpreted as nonselective, task-interfering as it correlate with

decreased task performance. A longitudinal fMRI investigation was also completed by Colcombe et al. (2004), and targeted the direct effects of exercise intervention on sedentary populations during the same task. In this study component, participants were either divided into a group engaging in an aerobic exercise program or a sedentary control group. Older adults who engaged in the exercise intervention program tended to show faster and more accurate performance on memory search task in behavioral testing. Further, exercising older adults evidenced changes in brain activity during fMRI of the same task that more closely resembled activation patterns characteristic of younger adults.

**Interhemispheric Suppression as a Marker of Biological Age**

While for many years, the dominant ethos regarding neurological systems offered that aging is a process of subtraction and decline, findings now exist which indicate a potential for the motor system to maintain younger interhemispheric motor activity patterns despite increasing age. In McGregor et al., (2009), elderly and younger adults were tested using an fMRI protocol involving unimanual button press. In all reported sedentary (determined via self-report) elderly adults engaging in fMRI unimanual response tasks showed patterns of primary motor activity consistent with group averages in older adults (Riecker et al., 2006; Talelli et al., 2008a). That is, during the execution of the button press with the right hand, all elderly participants excepting one evidenced increased levels of positive BOLD activity in bilateral primary sensorimotor cortex. The elderly participant (aged 68 years) that did not evidence the bilateral recruitment pattern reported that they were a lifelong distance athlete. Investigation of this participants' motor cortex activity during the fMRI task revealed patterns of activity typical of young adults (see Figure 1-1).

In addition to findings from McGregor et al., (2009), evidence exists from a multimodality investigation offering support for biological and not chronological age as being responsible for changes in patterns of interhemispheric suppression. Talleli et al. (2008b) conducted a study involving both fMRI and TMS in the investigation of patterns of interhemispheric activity from thirty individuals selected from age groupings across the lifespan. Using a paired-pulse protocol to investigate interhemispheric inhibition (IHI) with TMS, Talelli et al. (2008b) noted that chronological age was associated with a larger MEP amplitude in electromyography (decreased IHI) of ipsilateral thenar hand muscles during paired pulse stimulation. The group also asked the same participants to engage in a unimanual target force matching task during fMRI to investigate potential changes in primary motor cortex activity. In an analogous finding to the TMS data, fMRI revealed that chronological age was correlated with increases in activity in the lateral ipsilateral motor cortex. That is, during fMRI, chronologically older adults tended to show a positive BOLD signal in the ipsilateral motor cortex.

However, Talleli et al. (2008b) also completed a regression analysis involving the prediction of both the TMS and fMRI data based on either chronological age or cortical reactivity measures. Cortical reactivity is a TMS measure relating to the amount of stimulator output (current to coil) required to generate motor evoked potentials (MEP) in the target muscle. This measure has been offered as a potential marker of biological age (Oliviero et al., 2006; Fathi et al., in press) and has been correlated with changes in interhemispheric inhibition (Fathi et al., in press). Interestingly, it was the cortical reactivity measure (not chronological age) that best predicted the changes in interhemispheric suppression as indexed by both fMRI and TMS. Further, the group reported that when the upper age groups were removed from analysis, cortical reactivity

continued to predict decreases in ipsilateral suppression in participants in young middle age (40-50).

Patterns of change in cortical activity due to aerobic exercise have also been reported in TMS related literature including those involving the rehabilitation of motor pathology (Lefaucher et al., 2004; Buhmann et al., 2004). Recently, Fisher et al., (2008) investigated the effects of exercise on TMS measures of individuals afflicted with Parkinson's disease. After enrolling thirty participants matched for disease severity (using Unified Parkinson's Disease Rating Scale scores), the group evenly divided the individuals into three groups: a) a high-intensity body-weight supported treadmill training program; b) low intensity (light resistance training, chair to standing, etc.); or c) a zero physical training education group. As Parkinson's disease has been reported to decrease levels of intracortical (Cantello et al., 2007) and interhemispheric inhibition (Li et al., 2007; Fisher et al., 2008), the group hypothesized that the regular aerobic exercise activity would increase these measures. The authors employed TMS and tested participants prior to and after intervention. In support of their hypothesis, only patients in the high-intensity aerobic exercise group evidenced both increases in cortical reactivity and increased levels of cortical inhibition as compared to their first session. Other groups did not evidence a significant change from baseline.

**Cerebral White Matter and Interhemispheric Communication**

An investigation into the patterns of change in interhemispheric activity associated with aging is limited in scope without addressing a mechanism by which such changes occur. Interhemispheric communication in primary motor areas is believed to be largely mediated by the corpus callosum. Support for this using both fMRI (Reddy et al., 2000) and TMS (Meyer et al., 1998; Meyer et al., 1995) has come from investigations of

interhemispheric inhibition with individuals afflicted with callosal agenesis or after callosotomy (for alleviation of epilepsy). Using TMS, Meyer et al., (1998) compared the ipsilateral silent periods of healthy controls with patients with either partial or complete callosal agenesis. The group found that the silent period was either absent or severely degraded in all patients with abnormalities in the medial and posterior truncus of the corpus callosum.

Evidence from populations afflicted with multiple sclerosis (MS) also indicates a relationship between interhemispheric suppression and white matter integrity. In addition to the deleterious effects MS has on neural communication in the contralateral corticospinal tract (typically measured by changes in central motor conduction time; see Höppner et al., 1999; Kale et al., 2009), the disease also results in focal destruction of transcallosal fibers affecting interhemispheric transfer. Investigations with TMS have revealed significant decreases in levels of interhemispheric inhibition in comparisons of MS patients with age-matched controls (Boroojerdi et al., 1998). fMRI studies have also revealed changes in interhemispheric communication due to MS. In a large (N=116), multi-center study using fMRI, Manson et al., (2008) recently investigated the potential relationship between levels of ipsilateral suppression (measured by BOLD signal in ipsilateral sensorimotor cortex) and MS disease severity. During functional image acquisition, the group asked participants to engage in a unimanual hand flexion-extension task presented in a block paradigm. Analysis of the fMRI data indicated that disease severity was positively correlated with increased BOLD activity in the ipsilateral cortex during fMRI potentially indicating that more severely affected patients evidenced decreases ipsilateral suppression.

A technology which has offered great promise in the imaging of white matter pathways in the brain is diffusion tensor imaging (DTI). The inclusion of this structural imaging technique with measures of interhemispheric suppression could add a great deal to our understanding of the role of callosal integrity in interhemispheric communication. However, to date, only one reported study has combined both TMS and fMRI to investigate the effects of MS on interhemispheric communication. Lenzi et al., (2007) compared 16 MS patients with 16 age matched controls (median age: 36) using fMRI (BOLD activity in ipsilateral sensorimotor cortex during unimanual tasks) and TMS (transcallosal inhibition) to measure levels of ipsilateral suppression. Lenzi et al. also acquired a six-direction diffusion weighted scan for tensor fitting and estimation of fractional anisotropy (FA) and mean diffusivity (MD). FA and MD measures can be used to estimate the regional integrity of white matter. The group reported that the MS patients evidenced significant differences in BOLD activity in the ipsilateral sensorimotor cortex (M1S1) during fMRI and decreased levels of transcallosal suppression as compared to controls. Importantly, Lenzi et al., found that the variation in both TMS and fMRI measures was highly correlated with levels of FA and MD from DTI.

As these reports strongly implicate the role of white matter decline in altered patterns of interhemispheric communication, it is relevant to note that aging in healthy populations has also been associated with decreases in white matter integrity. In aging related literature using DTI (see Madden et al.,2009 for review), increasing age has been associated with decreases in FA and MD, particularly in motor related (corticospinal and transcallosal) fiber tracts. In a recently reported investigation, Westlye et al. (in press) acquired 30-direction DTI scans on 430 individuals across age groups. The results of the study indicated that white matter tracts tend to show a somewhat

linear decrease in FA beginning in young adulthood (~28 years). This linear trend in decline continues through early middle age after which the white matter FA decreases begin to accelerate. Interestingly, while some researchers have claimed that motor fibers are less impacted by aging related decline as compared to prefrontal areas or associative white matter pathways (see Sullivan and Pfefferbaum, 2006), Westlye et al. (in press) showed that fibers from both the motor transcallosal and corticospinal tract both evidence accelerated decline beginning around 55 years of age. It is possible that aging related white matter decline is responsible for the reported differences in interhemispheric communication across age groups (McGregor et al., 2009; Ward et al., 2008; Talelli et al., 2008b).

## Current Investigation: Multi-modal Investigation on the Effects of Aerobic Fitness on Aging Related Changes in Interhemispheric Primary Motor Cortex Suppression

The present study was designed to investigate the effect of aerobic activity level on aging related changes in measures of interhemispheric suppression. Employing both fMRI and TMS paradigms that have been shown previously to be sensitive to aging related change in interhemispheric communication, the current investigation compared data on both measures from a grouping elderly adults who engaged in regular aerobic exercise with sedentary elderly adults. Data from a group of younger adults was also collected. In addition to fMRI and TMS measures, diffusion tensor imaging data was collected and analyzed for potential group differences.

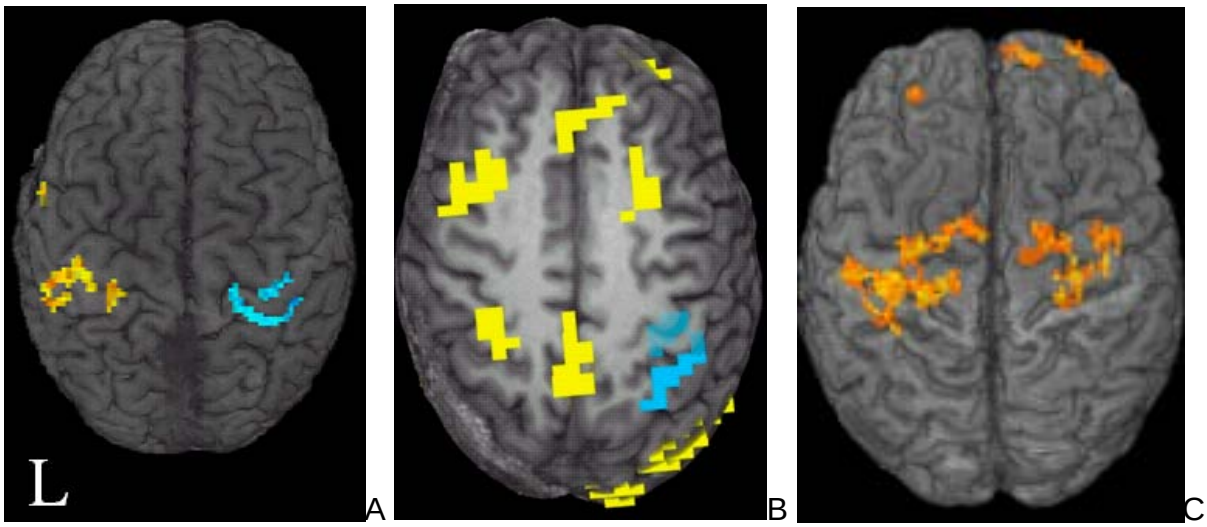



Figure 1-1. Shown are fMRI data from unimanual button press tasks from A) a younger adult and B) 68-year old highly trained aerobic athlete and C) from a sedentary older adult. Hue indicates significance at p<.0001, uncorrected: “Warm” colors (orange, yellow, red) indicated positive BOLD response, “cold” colors (blue) indicate negative BOLD response. In right primary motor cortex (rM1), both younger and highly aerobically trained older adults exhibit negative BOLD response.

# CHAPTER 2
# HYPOTHESES

## BOLD fMRI

I hypothesized that young adults as well as older adults engaging in high levels of aerobic activity will have, on average, a negative BOLD response in primary motor cortex ipsilateral to the moving hand during fMRI of unimanual hand movements. During the same tasks, sedentary older adults will have on average a positive BOLD response in ipsilateral motor hand cortex. Time courses of the hemodynamic responses in ipsilateral primary motor cortex will differ between sedentary older adults and both younger adults and aerobically active older adults.

Assessed level of aerobic activity ("fitness") was hypothesized to correlate with amplitude and direction of these fMRI measures in the ipsilateral primary motor areas at the level of individual participants. Specifically, the composite index used to assess aerobic activity or "fitness" assigns a low score for a high degree of aerobic activity, while sedentary results in a high score. Thus, the sedentary older adults will typically have a high composite activity index and typically positive BOLD fMRI, while younger adults will typically have a low composite activity index and typically negative BOLD. Aerobically active older adults presumably will lie somewhere between these extremes on both their composite activity indices and their BOLD responses.

## TMS

I hypothesized that the average ipsilateral silent period of aerobically active older adults will be longer in duration than that of the sedentary older adults. Younger adults are predicted to have the longest average ipsilateral silent period.

Transcallosal conduction time (TCT), derived as the difference between ipsilateral silent period latency and contralateral silent period latency, is expected to be shorter on

average in aerobically active older adults as compared to sedentary older adults. Younger adults will on average have the shortest TCT.

Cortical reactivity, measured by motor threshold currents and cortical recruitment curves, is expected to differ between on average between aerobically active and sedentary older adults. Aerobically active older adults are expected to show higher levels of cortical reactivity when compared to sedentary older adults.

**DTI**

Composite activity index scores will correlate negatively with fractional anisotropy (FA) characterizing white matter in the older age groups. Physically fit (lower scoring) older adults are predicted to exhibit larger FA, or more directionality in the diffusion of water, in the posterior trunk of the corpus callosum. I hypothesized that participants will show negative correlation between BOLD responses in ipsilateral primary motor hand cortex and FA in posterior corpus callosum. For sedentary older adults, as FA decreases in the corpus callosum participants will show increased levels of positive BOLD. For both younger and aerobically active older adults the predicted positive correlation will reflect that as FA decreases in the corpus callosum participants will show decreased levels of negative BOLD.

# CHAPTER 3
# METHODS

## Participants

Right handed, native English speaking participants enrolled in the current study and were reportedly healthy at the time of screening and study participation. Handedness was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971). As the current study involved a submaximal exercise assessment, all elderly participants were required to obtain a physician's clearance (see Appendix A) prior to participation in accordance with recommendations set forth by the American College of Sports Medicine (ACSM). To ensure participant safety, we excluded, after consultation with a medical doctor, all individuals with cardiac history (angina, prior cardiac arrest, uncontrolled hypertension) contraindicating tests of aerobic fitness. Also excluded were individuals with history of dementia, neurological disorder (tremor, stroke, motor disorders, multiple sclerosis, etc.), major psychological disorder (major depression, schizophrenia, etc.), hearing difficulties. A medication history was also taken for each participant. Persons with conditions or on medications that were contraindicated for MRI (see Appendix B) were also disqualified from the study. Cortical activation characteristics in primary motor cortex may be altered by skilled (Krampe et al., 2002; Jäncke et al., 2002) or repeated digit movement practice (Gordon et al, 1998) so participants were screened and excluded if they engaged in repeated skilled finger practice (specified as at least four one-hour training sessions performed on a weekly basis). Study personnel completed the informed consent process with each participant following protocols approved by the University of Florida's Institutional Review Board (IRB-01).

We enrolled participants from two adult age groups in the current study: younger (n=16; range: 18-37 years) and elderly (n=32; range: 60-85). Due to complications with TMS or scheduling (see Results Section), six participants (two from each group) were removed from study participation. As a result, data from forty-two participants (n=14 per group) were considered for the study. Elderly individuals were divided in two categories based on reported exercise activity on a physical activity inventory (see Appendix C). The first group (n=14) was comprised of healthy elderly adults that engaged in voluntary aerobic activity for fewer than 45 total minutes per week and was termed the “sedentary group”. The second group of elderly adults (n=14) was comprised of healthy individuals who engaged in three bouts of voluntary moderate to strenuous exercise lasting at least 45 minutes at least three times per week. This group was termed the “aerobically active group”. Physical activity inventories were also completed for younger adults, but not used as a criterion for exclusion or differentiation within age group. Participants were recruited from three primary sources: the Veteran community at the Malcom Randall VA Medical Center, a database of older adults at the Claude Pepper Center at the University of Florida’s Institute on Aging, and through advertisement in local media. Participant characteristics are listed in Table 3-1.

Significant differences were found between older (sedentary and aerobically active) and younger groups. No differences were found between groups on level of education or score on the Mini-Mental Status Exam. Group comparisons of handedness using the Edinburgh Handedness inventory did not reveal significant differences between any of the sampled groups. While gender was not symmetric between groups, the differences were not statistically significant.

Table 3-1. Participant Characteristics

| | Active Elderly | Sedentary Elderly | Young |
|---|---|---|---|
| Age | 69.2 (6.24) [60-85] ^ | 70.56 (7.2) [63-83] * | 22.6 (2.46) [19-37] *^ |
| N/Gender | 14 / 7 Female | 14 / 9 Female | 14 / 5 Female |
| Education | 16.7 (1.85) [15-20] | 15.7 (3.07) [12-20] | 16.6 (1.62) [13-20] |
| MMSE | 29.1 (0.57) [28-30] | 28.8 (1.20) [27-30] | 28.8 (0.68) [28-30] |

Cell values denote group means. Parentheses indicate standard deviation within cell. Bracket indicates range. Student's t-test contrast significance at $p<.05$ denoted by: * = Younger vs. Sedentary; ^ = Younger vs. Active; ° = Sedentary vs. Active.

## Participation Sessions and Procedures

Participation for the study occurred over two 3-hour sessions separated by at least 8 calendar days but not more than 21 days. Participants were asked to refrain from drinking caffeinated beverages at least three hours prior to each session to prevent potential signal alteration in imaging (see Liu et al., 2004).

### Session 1: Neuropsychological testing and exercise challenge

At the beginning of the first session, participants were again fully informed of the details of participation in the study and completed an informed consenting process with researchers using an approved IRB protocol (#474-1997). After consent was given, participants underwent a battery of neuropsychological tests both paper and computer based. The neuropsychological measures involved the following examinations (*denotes computer based testing): Mini-Mental State Examination (MMSE); Hopkins Verbal Learning Test (HVLT); Stroop Interference Test; Trail Making Test; Letter series; Letter-number sequencing; Symbol digit*; Number copy*; Erickson Flanker Task*; N-back*; Wechsler Adult Intelligence digit span test; Controlled Oral Word Association (COWA); Naming task*; Finger tapping*; and a dual-performance (overt category member generation during finger tapping) language task*. The duration of the

neuropsychological tests was between two hours and two hours and fifteen minutes. Two ten-minute breaks were programmed into the testing protocol at 45 and 75 minutes, respectively. Additional 5-minute breaks were granted as requested by participants.

**Exercise challenge**

After completion of the neuropsychological battery, participants were granted a restroom break after which the 12-minute exercise assessment commenced. The exercise test was administered by two CPR-certified research personnel and at all times, a phone was available to call for emergency assistance in case of an adverse health event. Prior to testing, the participant's sitting blood pressure was taken with an automated blood pressure cuff to assess potential Stage I hypertension (blood pressure reading of above 140/90 mmHg), which would contraindicate performance of the exercise test. A chest strap heart rate monitor was then given to the participant, and their standing heart rate was taken. Maximum recommended heart rate (calculated as 217-[age x .85]; from Miller et al., 1993) during the treadmill was derived from this measure. If a participant exceeded 85% of maximal heart rate at any time during the exercise session, the participant was asked to slow their pace. During the 12-minute test, heart rate was recorded at 1 minute intervals though continuously monitored for safety.

An exercise physiologist (Todd Manini, PhD) assisted with the design and implementation of the submaximal physical fitness assessment. The test followed submaximal fitness testing guidelines as prescribed by the American College of Sports Medicine (ACSM) and proceeded as follows. Prior to the participant stepping onto the treadmill (Weslo Cadence 440, ICON Health, Logan, Utah) a researcher gave basic

instruction as to the device's operation. After confirming understanding, the participant mounted the treadmill and engaged the device at a low speed until the researcher confirmed the participant's balance and comfort. The participant was then instructed to: "travel as far as you feel comfortable for 12 minutes". Upon receiving confirmation of the participants' understanding and willingness to proceed, the researcher reset the treadmill's distance counter and began the recording period. A continuous dialogue was maintained with the participant to ensure submaximal effort expenditure and normal pulmonary function over the 12-minute span. If a participant evidenced extremely labored breathing or prolonged inattention to the dialogue, they were instructed to slow their pace. At the 12 minute mark, the researcher recorded the distance traveled and instructed the participant to "cool down" (walk at slow speed) for one minute, after which they were to dismount the treadmill. Researchers again recorded the participant's sitting blood pressure after five minutes of rest and began instruction of the actigraphy portion of the study.

**Actigraphy**

Immediately prior to departure from the first participation session, the participant was given an 85-gram hip mounted tri-axial accelerometer (Model X1A, Gulf Coast Data Concepts, Gulfport, MS) along with instruction on its use. The participant was asked to wear the accelerometer on their right hip at all times (excluding water activities and sleep) for the period of seven days beginning with the next calendar day after the first participation session. The accelerometer recorded G-force changes (transformed from device specific "counts") at a rate of 8Hz continuously throughout the monitoring session and stored this data on a 1GB mini-SecureDigital (miniSD) non-volatile memory card in comma-separated value format. The device was set to omit G-force changes

frequencies not typically associated with human movement (i.e. - <.09Hz or >5Hz). The count data from the accelerometer was later converted to metabolic equivalent task (MET) units. The total MET expenditure and average MET expenditure for bouts of activity were later calculated for each participant from this data using XLR8 2.0 software provided by the device's manufacturer. During the weeklong activity assessment, the participant was also asked to report activity using a daily record form (Appendix D), which was included in the overall fitness assessment. Upon leaving the session, participants were asked to move in their normal pattern of activity in attempt to limit potential changes in activity levels due to monitoring (demand characteristics).

**Session 2: Functional Imaging and Transcranial Magnetic Stimulation**

After at least eight calendar days, which allowed for the actigraphy, the participant was scheduled for the second and final participation session at which time they were to return the actigraph and activity log. At the beginning of this session, the participant was greeted and brought to the Brain Rehabilitation Research Center's (BRRC's) Transcranial Magnetic Stimulation Laboratory (TMS Lab) for the TMS procedure. Immediately prior to the application of TMS, participants gave informed consent to the testing protocol (using IRB-01 #462-2006) including the completion of a TMS screening form (see Appendix E) and removed any metal or contraindicated apparel (watch, bracelets, glasses, etc.) from their person.

**Single-pulse transcranial magnetic stimulation**

For the TMS procedure, participants sat in a comfortable chair within the confines of a stereotactic frame used to position the head for neuro-navigated stimulation. Electromyography (EMG) was taken from the FDI muscle on both hands. Muscle activation was monitored with a real-time oscilloscope software package (Scope 4.0,

ADInstruments Ltd, Colorado Springs, CO). A Magstim 200 magnetic stimulator (The Magstim Company Ltd, Carmarthenshire, UK) and an iron-core figure of 8 coil was used to stimulate the left primary motor cortex during the initial mapping procedure. Neuronavigation of the stimulation to target cortex was accomplished using coil registration to a standardized brain image or “stock brain” provided by BrainSight software (BrainSight Ltd, Montreal, Quebec). During stimulation, the coil was placed tangential to the scalp with the handle pointing backwards and 45 degrees away from the midline. The scalp site corresponding to the lowest stimulator output sufficient to generate a magnetic evoked potential (MEP) of at least 50 mV in 6 out of ten trials was defined as the area of lowest motor threshold (LMT), also known as the “hotspot”. This hotspot was the single site of stimulation for all measures in the current investigation, which are described below.

Five single pulse TMS measures were taken for the current study: latency and duration of contralateral silent period (cSP) and ipsilateral silent period (iSP), transcallosal conduction time (TCT).

The contralateral and ipsilateral silent periods were determined using a procedure based on a longstanding method (Wasserman et al. 1993). For contralateral silent period, the right FDI muscle was contracted via pinch grip at 25% maximal voluntary contraction (determined by grip dynamometer) and an 80% LMT stimulus was delivered to the left primary motor area FDI "hotspot", previously determined by an initial sensitivity assessment. For the ipsilateral silent period assessment the left FDI muscle is contracted at a 50% of MVC. Stimulator output equivalent to 150% LMT is delivered to the left FDI hotspot.

**Functional imaging**

After the TMS session, the participant was brought to the McKnight Brain Institute for the MRI portion of the study.

**Parameters.** Magnetic resonance images were acquired on a 3 Tesla Achieva Whole-Body Scanner (Philips) using an 8-channel SENSE radio frequency head coil. Head motion was minimized using foam padding. Before functional imaging sequences, structural images were also acquired (160 × 1.0 mm thick sagittal slices, using a 3D T1-weighted sequence: time of echo (TE) = 4.13 ms; time of repetition (TR) = 9.8 ms; flip angle (FA) = 8). Whole brain high-resolution echo planar functional images (EPI) were acquired using 55 × 2 mm thick axial slices (TE = 30 ms; TR = 4000 ms; FA = 90). For DTI, a 7-minute single-shot echo-planar, T2-weighted sequence was used to acquire diffusion-weighted data with the spatial resolution of 2 × 2 × 2 mm. The sequence parameters were TE/TR = 55/8000 ms, with 33 diffusion-weighted directions and two diffusion weighing B values of 0 (reference volume) and 1000.

Stimuli were presented on a custom-built, first surface mirror presentation system situated at the rear bore aperture of the magnet. Stimuli were sent via personal computer (PC) to an Optoma projector (Optoma Inc., Milpitas, CA) at a field of 1024x768 pixels.

**Tasks.** Two block-design right-hand motor tasks were used to evaluate interhemispheric cortical activation patterns. Both tasks have been reported sensitive to aging-related differences in interhemispheric suppression (McGregor et al., 2009-Chapter Two); Ward et al., 2008). Blocks consisted of seven images (28 seconds) for both rest and active conditions and six block cycles (alternating between 7 rest images and 7 active images) comprised each run (5 minutes 36 seconds). In the scanner,

participants engaged in two runs of each motor task and all performance data (accuracy, reaction times) was saved for later analysis. Participants trained on the both tasks outside of the scanner and again inside the scanner immediately prior to data acquisition. Between runs, participants again verified their understanding of each upcoming task via verbal report.

Mirror movements (symmetric movement of the opposite hand) were of concern for unimanual digit manipulations (see Hoy et al., 2004). To monitor for such movements, force output of the left first dorsal interosseous muscle (FDI) was recorded during practice sessions outside the scanner. During this procedure, a standard hand clench bulb dynamometer (Baseline Systems, Modesto, CA) was placed in the right hand of the participant. A second bulb dynamometer connected to a laptop computer was placed in the left hand of the participant and the participant's maximum voluntary contraction for both devices was taken. During the mirror movement assessment, the participant was asked to maintain a 25% MVC load on the right hand dynamometer and a 2% MVC load with the left hand, which served as the baseline for the task. Participants performed three trials of 5 seconds in squeeze duration. Deviation of over 5% MVC in the left dynamometer during right FDI contraction was interpreted as evidence of mirror movements. A brief practice period was given to the participants prior to the assessment.

**Finger opposition ("tapping") motor task.** The first motor task was a block presentation of a repeated button press using opposition of the index finger and thumb ("tapping"). This task has been shown (Allison et al., 2000; Riecker et al., 2006) to exhibit a negative BOLD response in ipsilateral primary motor cortex (M1) in younger adults at spatial resolutions comparable to those planned for the present investigation.

Performance of similar tasks in sedentary elderly samples, however, shows positive BOLD responses in ipsilateral M1 (McGregor et al., 2009-Chapter Two). Stimuli were presented using E-Prime software (PST Software, Pittsburgh, PA) on a paradigm designed by the author. Button responses were made on a RP04U button response unit (BRU) manufactured by MagConcept (Sunnyvale, CA) connected to the presentation computer.

During the functional run, participants fixated gaze on a central fixation cross of a computer screen throughout each of 2 runs. Blocks were cued by the change of fixation cross varying between and the word “Squeeze” (movement condition) or the word “Rest” (rest condition). During the movement condition, participants were instructed to time button presses with the flashing visual stimulus (2 Hz). Trials were briefly practiced in the scanner prior to image acquisition. Researchers in the scanner operation room monitored subject performance during the task.

**Force matching task.** A second motor task was employed in attempt to differentiate the effect of muscle recruitment on patterns interhemispheric activity. As previous studies (e.g. - Spraker et al., 2007) have indicated that increasing muscle recruitment may influence levels of ipsilateral suppression, the inclusion of a target force matching task of a specific intensity may quantitatively describe such activity. In this task, we asked participants to match grip force to a target level (35%) set at of the participants’ maximum voluntary contraction (MVC), which was taken in the scanner immediately prior to image acquisition. During scanning, participants performed a series of isometric pinch squeezes in block cycle presentation with the index and middle fingers of dominant right hand using a MRI-compatible manipulandum (BioPac, Inc., Goleta, CA; see Figure 3-2) customized for the project by the author.

Stimuli were presented using software designed by the author using the LabView 8.6 Development Environment (National Instruments, Austin, TX). Throughout the trial, either a visual fixation point remained in the center of the screen or force feedback cues (represented as a vertical bar) were presented on the screen. Within trial blocks, target force for the hand grip were visually cued using horizontally presented line parallels with vertical offset equal to +/-3% (relative to MVC). During trials, the participant was instructed to position the horizontal force feedback bar (white in color) in between the target force parallels (see Figure 3-3). Presentation timing was based, in part, on previous studies involving force generation (Spraker et al., 2007), and consisted of 28 second pinch squeeze blocks followed by symmetric rest. A total of 12 block cycles were presented across two runs (6 per run). Prior to image acquisition, participants engaged in a trial run to verify task competency and understanding. Between runs, task instructions were again repeated to the participant and verified via verbal report.

## Analysis

### Behavioral Measures

Group data for behavioral measures were compared using between-subjects Student's t-test and p-values ≤ 0.05 were considered statistically significant. Statistical analyses were completed using the application JMP 7.0 (SAS Institute, Cary, NC), unless otherwise specified.

**Reaction time.** Responses on the computer-based visuomotor reaction time task were analyzed between groups.

**Aerobic activity composite.** Different aspects of aerobic fitness have been reported to vary between participants both highly fit and sedentary (Buchman et al., 2007; Maddison et al., 2009; Lamb & Brodie, 1990). As such, the current study indexed

aerobic exercise using an index of three measures (activity survey, 12-minute treadmill test, actigraphy) rather than a single assessment. A common method used in exercise related research is to generate a composite score of all measures into a ranked aerobic activity index. To this end, a composite score of aerobic activity in the current study was generated by rank ordering scores within each measure across all participants and then summing each individuals rank score across measures. A lower score indicates a higher level of aerobic activity. Composites between groups were analyzed using between-subject's Student's t-test.

**fMRI task measures.** Grip strength and performance accuracy on fMRI tasks (tapping rate and force production) were compared between groups.

**Neurophysiological measures**

**Transcranial magnetic stimulation.** Four measures were analyzed from TMS: latency and duration of ipsilateral silent period (iSP) and of contralateral silent period. Transcallosal conduction time (TCT) was derived from those measures. All EMG data was rectified prior to analysis. The latency of MEPs was measured from the onset of the stimulus presentation to the onset of the MEP (see Figure 4-1 for illustration of electromyograph measures). Onset and end latency of the cSP and iSP were taken at the initial and final intersections of the averaged signal with baseline indicating 80% of the background EMG level; the duration of EMG suppression between these two points was computed. Transcallosal conduction time was calculated as: iSP latency – cSP latency (Deftereos et al., 2008). Group comparisons of TMS measures were analyzed by between-subjects Student's t-test and p-values $< 0.05$ were considered statistically significant.

## Neuroimaging

### fMRI

Functional images were analyzed and overlaid onto structural images with the Analysis of Functional Neuroimaging (AFNI) program (Cox, 1996). To mitigate spatial deviation from the structural to functional images, a local Pearson correlation registration procedure was implements with AFNI's 3dAllineate program. To minimize the effects of head motion, time series images were spatially registered in 3-dimensional space using a linear rigid-body transform as implemented by AFNI's 3dvolreg. A subject's data was excluded from further analyses if any time series of a subject is judged from visual inspection to contain a significant number of images with gross artifacts or residual motion. To control for multiple comparisons, a False Discovery Rate correction (Genovese et al., 2002) procedure was utilized on fMRI statistical maps using AFNI's 3dFDR program.

**fMRI Baseline Comparison.** The current study was concerned with the response of the ipsilateral (right) primary motor cortex during actions performed by right hand. It was hypothesized that sedentary elderly adults would show an increase in metabolic activity (i.e. – a positive BOLD response) in this area, while younger adults and aerobically active elderly adults will show suppression (i.e. - a negative BOLD response). To assess this, a within-group analysis of average hemodynamic response functions in primary motor cortex was performed. For this procedure, functional images were spatially smoothed using a 3 mm full-width half-maximum (FWHM) Gaussian filter to compensate for variability in structural and functional anatomy across participants. Anatomic and functional images were then interpolated to volumes with 1 $mm^3$ voxels, registered using manual spatial markers and converted to stereotaxic space of Talairach and Tournoux (1988) as implemented by AFNI. Estimates of hemodynamic

response functions (HRF) were generated from a 12-lag Dirac delta function (model free) deconvolution procedure (as implemented by AFNI's 3dDeconvolve) for each participant. Area-under-the-curve (AUC) of each voxel's estimated HRF during active response were entered into a voxel-wise t-test (AFNI's 3dttest) against a null baseline comparator for each functional task with $p<.01$ (False Discovery Rate corrected) held as the statistical criterion for significance.

**fMRI group analysis.** Comparisons were made between groups of estimates of hemodynamic response functions (HRF) derived from deconvolution analysis (as above. For this procedure, functional images were spatially smoothed using a 5 mm full-width half-maximum (FWHM) Gaussian filter. A slightly larger smoothing kernel was selected in the group analyses to compensate for variability in structural anatomy across participants and age groups. Anatomic and functional images were then interpolated to volumes with 1 $mm^3$ voxels, registered using manual spatial markers and converted to stereotaxic space of Talairach and Tournoux (1988) as implemented by AFNI. Area-under-the-curve (AUC) of each voxel's estimated HRF were entered into a voxel-wise between subjects t-test (using AFNI's 3dttest) for each functional task with $p<.05$ (False Discovery Rate corrected) held as the statistical criterion for significance for the comparison.

**M1 hemodynamic response function estimate analysis.** The output of the t-test for the group analysis described above compares magnitude differences across groups using the dependent variable of area-under-the-curve of the estimated impulse response derived from deconvolution. As such, this analysis is insensitive to information regarding the direction of the BOLD response (positive or negative) in regions of interest. To test the hypothesis that younger adults and aerobically active fit adults

evidence directional changes in the profile of the hemodynamic response in ipsilateral motor cortex, the following procedure was used.

Regions of interest were selected based on output from group comparisons from AUC analysis and correspondence to motor hand area of the left and right primary motor cortex. These regions were identified on a Talairach structural image by locating the following key landmarks. First, in sagittal view of the medial wall of the hemisphere, the ascending marginal ramus of the cingulate sulcus was located. Second, the next sulcus forward passing over the crest of the brain was taken as the candidate for central sulcus. Third, from sequential axial views or from a volumetric rendering, the precentral sulcus was located by its T-shaped intersection with the superior frontal sulcus, and the next sulcus back was taken as the candidate for central sulcus. Fourth, on a high axial view, the candidate central sulcus was confirmed if it showed an inverted omega-shaped “hand knob” (Yousry et al. 1997; Dum & Strick, 2004, 2005) deep from the lateral surface. The cortex anterior to the fundus of the central sulcus at this area was defined as primary cortex (M1).

After identification of both left and right M1, voxel clusters within these areas for each group were exported to a volumetric constraint mask if evidencing differences ($p<.01$, FDR corrected) in AUC measures. Only M1 voxel clusters evidencing significant activity across a union of all groups were entered into the final constraint mask for the hemodynamic response function estimates (HRF). HRF values constrained to this mask were then compared between groups using a mixed-model multivariate ANOVA (group as between-subjects factor, HRF lag values as within-subjects factor).

**Analysis of Covariance of AUC fMRI Data.** Additional regression analyses were completed with the fMRI data from each task in attempt to account for the contributions

of behavioral and neurophysiological measures towards fMRI amplitude change as estimated by the area-under-the-curve values derived from deconvolution. To this end, AFNI's 3dRegAna application was employed using linear regression with the following measures: ipsilateral silent duration, chronological and aerobic activity level composite. Hypothesis testing was completed both for each regressor in a partial model using Student's t-test. Statistical significance was held to $p<.05$, FDR corrected for all hypothesis tests.

**DTI Analysis**

DTI analysis was performed with 64-bit version of FSL computer software (Smith et al., 2004) on the Linux platform. A group analysis of measures of fractional anisotropy (FA) using FSL's tract based spatial statistics (TBSS) was completed from the 33-direction DTI sequence. FA maps were generated after tensor fit for each subject. Every FA map was non-linearly co-registered to standardized (MNI152) space. A mean FA image was generated by averaging all resampled FA maps, and a group skeleton was automatically constructed from these maps. Age grouping (sedentary elderly adults, aerobically active elderly adults, younger adults) FA analysis was completed on two motor-related callosal subregions (defined by Witelson, 1989; see Figure 4-12) of interest using a between-subjects Student's t-statistic. A cluster analysis was used on the resulting statistical maps to account for multiple comparisons with an FDR corrected probability value of .05 and superimposed on the mean FA or mean diffusivity (MD) image and the group skeleton.

**Correlation of Age, Aerobic Activity and Measures of Ipsilateral Suppression.**

A correlation analysis was completed across all participants and within participant groupings for measures of ipsilateral suppression (fMRI AUC of rM1 during motor

tapping task and TMS ipsilateral silent period), age and aerobic activity composite score.

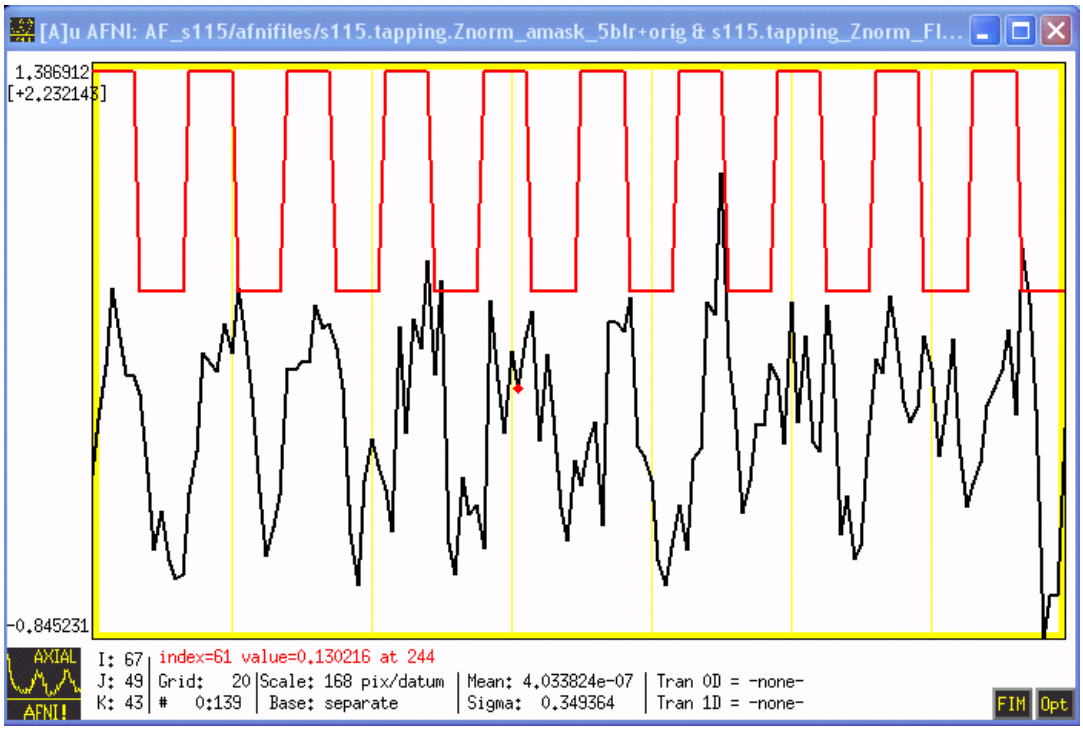



Figure 3-1. Screen capture of stimulus presentation design and fMRI response in a sample participant for fMRI finger tapping task. Red boxcar function indicates stimulus presentation and black response timeseries represents single voxel timeseries from EPI acquisition. Data represents two concatenated runs.

Figure 3-2. MRI-compatible manipulandum used for the force matching task.

Figure 3-3. Screen capture of force matching presentation to participant. Parallel red bars indicate +/- 3% upper and lower bounds of 35% of maximum voluntary contraction. White bar represents participant's force output, also relative to maximum voluntary contraction. Accurate performance on the task is achieved by maintaining the white bar between the red bars for the duration of their presentation.

# CHAPTER 4
# RESULTS

## Participant Exclusions

Two participants (1 sedentary elderly; 1 active elderly) were excluded from participation due to lack of silent period or high motor stimulation threshold (LMT > 66% of maximum stimulator output). Four other participants (1 sedentary, 1 active elderly, 2 younger adults) were excluded due to incomplete data.

## Behavioral Measures

Table 4-1 shows group means and t-test comparisons for behavioral measures with $p<.05$. Significant differences existed between all levels of age and activity group in regards to the aerobic activity composite. The younger group showed the highest assessed level of aerobic activity and the sedentary older group showed the lowest.

Table 4-1. Behavioral Measures

| | Aerobic Activity Composite | Visuomotor Reaction Time | fMRI Tapping Error Rate | fMRI Force Error Rate | Maximum Right Hand Squeeze Force |
|---|---|---|---|---|---|
| Active Elderly | 54.5 (8.2) ^° | 361 ms (49.1) ^ | 11.8% (4.1) | 11.1% (5.7) | 12.9 lbs (6.6) ^ |
| Sedentary Elderly | 70.8 (9.8) *° | 407 ms (112.2) * | 12.7% (6.1) | 7.8% (2.3) | 12.5 lbs (7.2) * |
| Younger | 34.5 (7.3) *^ | 270 ms (28.6) *^ | 13.2% (3.7) | 7.2% (4.9) | 15.2 lbs (5.9) *^ |

Cell values denote group means. Parentheses indicates standard deviation within cell. Student's t-test contrast significance at $p<.05$ denoted by: * = Younger vs. Sedentary; ^ = Younger vs. Active; ° = Sedentary vs. Active.

## Mirror Movement Assessment

None of the participants showed mirror movements (+/- 5% pressure deviation in ipsilateral hand squeeze) during squeeze assessment. During fMRI, no participants evidenced overt mirror movements (monitored by visual observation) or reported such movements after inquiry.

## Transcranial Magnetic Stimulation Measures

TMS summary data and group comparisons are presented in Table 4-2.

Table 4-2. Means and group comparisons for TMS measures.

| | Active Elderly | Sedentary Elderly | Young |
|---|---|---|---|
| iSP Duration | 37.1(12.4) [23-68] ^° | 26.3(4.4) [19-33] *° | 49.9(10.5) [28-68] *^ |
| iSP Latency | 34.1(3.3) [32-41] | 34.9(3.4) [29-45] | 33.3(4.1) [29-39] |
| cSP Duration | 41.4(10.7) [28-67] ^° | 35.2(7.4) [25-51] *° | 51.4(9.6) [37-68] *^ |
| cSP Latency | 37.1(2.9) [27-36] | 32.1(4.1) [26-40] | 36.3(3.1) [32-44] |
| TCT | 3.0 (1.1) | 2.8 (1.7) | 3.0 (0.8) |

Cell values denote group means. Parentheses indicate standard deviation within cell. Bracket indicates range. Handedness based on Edinburgh handedness inventory (1=purely right handed; -1=purely left handed); Student's t-test contrast significance at p<.05 denoted by: * = Younger vs. Sedentary; ^ = Younger vs. Active; ° = Sedentary vs. Active.

### Silent Period Comparisons

Figure 4-1 shows representative electromyography (EMG) data from both sedentary and aerobically active older adults. These samples show ipsilateral silent period duration. Each EMG record plots the number of microvolts recorded from skin surface electrodes as a function of time. Skin surface electrodes were placed on the belly of the first dorsal interosseous (FDI) muscle on both hands.

### Silent period duration

Younger adults evidenced the longest silent periods in both ipsilateral and contralateral assessments showing significant differences between both elderly groups across both conditions. Aerobically active older adults evidenced significantly longer ipsilateral silent periods as compared to sedentary older adults. Group means and comparisons for duration of both ipsilateral and contralateral silent period are presented in Figure 4-2.

### Silent period latency

Group averages of latency (in ms) of ipsilateral and contralateral silent periods are presented in Figure 4-3. No significant differences were found between groups.

### Transcallosal Conduction Time

Transcallosal conduction time (TCT) was calculated as ipsilateral silent period latency - contralateral silent period latency. TCT did not evidence significant differences between groups.

## Functional Neuroimaging

Head motion during the force matching task was a problem across participant groups in the current study. Uncorrectable head motion (> 5 mm maximal inter-image spatial displacement) required the removal of 13 subjects (4 active elderly; 6 sedentary elderly; 3 younger adults) from consideration. Additionally, four other participants (1 active elderly; 1 sedentary elderly; 2 younger adults) evidenced 3 mm of movement or greater. As such, planned between-task group comparisons were not performed due to power limitations and high frequency variability typical of head movement in the profile of estimated hemodynamic response.

### Tapping Task Baseline Comparison in Right Primary Motor Cortex

Presented in Figure 4-4 are data from an area-under-the-curve (AUC) analysis of active block acitivity taken against a null baseline. A sensorimotor mask has been applied from a Talairach template involving Brodmann Areas 1, 2, 3, 4 and 5. During the tapping task, both younger adults and aerobically active older adults evidenced decreased AUC values relative to baseline in right M1 while older adults showed increased AUC values in right M1. Activity in the Figure is depicted at $p<.05$, False

Discovery Rate corrected. A 7mm region of the dorsal frontal lobe has been cut away for better visualization of the motor hand area.

### Tapping Task AUC Group Comparisons

Group comparisons on area-under-the-curve (AUC) of estimated hemodynamic response profile during motor tapping tasks are presented in Figure 4-5. Hue in the figure indicates direction (hot colors indicate the first group showed a larger magnitude AUC response, while cold represents a larger magnitude response in the second group; $p < .05$, False Detection Corrected) of the comparison. Figure 4-5A depicts a t-test comparison between active elderly adults and sedentary elderly adults. Figure 4-5B indicates comparison of sedentary elderly against young adults. Finally, Figure 4-5C indicates comparison between active elderly adults against younger adults. As compared to sedentary older adults, both aerobically active older adults and younger adults evidenced significantly more extreme values of AUC in right M1 during task activity. Comparisons of rM1 motor activity between active older adults and younger adults did not reach significance.

### Group Comparisons of Estimates of Hemodynamic Response in Right Primary Motor Cortex

Graphs of group averages of Talairach-transformed estimated hemodynamic response profiles (HRF) from rM1 are presented in Figure 4-6. The response function estimates were constrained to a union of voxels in right primary motor cortex (BA 4) evidencing significant ($p < .05$, FDR corrected) activity across groups during the motor tapping task derived from 12-lag Dirac-delta function deconvolution. A multivariate ANOVA indicated significant (Wilk's Lambda = .06, $F(22,58) = 8.01$, $p < .01$) differences between the groups across the hemodynamic response profile. A one-way ANOVA

comparing group HRF means at lag time intervals yielded significant group differences ($p < .05$) at lags 2-8 of the 12-lag HRF (see Figure 4-7).

**Analysis of covariance (ANCOVA) of AUC fMRI data.** ANCOVA analysis was completed with AFNI's 3dRegAna application testing relationship of AUC measures during the motor tapping task with: A) ipsilateral silent period assessment, B) chronological age, C) assessed aerobic activity level from physical activity composite.

**Ipsilateral silent period.** As shown in Figure 4-8, ipsilateral silent period (iSP) was negatively correlated with activity in rM1 when both considering all participants and constraining analysis to older groups. Hue indicates direction of significant ($p<.05$, False Discovery Rate corrected) t-test of slope of iSP values in prediction of whole-brain area-under-curve (AUC) values from fMRI (hot colors indicate positive slope; cold colors indicate negative slope).

Presented in Figure 4-9 are regression analysis of iSP with AUC data, as in Figure 4-8, but broken down by participant group. Figure 4-9A presents t-test comparison of slope across all participants (as in Figure 4-8A) with panels B, C, D depicting younger, sedentary older, and aerobically active groups, respectively. fMRI data was z-transformed prior to AUC analysis.

**Chronological age.** Figure 4-10 depicts results from whole brain ANCOVA analysis on the prediction of deconvolution-derived area-under-the-curve (AUC) values from the fMRI motor tapping task based on chronological age. Chronological age does predict activity in right primary motor cortex (rM1) during motor tapping across in analysis involving all participants, but when broken down by age group, no voxel clusters survive multiple comparison correction in rM1. Hue areas (orange=positive; blue=negative) indicate significance ($p<.05$, FDR corrected) of Student's t-test of slope

change of chronological age in prediction of whole-brain values of AUC. A 7mm region of the dorsal frontal lobe has been cut away for better visualization of motor hand area.

**Aerobic activity index.** Figure 4-11 depicts results from whole brain ANCOVA analysis on the prediction of deconvolution-derived (12 response lag) area-under-the-curve (AUC) values from the fMRI motor tapping task based on aerobic activity index. As a lower score on the activity index represents higher levels of aerobic activity, a positive correlation indicates that as fitness level decreases (higher fitness composite score) AUC values increases. Analysis across all participants indicated a positive correlation in right motor cortex (rM1) with respect to aerobic activity level. Hue areas (orange = positive; blue = negative) in Figure 4-11 indicate significance ($p<.05$, False Discovery Rate corrected) of Student's t-test of slope change of chronological age in prediction of whole-brain values of AUC. A 7 millimeter region of the dorsal frontal and parietal lobes has been cut away for better visualization of motor hand area. Figure 4-11a presents all participants while images b-c present data from individual groups.

## Diffusion Tensor Imaging

Tract based spatial statistical (TBSS) analysis was completed on a voxel by voxel basis for the comparison of fractional anisotropy (FA) measures across groups. After correction for multiple comparisons, significant differences were not found across any group comparison. Uncorrected TBSS group analysis yielded significant age differences (sedentary older vs. younger; aerobically active older vs. younger) in FA ($p < .05$) in bilateral frontal forceps and along the columns of fornix bilaterally.

ANCOVA analyses comparing FA values across groups using TBSS were then completed using ipsilateral silent period and chronological age as covariates. Neither covariate had an effect on group FA TBSS comparisons.A region of interest (ROI)

TBSS analysis with FA was then conducted across groups using the posterior corpus callosal segments (area 3: posterior body and area 4: isthmus from Witelson,1989; see Figure 4-12) as ROI. No differences in FA were found across groups in these areas.

## Correlation of Age, Aerobic Activity Index and Measures of Ipsilateral Suppression

Correlation analyses were completed for measures of ipsilateral suppression (ipsilateral silent period, area-under-the-curve of estimated hemodynamic response profile in rM1), chronological age and aerobic activity level ("aerobic activity composite score"). Results from the analyses are presented in Figures 4-13 through 4-16.

### Correlations Across Groups

Consider Figure 4-13 as an array of 16 related plots organized into rows (1,2,3,4) and columns (A,B,C,D). The particular plot in the top left corner (column A row 1) concerns the length of the ipsilateral silent period (iSP). The abscissa labels for the values of iSP are shown below column A. All four plots in column A use this abscissa. The heights of bars plotted in column A row 1 show the frequency histogram for iSP across all participants. The numeric count of frequency is printed adjacent to each bar. The ordinate labels to the left of row 1 actually reproduce the values of iSP that are used as the abscissa for this particular histogram. This ordinate applies to the other three plots in row 1 but it does not apply to the histogram just described. Proceeding along the diagonal from top-left to bottom-right of this 16 plot array, three more frequency histograms are encountered: histogram for Age in column B row 2, histogram for Area Under the Curve (AUC) of fMRI hemodynamic response in column C row 3, and histogram of Fitness Composite score in column D row 4. Please notice that, just as the row 1 ordinate has the same labels as the column A abscissa, the row 2 ordinate matches the column B abscissa, the row 3 ordinate matches the column C abscissa,

and the row 4 ordinate matches the column D abscissa. As was also true for the initial example, the numeric counts of frequency for each histogram are printed adjacent to the histogram bars and are not referenced to their row's ordinate labels. The other three non-histogram scatter plots in a given row are all referenced to that row's ordinate labels. All four plots in a given column are referenced to that column's abscissa labels. Therefore, scatter plots showing a relationship between iSP and Age are found in column A row 2 and also in column B row 1. In column A the abscissa reports values of iSP , in row 2 the ordinate is Age, such that the plot in column A row 2 shows Age as a function of iSP. In column B the abscissa reports Age, in row 1 the ordinate is iSP, such that the plot in column B row 1 shows iSP as a function of Age. There are 6 pairs of redundant plots like these reflected about the diagonal of the 16 plot array. The two members of each redundant pair show identical Pearson correlation coefficients. The abscissa for one member of a pair is the ordinate for the other member, and vice versa.

**Correlations in Younger Adults**

Presented in Figure 4-14, are data as in Figure 4-13, but restricted to younger adults. Both age and AUC measures significantly correlated with iSP assessment in younger adults. A significant correlation of AUC with the aerobic activity composite score was also present in this age grouping.

**Correlations in Sedentary Older Adults**

Presented in Figure 4-15, are data as in Figure 4-13, but restricted to sedentary older adults. A trend for significance was found between age and AUC measures ($p=.08$).

**Correlations in Aerobically Active Older Adults**

Presented in Figure 4-16, are data as in Figure 4-13, but restricted to aerobically active older adults. Significant correlations between iSP on both AUC measures and aerobic activity composite were found in aerobically active older adults.

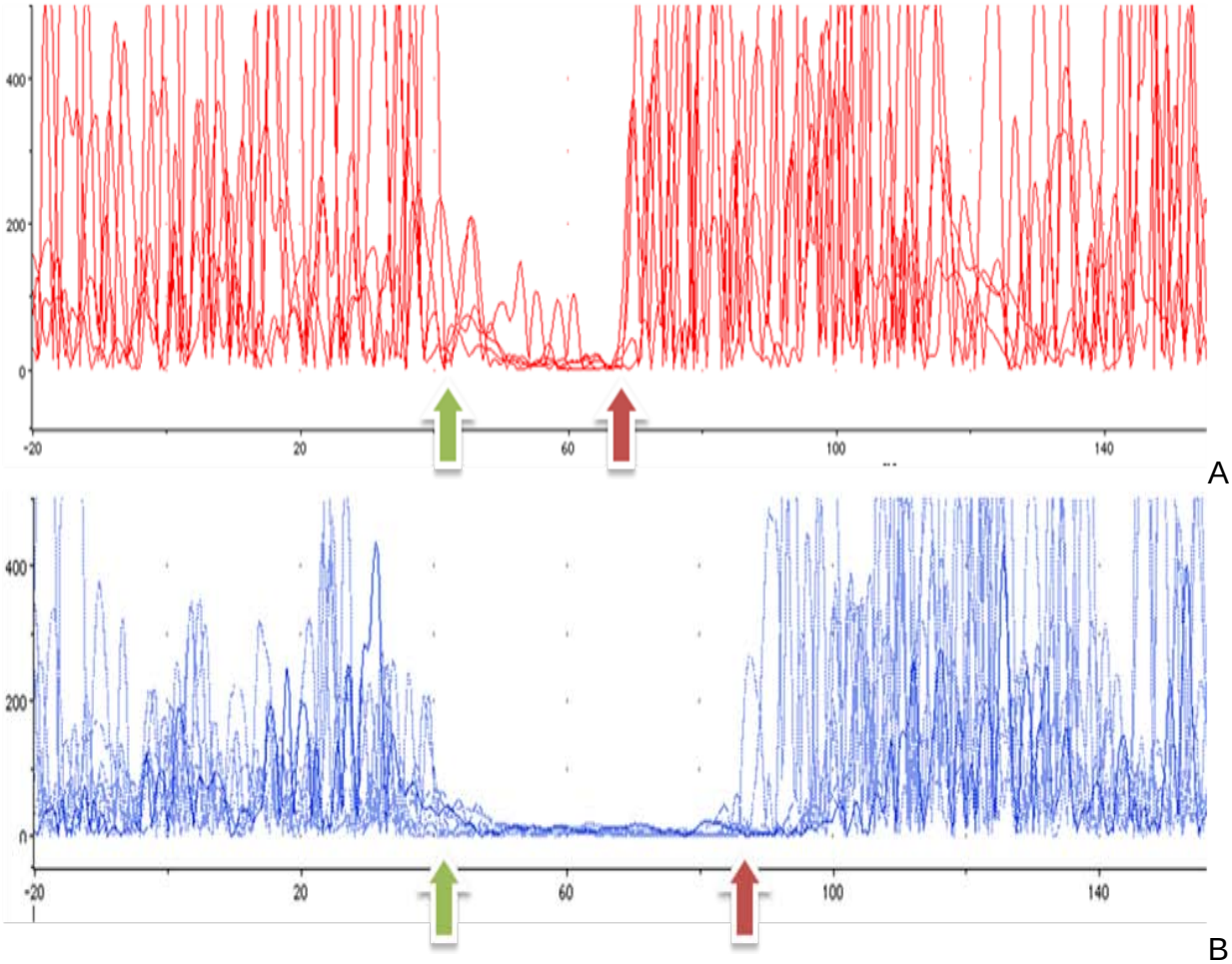
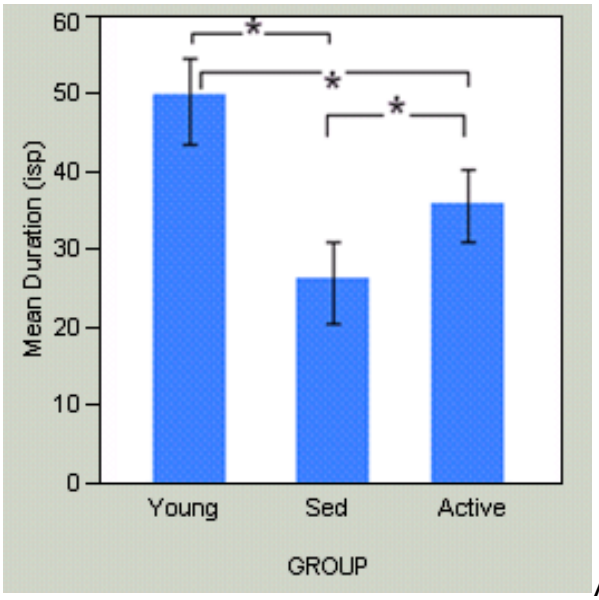
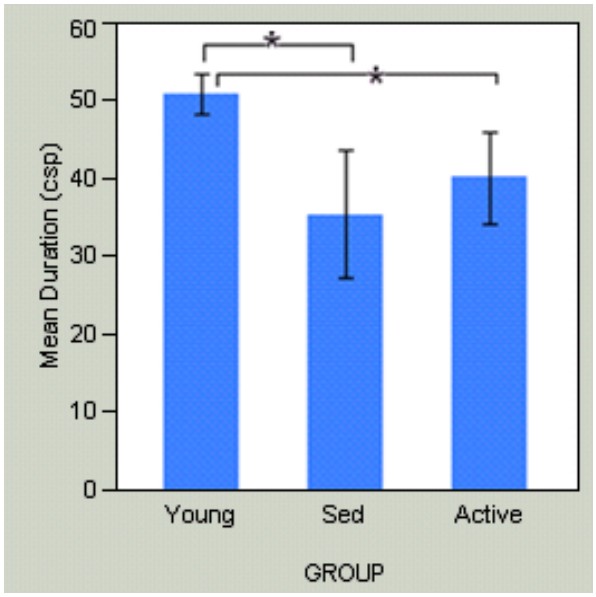



Figure 4-1. Representative examples of electromyograph (EMG) output over time (abscissa, in ms) from first dorsal interosseous muscle exhibiting ipsilateral silent period in: A) a sedentary older adult and B) an aerobically active older adult. Silent period is defined as an 80% reduction in rectified EMG taken against baseline. Green arrows indicate onset (latency) of silent period and red arrows indicate time of termination.

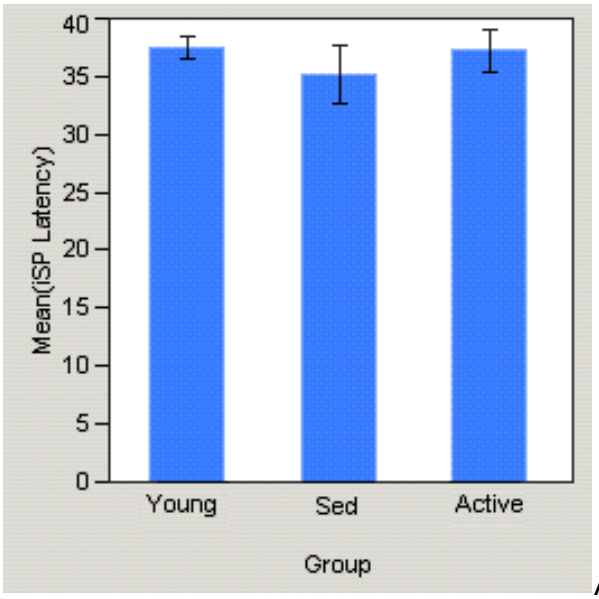



A

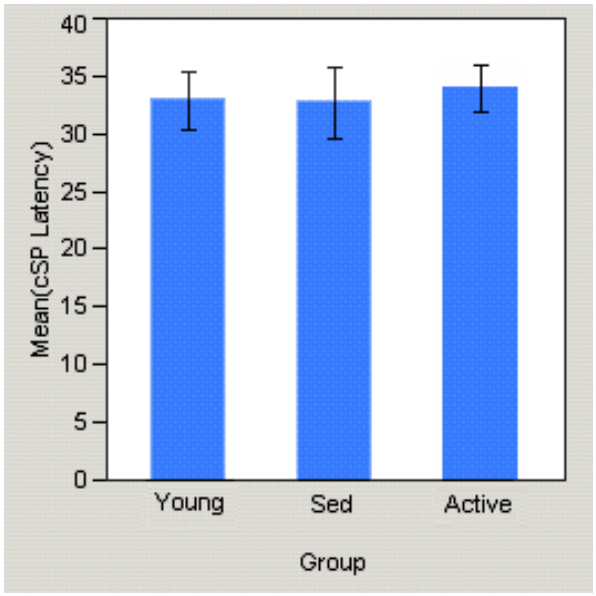



B

Figure 4-2. Group means from TMS measures of: A) ipsilateral silent period duration (in ms) in left FDI muscle, and B) contralateral silent period duration (in ms) in right FDI muscle. Error bars indicate standard error. Black asterisks indicate differences between selected groups at p<.05.




A




B

Figure 4-3. Group means of latency (in ms) for A) ipsilateral silent period and B) contralateral silent period from TMS. Error bars indicate standard error. No significant differences were found between groups. Trancallosal conduction time was derived from this measure and was calculated as: ipsilateral silent period – contralateral silent period. No significant differences were found between groups.

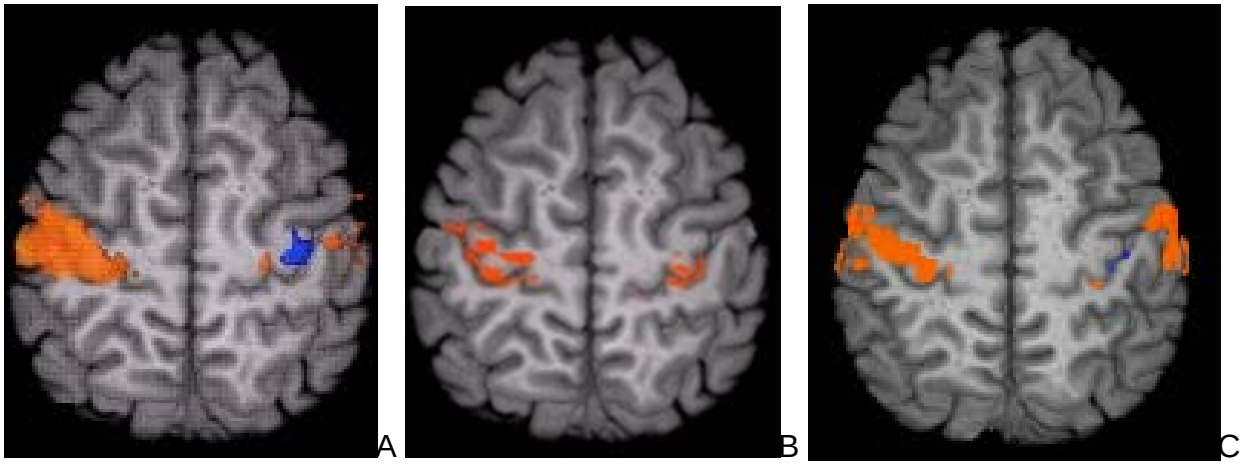



Figure 4-4. Sensorimotor mask of comparisons of area-under-curve of the deconvolved hemodynamic response during performance of a tapping task taken against a null baseline condition with significance set to p<.05, False Discovery Rate corrected (Hues: orange indicates positive t-statistic, blue indicates negative t-statistic). Data shown for: A) younger adults, B) sedentary older adults, C) aerobically active older adults. Both aerobically active older adults and younger adults showed a negative to baseline pattern of activity in rM1, while sedentary older adults showed positive to baseline activity in rM1. Anatomical underlay is a skull-stripped standardized (Talairach) T-1 image.

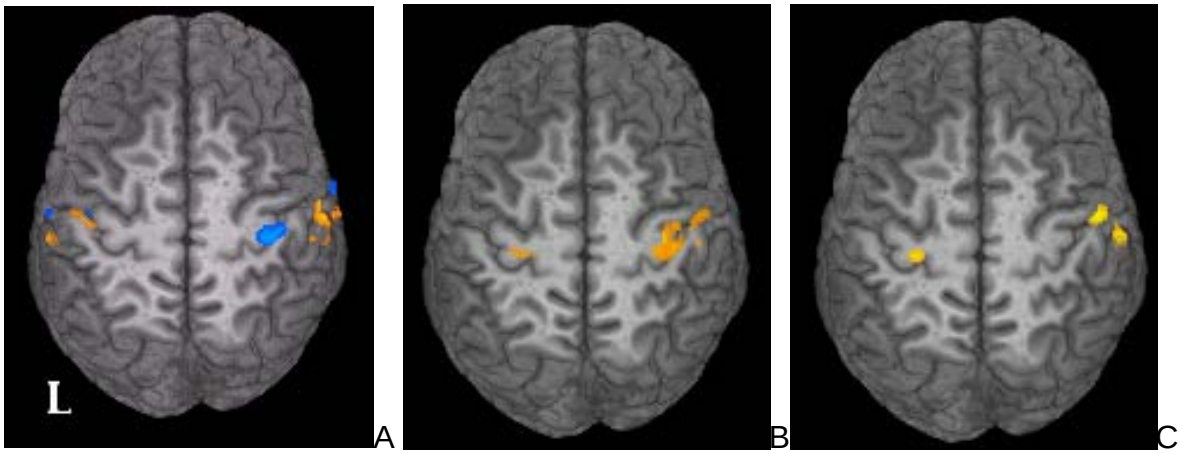



Figure 4-5. Sensorimotor mask of group differences in area-under-curve group comparisons on tapping task at p<.05, False Discovery Rate (FDR) corrected (Hues: orange indicates positive t-statistic, blue indicates negative t-statistic). Panels present: A) comparison of aerobically active elderly group against sedentary elderly, B) comparison of sedentary elderly group against young adults, C) comparison of aerobically active elderly group against young adults. Both Aerobically active older adults and younger adults evidenced significant differences in right primary motor cortex with sedentary older adults.

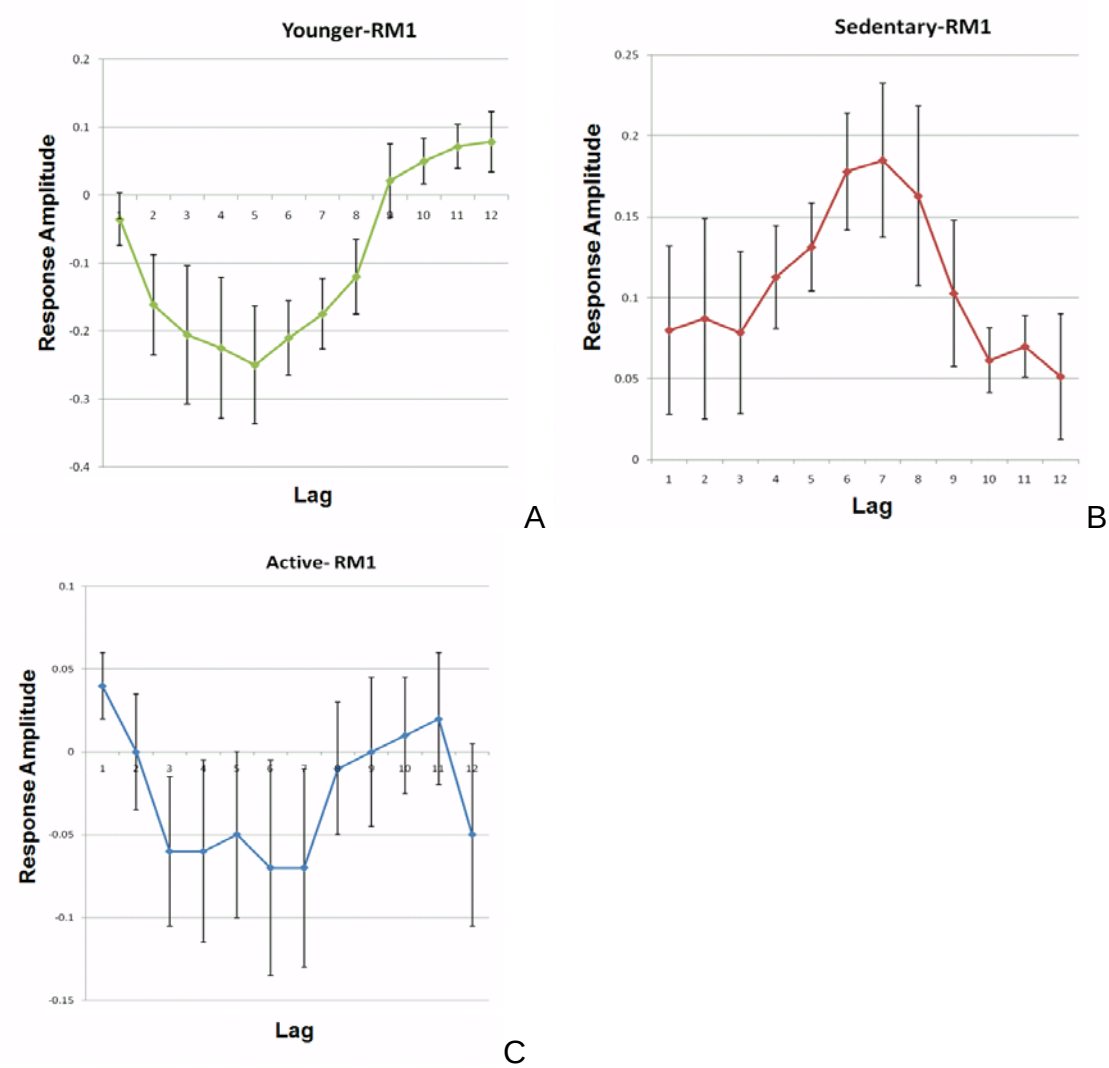



Figure 4-6. Average estimates of hemodynamic response profiles across 12-image deconvolution interval (Lag, abscissa) for right primary motor cortex (rM1) per group during motor tapping task. Graphs presented are for: A) Younger adults, B) Sedentary elderly adults, C) Aerobically active elderly adults. The Z-score transformed data was constrained to areas in rM1 that were coincidentally active across groups ($p < .05$, FDR corrected) in area-under-curve analysis. Error bars reflect standard error.

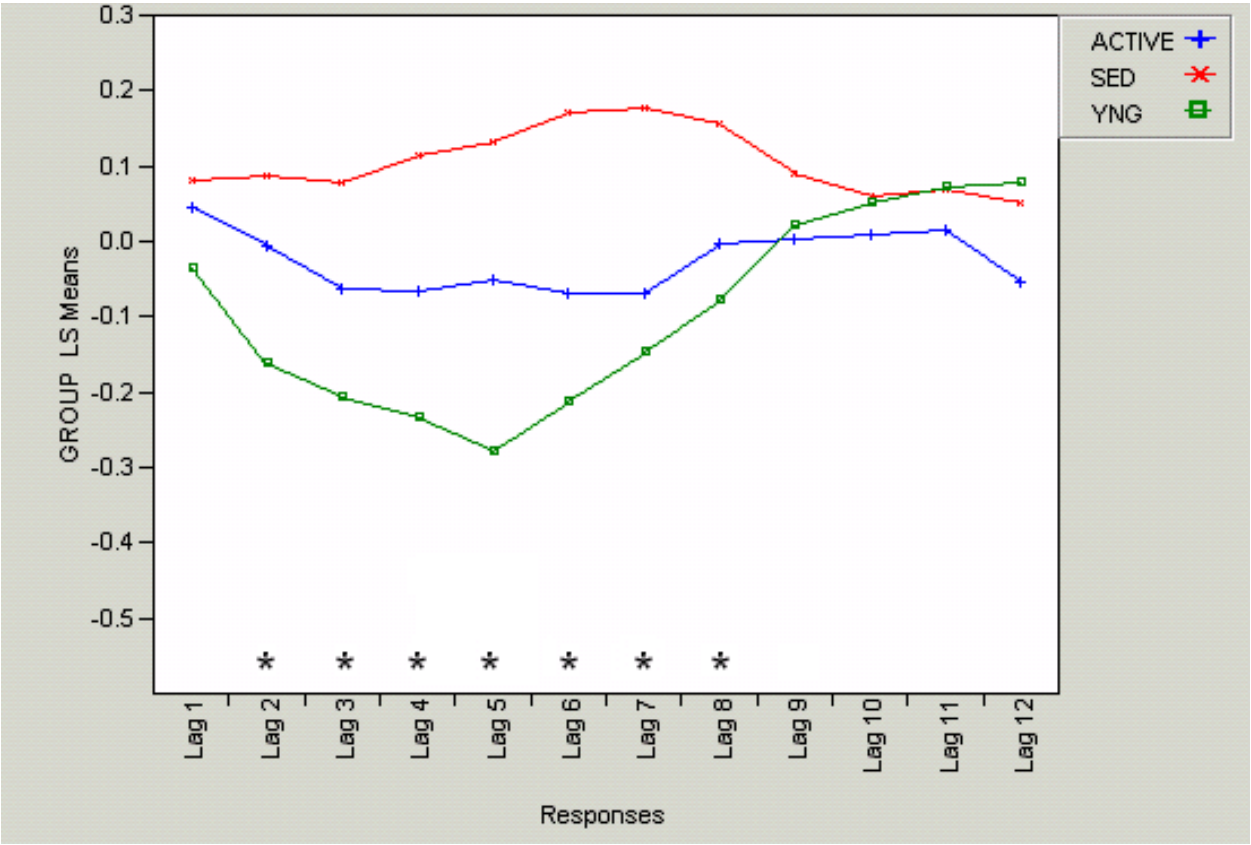



Figure 4-7. Overlay of group averaged estimates of hemodynamic response function profiles (HRF) across 12- lag deconvolution interval for right primary motor cortex (rM1) during motor tapping task. The Z-score transformed data was constrained to voxels in rM1 evidencing group differences ($p < .05$, FDR corrected) in AUC analysis. Black asterisks along X-axis indicate significant ($p<.05$) group differences of means for one-way ANOVA at each lag interval.

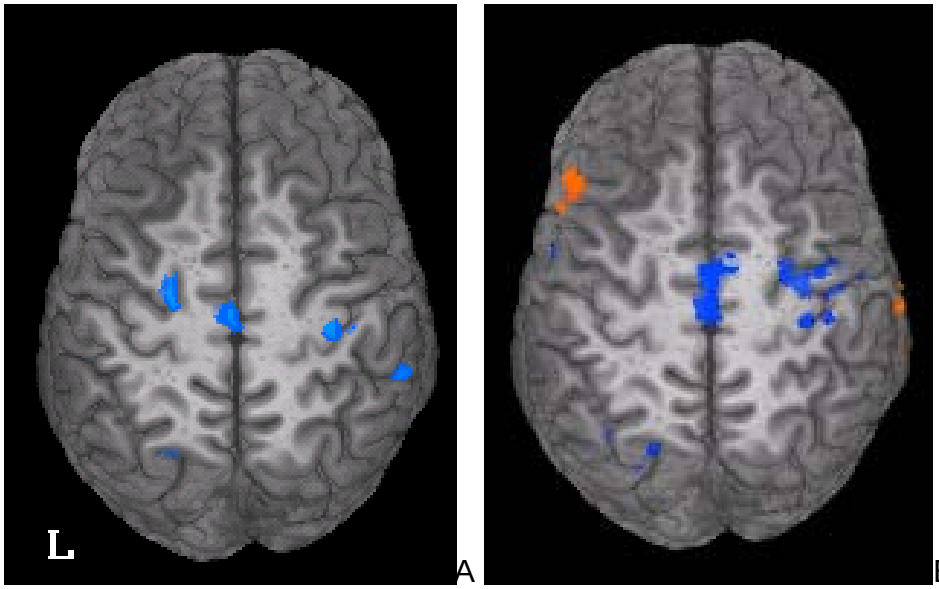



Figure 4-8. A) Skull-stripped Talairach standardized brain with overlay of regression analysis across all participants testing prediction of area under curve (AUC) values during motor tapping task based on ipsilateral silent period (iSP) measure from TMS. B) Analysis as in A, but constrained to older adults (both sedentary and aerobically active). Hue (orange=positive; blue=negative) indicates significance ($p<.05$, FDR corrected) of Student's t-test of slope change of iSP values in prediction of whole-brain values of AUC. A 7mm region of the dorsal frontal lobe has been cut away for better visualization of motor hand area.

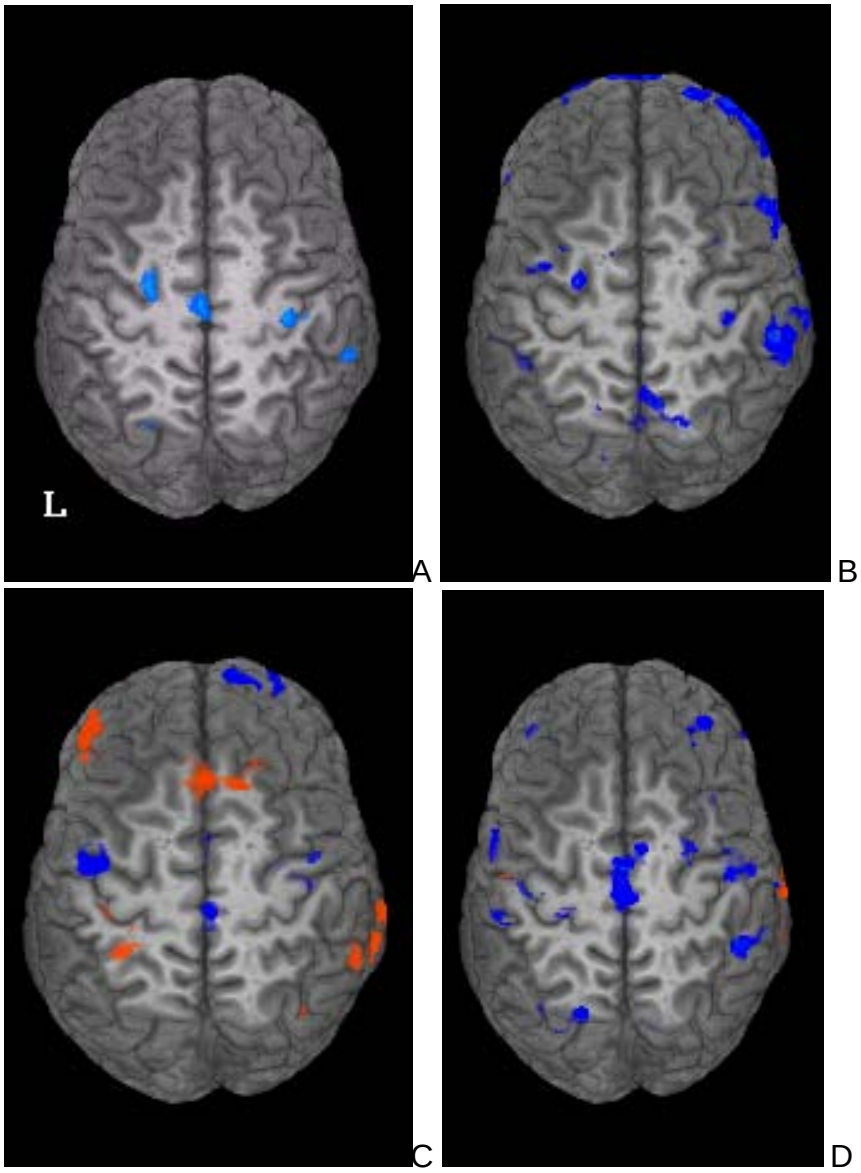



Figure 4-9. A) Skull-stripped Talairach standardized brain with overlay of regression analysis across all participants testing prediction of area under curve (AUC) values during motor tapping task based on ipsilateral silent period (iSP) measure from TMS. Other images represent analysis as in A, but constrained to B) younger adults, C) sedentary older adults, D) aerobically active older adults. Hue (orange=positive; blue=negative) indicates significance ($p<.05$, FDR corrected) of Student's t-test of slope change of iSP values in prediction of whole-brain values of AUC. A 7mm region of the dorsal frontal lobe has been cut away for better visualization of motor hand area.

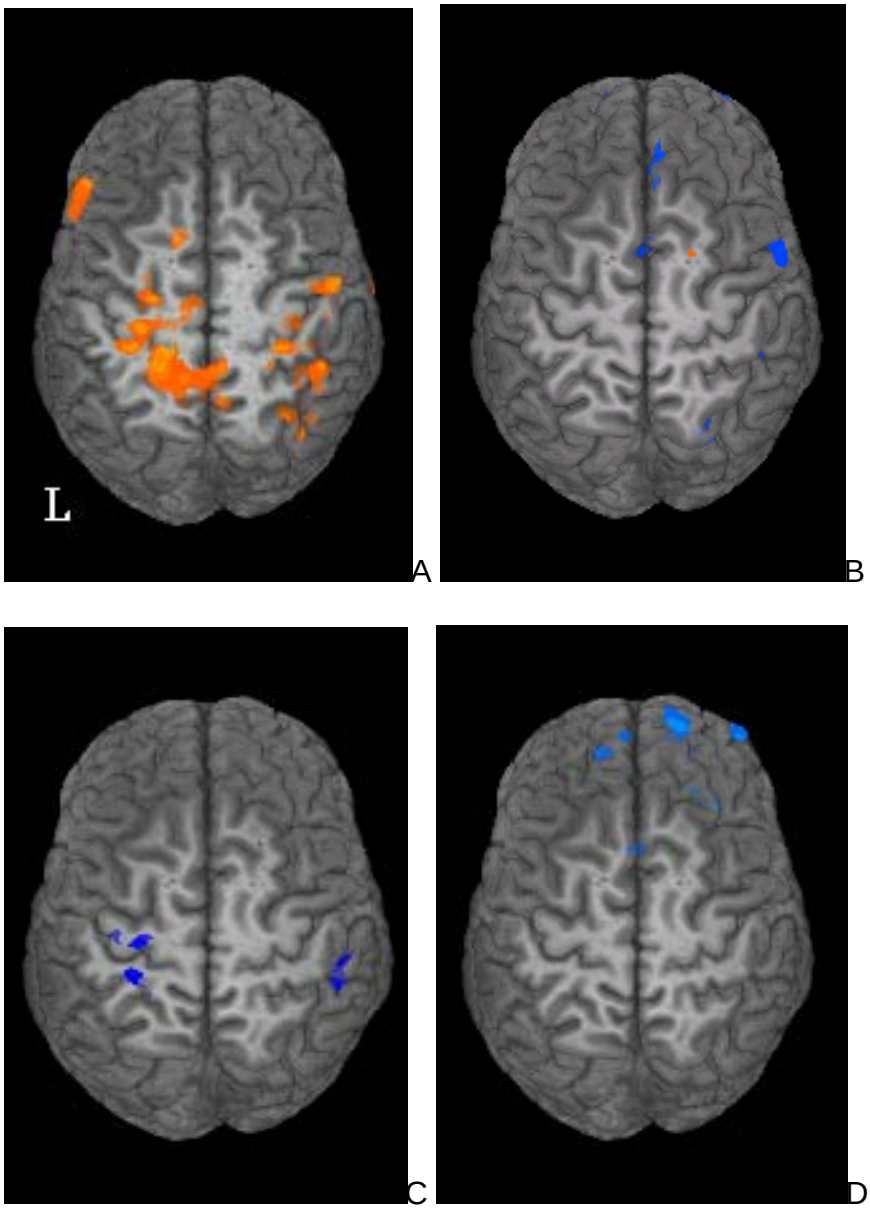



Figure 4-10. A) Skull-stripped Talairach standardized brain with overlay of regression analysis across all participants testing prediction of area under curve (AUC) values during motor tapping task based on chronological age (lower score on the composite represents higher aerobic activity level). Other images represent analysis as in A, but constrained to B) aerobically active older adults, C) sedentary older adults, D) younger adults. Hue areas (orange=positive; blue=negative) indicate significance ($p<.05$, FDR corrected) of Student's t-test of slope change of chronological age in prediction of whole-brain values of AUC. A 7mm region of the dorsal frontal lobe has been cut away for better visualization of motor hand area.

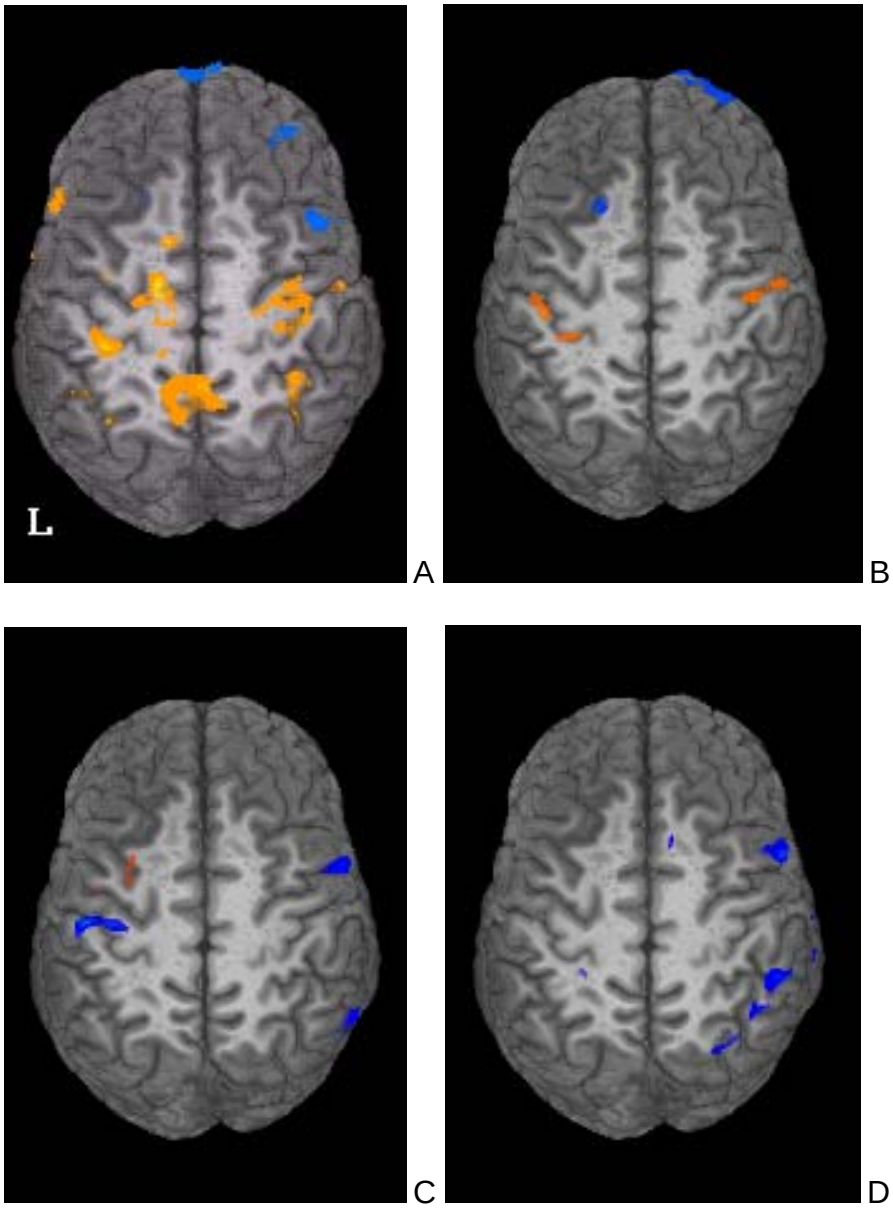



Figure 4-11. A) Skull-stripped Talairach standardized brain with overlay of regression analysis across all participants testing prediction of area under curve (AUC) values during motor tapping task based on aerobic activity index. Other images represent analysis as in A, but constrained to B) younger adults, C) sedentary older adults, and D) aerobically active older adults. Hue (orange=positive; blue=negative) indicates significance ($p<.05$, FDR corrected) of Student's t-test of slope change of aerobic activity index values in prediction of whole-brain values of AUC. A 7mm region of the dorsal frontal lobe has been cut away for better visualization of motor hand area.

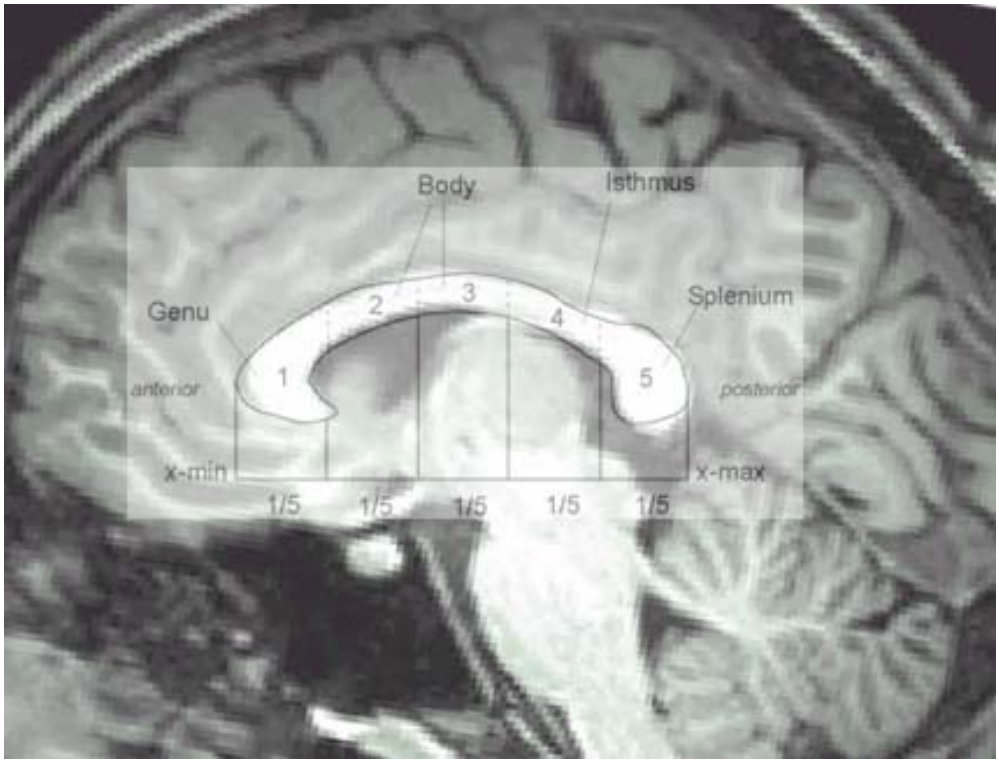



Figure 4-12. Overlay of Witelson delineation of corpus callosum on a sample Talaraich standardized brain from the current study. Sections 3 and 4 were used for group comparisons of fractional anisotropy measures derived from diffusion tensor imaging analysis. (Overlay source: http://psycnet.apa.org/journals/neu/21/2/images)

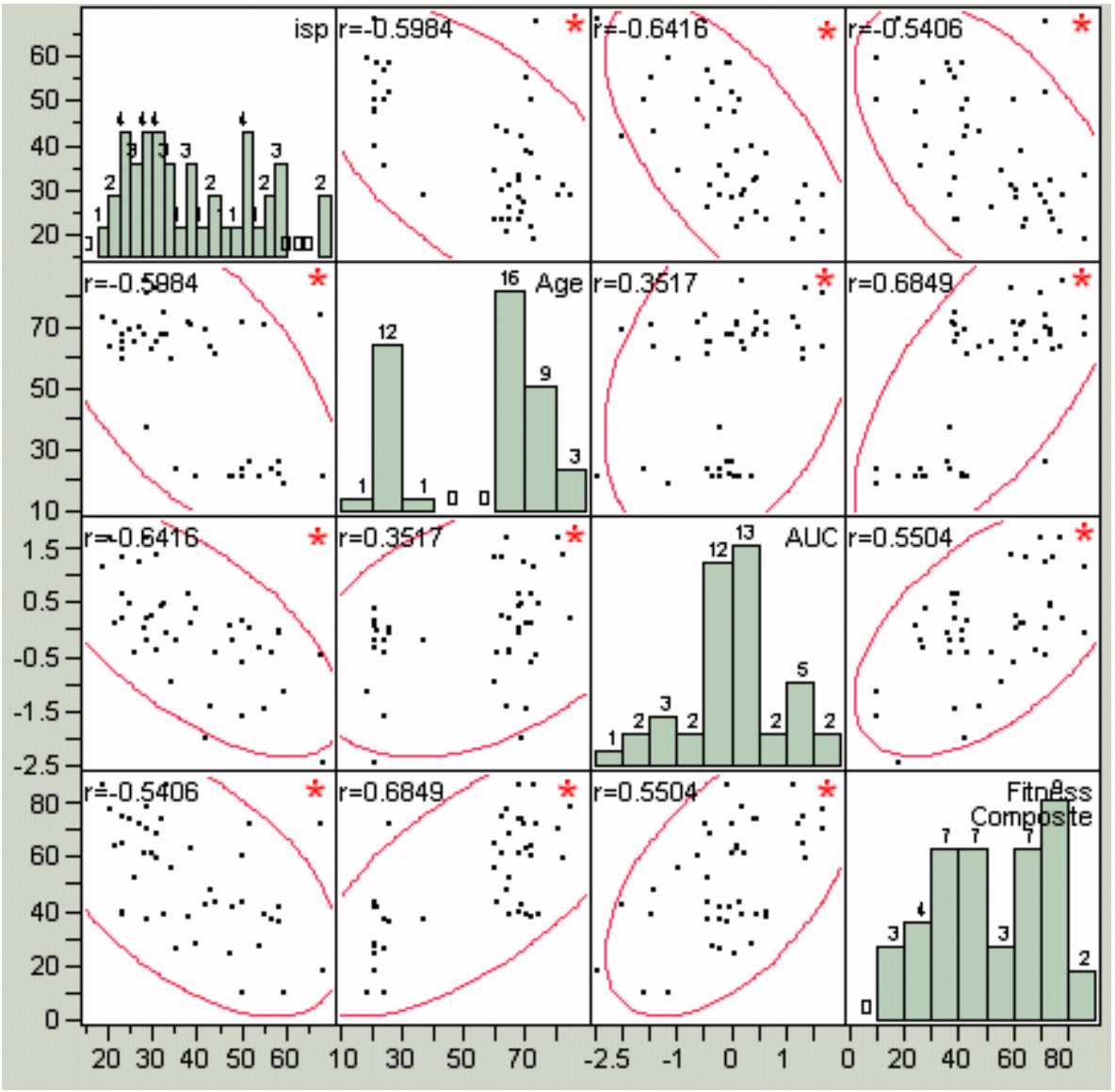



Figure 4-13. Data from all participants in a scatterplot matrix with Pearson correlations are shown above. Off-diagonal cells represent data from the following variables: ipsilateral silent period duration (top row); Age (upper middle row); average of right primary motor cortex area-under-the-curve values of estimated hemodynamic response from tapping task (lower middle); aerobic activity composite score (bottom row). Significant correlations ($p<.05$) are denoted by asterisks in top right of cell. Density ellipsoid at ($\alpha = .95$) is shown in red. Histograms in matrix diagonal represent sample distribution on each measure.

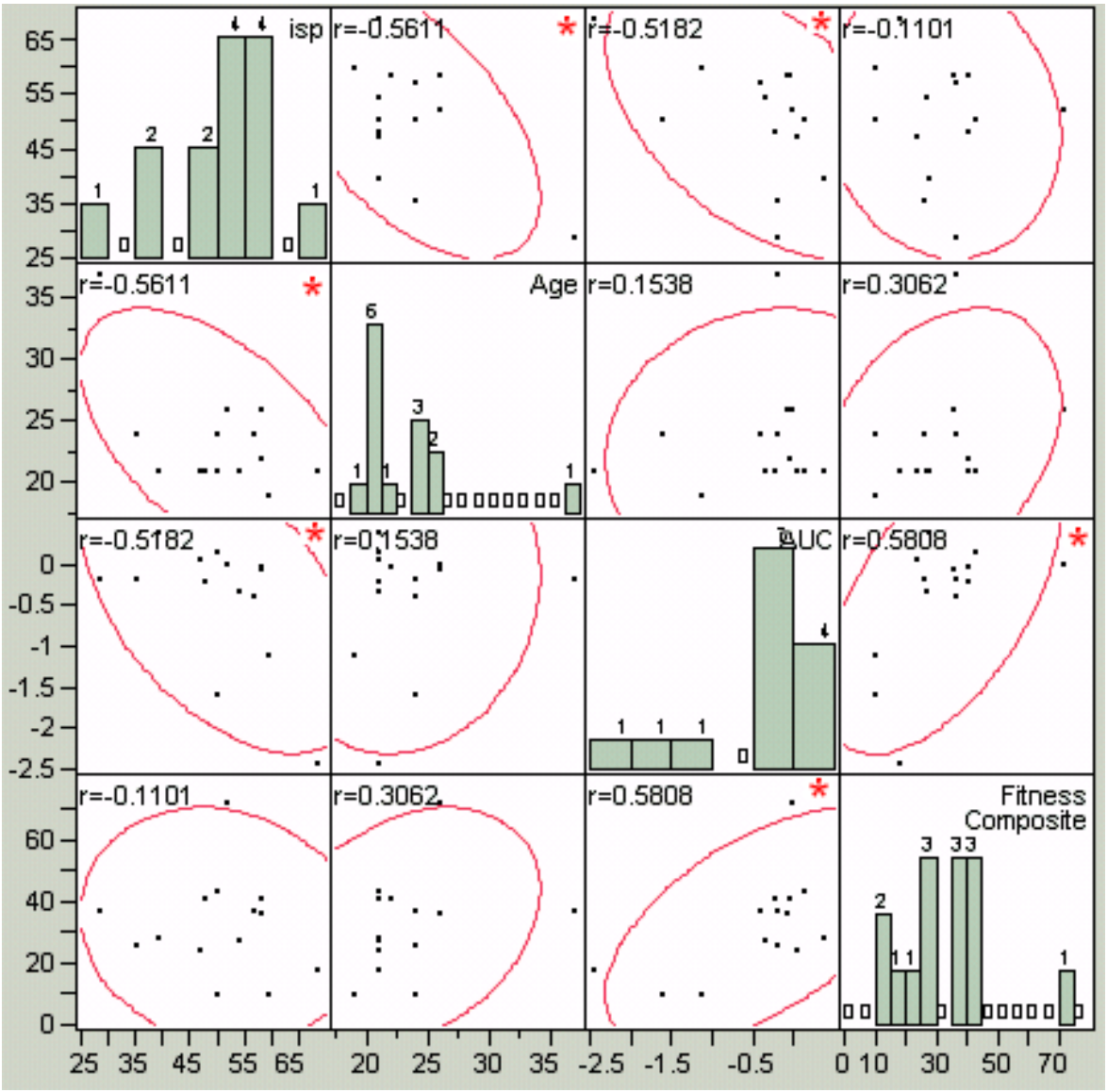



Figure 4-14. Younger adults' data in a scatterplot matrix with Pearson correlations are shown above. Off-diagonal cells for the following variables: ipsilateral silent period duration (top row); Age (upper middle row); average of right primary motor cortex area-under-the-curve values of estimated hemodynamic response from tapping task (lower middle); aerobic activity composite score (bottom row). Significant correlations ($p<.05$) are denoted by asterisks in top right of cell. Density ellipsoid at ($\alpha = .95$) is shown in red. Histograms in matrix diagonal represent sample distribution on each measure.

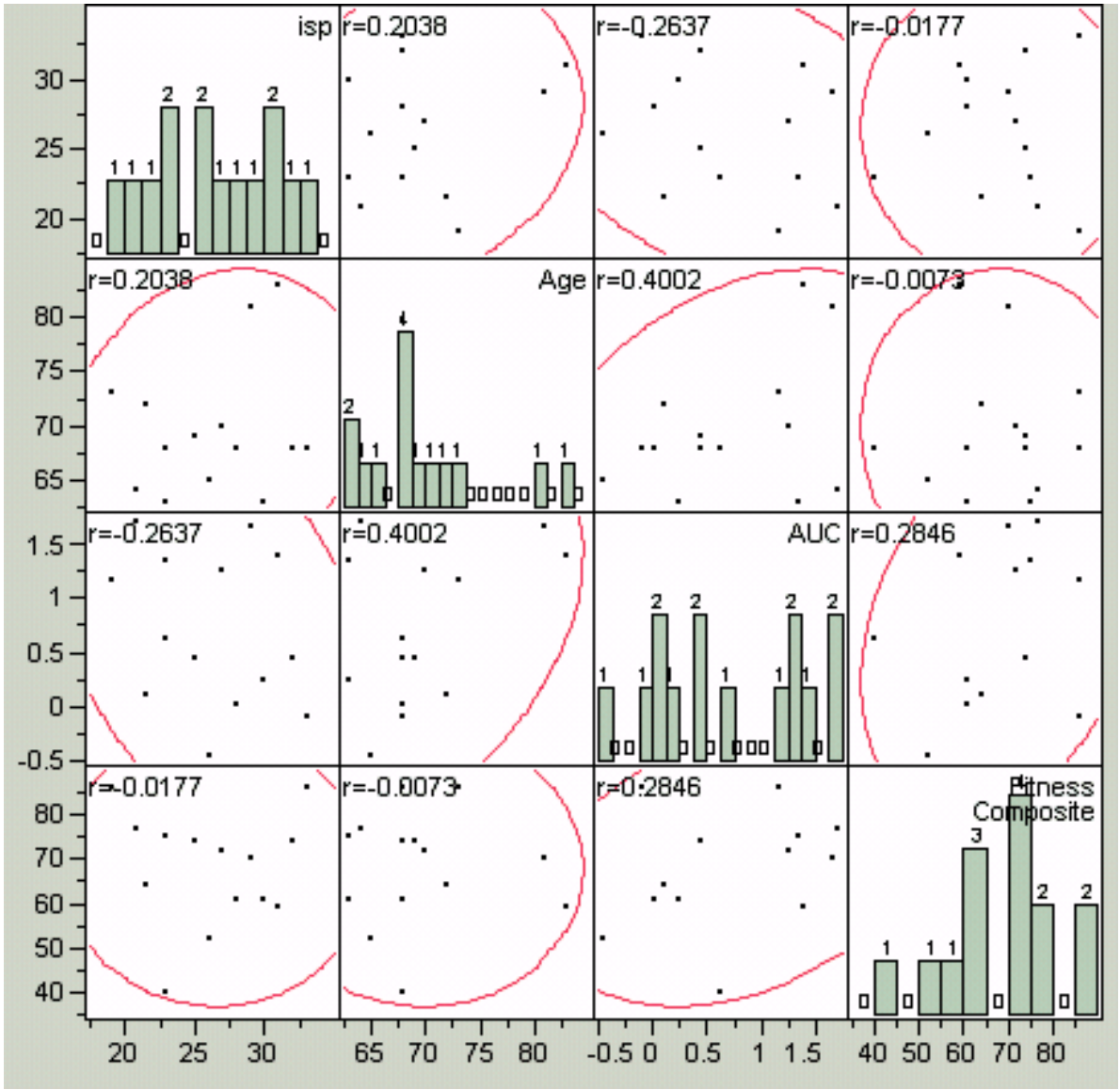



Figure 4-15. Sedentary older adults' data in a scatterplot matrix with Pearson correlations are shown above. Off-diagonal cells for the following variables: ipsilateral silent period duration (top row); Age (upper middle row); average of right primary motor cortex area-under-the-curve values of estimated hemodynamic response from tapping task (lower middle); aerobic activity composite score (bottom row). No significant correlations. Density ellipsoid at (α = .95) is shown in red in each cell. Histograms in matrix diagonal represent sample distribution on each measure.

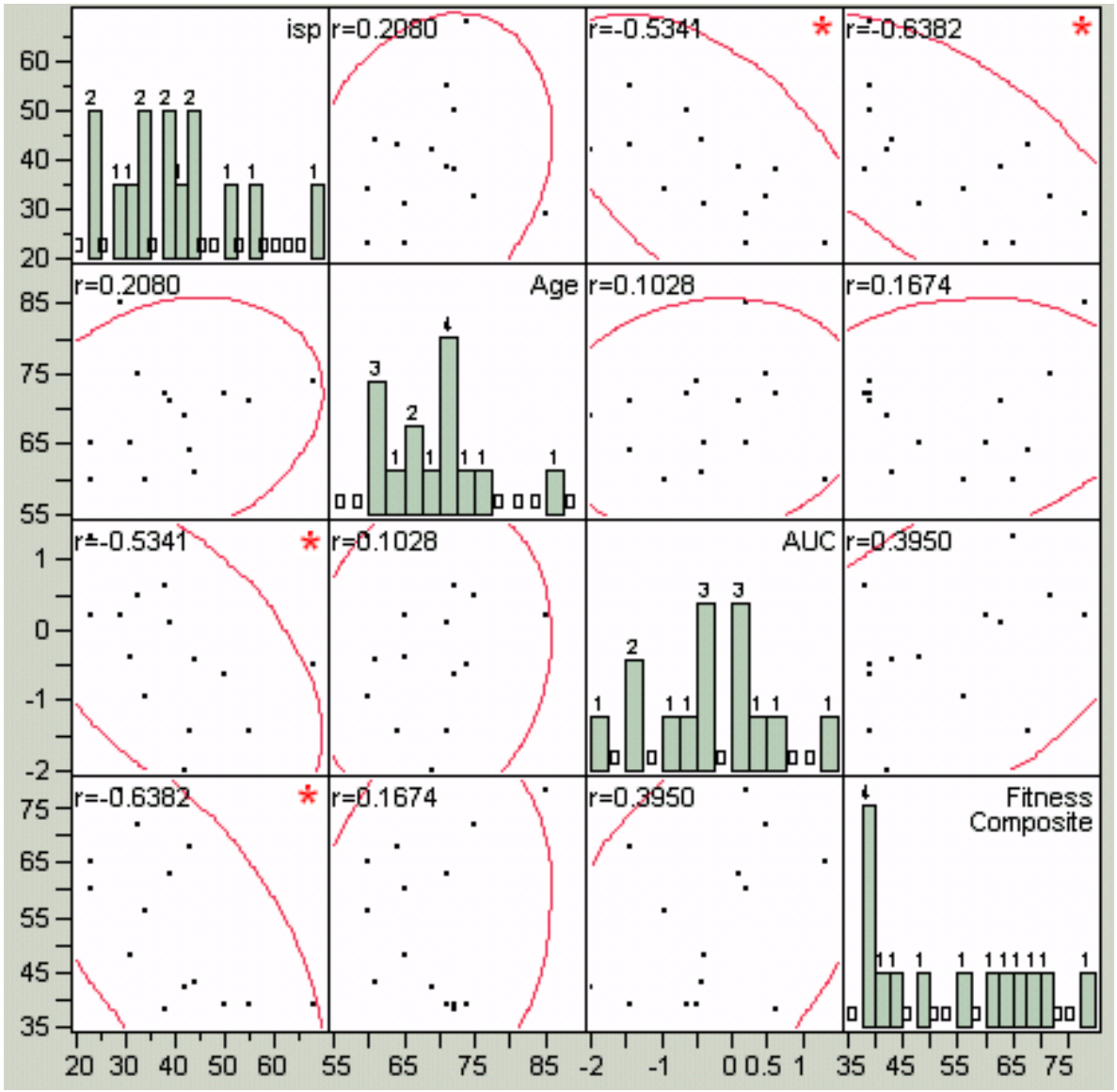



Figure 4-16. Active older adults' data in a scatterplot matrix with Pearson correlations are shown above. Off-diagonal cells for the following variables: ipsilateral silent period duration (top row); Age (upper middle row); average of right primary motor cortex area-under-the-curve values of estimated hemodynamic response from tapping task (lower middle); fitness composite score (bottom row). Significant correlations ($p<.05$) are denoted by asterisks in top right of cell. Density ellipsoid at ($\alpha = .95$) is shown in red. Histograms in matrix diagonal represent sample distribution on each measure.

# CHAPTER 5
# DISCUSSION

## Summary of Findings

The following represents a summary of findings in the current investigation. During unimanual activity, area-under-the-curve (AUC) measures of the estimated hemodynamic response in right primary motor cortex (rM1) evidenced decreases relative to baseline (i.e. – negative BOLD) in aerobically active older adults and in younger adults. In contrast, during the performance of similar unimanual tasks AUC measures from rM1 in sedentary older adults indicated an increase in positive BOLD activity relative to baseline. Group comparisons of AUC in rM1 during unimanual task activity show significant differences between aerobically active and sedentary older adults. Group comparisons of the ipsilateral silent period measure derived from TMS procedures also indicated significant differences between aerobically active and sedentary older adults. A regression analysis testing the prediction of the AUC fMRI data from the ipsilateral silent period derived from TMS indicated a correlation between the two measures in right primary motor cortex. In older adults, significant correlations were found between chronological age and measures of ipsilateral suppression. FA values from DTI did not evidence significant differences between any of the groups in motor regions of the corpus callosum.

## Aging Related Differences in Interhemispheric Communication

As compared to younger adults, older adults, particularly sedentary individuals, evidenced decreases in measures of ipsilateral suppression from both fMRI (BOLD activity in rM1) and TMS (ipsilateral silent period) during unimanual task performance. While similar findings have been reported from aging-related studies using a single modality (TMS: Sale & Semmler, 2005; fMRI: McGregor et al., 2009; Riecker et al.,

2006), we believe the present study represents the first report of significant correlation between the two measures in an aging investigation, adding to the evidence that negative BOLD is diagnostic of a change in interhemispheric communication with age (Shmuel et al., 2002; Stefanovic et al. 2004; Shmuel et al., 2006; Pasley et al., 2007).

The purpose of interhemispheric suppression during unimanual movement is a topic of debate. It is possible that the suppression of the ipsilateral motor cortex may serve to silence potentially task-interfering mirror movements of the non-active hand. Mirror movements are identical patterns of muscle activity in the opposite limb occurring during the execution of a unimanual task. Immature motor systems have typically shown the presence of mirror movements, as these are common in intended unimanual tasks performed by healthy children (Lazarus & Todor, 1987). Healthy adults, however, typically are able to restrict motor activity to a single laterality, a change that is coincident with the complete myelination of the corpus callosum (Mayston et al., 1999). The presence of unintended mirror movements (usually identified by EMG or force transduction measure) has been reported in healthy adults of advancing age (Ottaviani et al., 2008; Baliz et al., 2005) and is typically seen in volitional movement of the non-dominant hand (Ottaviani et al., 2008), particularly for right-handed adults (Uttner et al., 2007). In the present sample of older adults, a dominant hand (right) force transduction measure of mirror movements did not reveal the presence of mirror activity in ipsilateral (left) hand muscles across any of the sampled participants. As such, mirror recruitment of muscle groups in the ipsilateral hand as the explanation of aging related changes in interhemispheric suppression (AUC in rM1 or ipsilateral silent period) was not supported. However, it is possible that the selected force production paradigm used in the current study to assess mirror movement may lack the sensitivity offered by EMG

measures, currently the “gold standard” for the assessment of mirror movement. In the future, improvements in the measure of mirror activity in ipsilateral muscles would include the use of continuous EMG monitoring during hand movements, rather than assessments at different points in time as presently implemented.

Aging related alteration in interhemispheric suppression can also be considered in light of the HAROLD (Hemispheric Asymmetry Reduction in Older Adults; Cabeza, 2002) model of cortical activity changes across the lifespan. The HAROLD model describes an increasingly bilateral locus of functional activity (typically measured with fMRI) with increasing age during task performance that in younger adults tends to recruit only a single hemisphere. Given equivalent behavioral performance on such tasks across age groups, the bilateral pattern of activity in older adults has been argued to serve a compensatory purpose (Cabeza et al., 2002; Cabeza et al., 2004; Davis et al., 2008).

In the current study, older adults showed lower levels of interhemispheric suppression could indicate that proper performance on the selected unimanual tasks requires recruitment of ipsilateral motor substrates (rM1) and therefore may reflect a functional compensation. Support for this contention may be derived from a long-standing hypothesis of differential cortical recruitment based on movement complexity (Rao et al., 1993; Verstynen et al., 2005; Wu & Hallett, 2005). This hierarchical task complexity (HTC) hypothesis argues that the laterality of activation in the cortical motor system depends on the perceived complexity of the task. According to the HTC, simple tasks can be completed in the contralateral motor cortex, but increasingly complex tasks require the added computational capacity of ipsilateral substrates to achieve successful task resolution (Verstynen et al., 2005; Heuninckx et al., 2008; Hutchinson et al., 2002).

The posterior-anterior shift in aging (PASA) model (Davis et al., 2008) argues for an analogous pattern of recruitment respective of age and complexity, also potentially reflecting a functional compensation (see also Haaland et al., 2004). In light of these models, it could be argued that older adults in the current study, particularly those in the sedentary group, while performing unimanual tasks equally well (and lacking evidence of mirror movements), could only do so with the additional cortical resources provided by the ipsilateral motor cortex.

However, the HAROLD model (Cabeza, 2002) also acknowledges that increasingly bilateral patterns of activity in older adults may be the result of a dedifferentiation of neural recruitment. Recent neuroimaging findings in the motor domain have provided some support for this aspect of Cabeza's model. Using fMRI involving two types of coordinated movements between the hand and foot (isodirectional/phase-locked or anti-phase locked), Heuninckx et al., (2010) recently reported that younger adults activate a different motor network depending on the motor task condition. Older adults, however, tend to recruit a single motor network regardless of phase locking. Interestingly, the older adults showing the highest behavioral performance (anti-phase locking has been perceived as a difficult task) also had the lowest variability of regional activation indicating that the evidenced dedifferentiation served to benefit motor activity.

In the motor domain, a correlation of lower transcallosal inhibition level with impaired motor performance has been noted with individuals afflicted with Parkinson's disease (Li et al., 2007; Fisher et al., 2008), Kallmann's Syndrome (Verstynen et al., 2007; Cincotta et al., 2006), and schizophrenia (Hoy et al., 2007). Patients with these disorders often show evidence of mirror movements in conjunction with decreased

measures interhemispheric inhibition in TMS (Li et al., 2007; Cincotta et al., 2006). In healthy aging, Baliz et al. (2005) reported that increased cortical activity in ipsilateral M1 in older adults correlated with decreased unimanual task performance and the increased presence of mirror movements.

As such, it is currently unclear if aging-related loss in interhemispheric motor suppression is associated with positive or negative outcome in motor physiology or other types of decline. Given the relative novelty of such findings and the complications presented by a plastic human nervous system much additional study is required.

**Differences in Interhemispheric Activity Respective of Aerobic Activity Level**

The most striking findings of the current investigation are the group differences in ipsilateral motor activity during unimanual tasks between aerobically active older adults and their sedentary age cohort. Aerobically active older adults tended to show higher levels of negative BOLD in rM1 activity during finger tapping while sedentary older adults, on average, showed a positive BOLD signal. From TMS, aerobically active older adults reported a longer duration of ipsilateral silent period group in comparison with the sedentary older grouping. These results indicate that the long-term maintenance of high levels of aerobic activity could retard or reverse losses of interhemispheric suppression associated with chronological aging (McGregor et al., 2009; Riecker et al., 2006; Talelli et al., 2008b).

Aerobic exercise has recently been shown to mitigate aging-related physical and cognitive decline (Kramer et al., 1999; Castillo-Garzon et al., 2006; Pontifex et al., 2009). Higher levels of aerobic fitness has been associated with maintenance of structural volume of multiple neural substrates including the hippocampus (Erickson et al., 2009), prefrontal cortex (Colcombe et al., 2003; Colcombe et al., 2006; Gordon et

al., 2008), medio-temporal regions (Gordon et al., 2008), and parietal regions (Colcombe et al., 2006; Gordon et al., 2008). In addition to structural change, functional MRI has revealed differences in cortical patterns of activity correlated with increases in physical activity. Colcombe et al., (2004) reported that both highly fit older participants and those completing a six-month aerobic fitness intervention evidenced significant decreases in anterior cingulate activity (though to be task interfering) during the Erickson Flanker Task as compared to age matched sedentary older adults. Similar findings have been reported in individuals afflicted with multiple sclerosis (Prakash et al., 2009). While it is currently unclear if the results from the current study indicate that long-term aerobic activity exerts a beneficial effect on the human motor system, it is relevant to note that decreased levels of interhemispheric inhibition have been evidenced in individuals with numerous pathologies including diabetes (with concomitant neuropathic pain) (Andersen et al., 2006), Parkinson's disease (Fisher et al., 2008; Cincotta et al., 2006), stroke (Shimizu et al., 2002), schizophrenia (FitzGerald et al., 2004) and many other genetic disorders (Verstynen et al., 2007).

The neurochemical mechanisms underlying the exhibited changes in cortical activity have yet to be determined, but increasing evidence indicates that neurotrophic factors play a critical role in this process. Declines in two such factors, insulin-like growth factor (IGF-1) and brain-derived neurotrophic factor (BDNF) have been strongly implicated in loss of neural structure and function (behavior). In rodent models, altered levels of BDNF have been associated with severe limitations in memory function concomitant with decreases in hippocampal volume (Griffen et al, 2008; Hwang et al., 2006). In humans, some of the most promising findings involving the effects of BDNF involve the investigation of a specific genetic variation in chromosome 11. A genetic

polymorphism (sometimes referred to as Val66Met) in the gene that codes for the creation of BDNF can result in an altered expression of the neurotrophic factor. Individuals with this polymorphism have been reported to exhibit a higher incidence of depression (Montag et al., 2009), impaired cognitive function (Guerini et al., 2009), and neurodegenerative diseases including Parkinson's and Huntington's disease (see Zuccato & Cattaneo, 2009 for recent review). Importantly, TMS studies comparing individuals with the Val66Met polymorphism have shown the presence of the gene variation to be associated with lower levels of cortical plasticity (Kleim et al., 2006; Cheeran et al., 2008). Future research involving TMS measures of interhemispheric inhibition with individuals with the Val66Met polymorphism are warranted to investigate the potential role of BDNF in intracortical communication.

A growing body of research in both human (Gomez-Pinella et al., 2009) and animal (Griffin et al., 2009; Molteni et al., 2004) models has indicated that regular bouts of cardiovascular exercise have been shown to increase both serum levels of BDNF and performance on multiple behavioral measures. Increased level of physical activity has been associated with improved cognitive performance (Gomez-Pinella et al., 2009; Erickson et al., 2009), affect (Blake et al., 2009), regulation of metabolic function (Magkos et al., 2009), and volume of neural structure (Erickson et al., 2009). It is possible that the older adults engaging in high levels aerobic activity in the current study also had concomitant increases in BDNF level. Future research investigating the effects of aerobic activity on measures of intracortical communication should include BDNF assays to assess a possible correlation.

## Potential Limitations

The current investigation sought to compare the interhemispheric communication patterns of aerobically active elderly adults with a group of sedentary elderly. As such, aerobic activity level was used as a proxy for aerobic physical fitness, the assumed mechanism driving differences in group data. However, the “gold standard” measure of aerobic fitness is widely considered to be an assessment of the asymptotic rate of oxygen consumption during maximal exertion on a treadmill or cycling platform or a $VO_2$Max test. While each of the current study’s fitness measures are correlated with this standard, a direct $VO_2$Max test would more appropriately approach the study’s aim. Further, the use of a $VO_2$Max test for group assignment would negate instrumentation error typical of self-assessment, particularly on a metric with psychological impact (performance self-efficacy and self-esteem; see McAuley et al., 1997).

The current study’s assessment of mirror movements may have lacked sufficient precision to diagnose such activity. Force transduction used as an assessment of mirror movement activity has been reported to evidence some variability within subjects (Baliz et al., 2005; Uttner et al., 2007). A behavioral study investigating mirror movements may ask the participant to engage in over 70 trials with contralateral force production set to 50% of MVC (e.g. - Baliz et al., 2005). Assessment of mirror activity is then made respective of the number of trials in which force output increased in the ipsilateral hand. The current study, due to time constraints, used only three 5-second trials were completed by the participants. Additionally, the contralateral output force was set to 25% of MVC, which is less than that of previously reported behavioral studies showing aging related differences in levels of MM (Baliz et al., 2005; Ottaviani et al., 2008). While in the scanner, mirror movements in participants were visually monitored from the

scanner control room. This procedure, implemented due to cost constraints, has limited sensitivity in the detection of such activity. Future investigations should incorporate the use of MR-compatible muscle-attached potentiometers to measure mirror movement.

Muscle group recruitment and force output on the motor tapping task could not be reliably assessed during the current study. While the total force required to depress the response button on the hand response device is set to 3N, participants are free to exert any amount of force exceeding this value while still performing the task accurately. Systematic variation in force output and subsequent muscle group recruitment between groups, though unlikely, could contribute to the exhibited group differences on the task. The force matching task was implemented, in part, to control for this variance. It is unfortunate that head motion in that task precluded analysis of variance respective of force output.

Additionally, while the present investigation represents the largest known combined neuroimaging and neurophysiological investigation into neural correlates of aerobic activity to date, group membership was limited to 14 individuals. Due to the known variability in neuroimaging results, particularly in older adults (see D'Esposito et al, 2003), the present sample size could limit extrapolation of the study's findings to the general population.

APPENDIX A
PHYSICIAN'S CLEARANCE FORM

***Brain Imaging Rehabilitation and Cognition Lab*** *University of Florida*
*Project: Aerobic Exercise, Cognition, and Brain Functions* *P.O. Box 100165*
*in Older Persons* *Gainesville, FL 32610-0165*
*College of Public Health and Health Professions* *Phone (352) 376-1611 ext. 5395*
*Clinical & Health Psychology* *Fax (352)273-5888*

# NURSE/PHYSICIAN PERMISSION FOR RESEARCH PARTICIPATION

Physician's Name _____Phone # _____ Fax # _____

Patient's Name _____

Dear Dr. _____,

Mr./Mrs. _____ would like to participate in a research study being conducted at the University of Florida investigating how physical fitness affects brain activity and cognitive performance. Inclusion in the study requires that Mr./Mrs._____ participate in a fitness test where individuals will be asked to walk, jog, or run on a treadmill for 12 minutes.

Below is a brief description of tasks required for participation in the research study. A trained research staff will supervise all tasks:

- Participation in a 12 minute fitness test where participants will be asked to walk, jog, or run on a treadmill at their own pace
- Participant must be able to undergo magnetic resonance imaging scanning. Scanning sessions will last from 45 to 120 minutes.

Based on Mr./Mrs. _____ current health status and medical history, would you provide physician's clearance for participation in the study? (Please check "yes" or "no")

□ **YES / NO** □

**Nurse/Physician name** _____ **Date** _____

**Signature** _____

If you have any questions or concerns please contact the BIRC lab at (352) 376-1611 ext. 5395. You can return this letter via fax at (352) 273-5888.

Thank you for your time and input

APPENDIX B
MRI PHONE SCREEN

# Subject Phone Screening Form

**Study ID#_____**
**Future Referral: Yes No**
**Eligibility_____**

Name of Subject: _____
Phone: _____ Education: _____
Date called: _____ Date scheduled: _____
Age: _____ Date of Birth: _____
Gender: _____ City of Residence:_____
Ethnicity (Hispanic or Latino): Yes No
Race: American Indian or Alaska Native Asian Black or AA Native Hawaiian or Pacific Islander White
____ Right handed
____ Native English Speaker
Height: ____ Weight: _____
Height and weight requirements:
If weight = 175-200, then height must be 5'6" or greater
If weight = 200-225, then height must be 5'8" or greater
If weight = 225-250, then height must be 5'10" or greater
If weight = 250-299, then height must be 6' or greater
If weight is 300 or greater, the subject is disqualified
____ Claustrophobic
**Metal in Body**:
____ Aneurysm or surgical plates/clips/pins/rods/screws/wires/joints/staples/mesh
____ Dentures/partials/braces/non-removable retainer or other metal dental appliances
____ Non-removable body piercing
____ Internal electrodes/wires (pacing wire, cochlear implant)
____ Foreign metal body (shrapnel, bullet, BB, gunshot, metal fillings/slivers/shavings)
____ Heart valve/ear/penile/eye implant/prosthesis or hearing aid
____ Vascular or intravascular coil/filter/stent/access port/shunt/catheter
____ Implanted insulin/drug pump or infusion device
____ Internal birth control or supportive device of any type (diaphragm, IUD, pessary)
____ Tattooed eyeliner
____ Cardiac pacemaker/defibrillator or neurostimulator/biostimulator/bone growth stimulator
____ Artificial limb or joint
____ Halo vest or metallic fixation device
____ Major surgeries or medical procedures:_____

**Personal Background**:

____Dx of learning disability, attention deficit disorder, enrolled in special education classes
____Head injury with loss of consciousness
____Dx of cardiovascular disease (heart attack, angina)
____Dx of stroke, TIA
____Dx of hypertension
____Seizures or fainting spells
____Dx of neurological disorder (epilepsy, MS, PD, HD)
____Dx of dementia or mild cognitive impairment
____Dx of psychiatric disorder, or psychiatric hospitalization
____Tx for alcohol or drug abuse
Medications: _____
____Psychoactive prescription medications? _____
____Corrected vision? ____ contacts _____ glasses
____Color blindness
____Pregnant or trying to become pregnant
____Smoke? cigarettes/day _____
____Alcohol use; average number of drinks per week _____
____Other recreational drugs (i.e., marijuana, ecstacy)? _____
Current average use per week_____
History of use_____
____Caffeine intake; average amt per day _____ (Note: if minimal intake, then recommend that they abstain from caffeine prior to scan; if moderate intake (dependence) then recommend they consume typical amount before scan)
____ Kidney Disease?
____ Oxygen? If so, can you go 1 hour without oxygen?
____ Wheelchair? IF so, can you walk up six steps without help?
____ Hemolytic anemia?
____ Allergies?

Has patient ever had metal in eyes or worked in machine shop or similar environment?
If yes, were X-rays taken? Yes _ No _
Results:_____ Radiologist: _____

Have you had an MRI since the discovery/removal of metal from eyes? Yes _ No _

**If yes to the following two hearing-related questions, the subject is automatically disqualified from MRI scanning for the current research projects:**

1) Have you experienced transient hearing changes LASTING GREATER THAN 24 HOURS from the time of MRI scanning?

YES_____ NO_____

2) Do you have Meniere's disease or experience the following combination of symptoms: fluctuating hearing loss, ringing in the ears, and vertigo?

YES_____ NO_____

The above information is true to the best of my knowledge.

Name of Patient or Next of Kin (circle one): _____ Date: _____
Signature of Person Conducting Phone Screen: _____ Date: _____

Scheduled Scan: Yes_____No_____

Date of Scan: _____

APPENDIX C
EXERCISE DAILY RECORD

(Indicate Date mm/dd/yy) _____

Please answer this questionnaire **WHEN YOU AWAKEN IN THE MORNING**. Please enter **yesterday's day and date above,** and provide the information requested below.

**Instructions**: This is a scale that measures your leisure – time exercise (i.e., exercise that was done during your free time). **During the past 24 hours**, please indicate **how many times** you have engaged in strenuous, moderate, and mild exercise **more than 20 minutes** during your free time.

| Indicate **how many times** you did this activity **for 20 minutes or longer** in the **past 24 hours**: | **# times** |
|---|---|
| 1. **Strenuous exercise**: heart beats rapidly (e.g., running, basketball, jogging, hockey, squash, judo, roller skating, vigorous swimming, vigorous long distance bicycling, vigorous aerobic dance classes, heavy weight training) | |
| 2. **Moderate exercise**: not exhausting, light sweating (e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, popular and folk dancing) | |
| 3. **Mild exercise**: minimal effort, no sweating (e.g., easy walking, yoga, archery, fishing, bowling, lawn bowling, shuffleboard, horseshoes, golf) | |
| 4. **Total Number of exercise:** add the number of strenuous, moderate, and mild exercise and write that number to the right. | |

Using the **total number of exercise** calculated above, please indicate how many exercise bouts occurred indoors and how many occurred outdoors by placing the appropriate number in the corresponding column.

| Number of **Indoor** exercise bouts | Number of **Outdoor** exercise bouts |
|---|---|
| | |

**Instructions:** The next two items ask you to rate how you are feeling. Circle the **one number** that best describes your answer.

4**. Tiredness**: Rate how tired you feel right now. (Circle the best answer)

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **0** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** |
| Not at all | | A little bit | | | Moder-ately | | | Quite a bit | | Extreme-Ly |

5**. Energy**: How much of the time during the past 24 hours did you have a lot of energy? (Circle the best answer)

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| None of the time | | A little bit of the time | | Some of the time | | A good bit of the time | | Most of the time | | All of the time |

**Instructions**. The next two items ask you to rate how you are feeling. Circle the **one number** that best describes your answer.

6. **Pain level**: On a scale of zero to ten, where zero means no pain and ten equals the worst possible pain, what is your current pain level? (Circle the best answer)

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| No pain | | Mild | | | Mode-rate | | | Severe | | Worst possible pain |

7. **Pain and Activity**: During the past 24 hours, how much did pain interfere with your normal activity, including both activities outside and inside the home? (Circle the best answer)

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Not at all | | A little bit | | | Moder-ately | | | Quite a bit | | Extreme-Ly |

**Instructions**. The next questions ask about your sleep yesterday. Please answer the following questions for **yesterday**. (Indicate **yesterday's day and date**? _____ *e.g., Tues. May 7*)

| **SLEEP DIARY** | **Your answer** (yesterday) | **Example** |
|---|---|---|
| **8. NAP** (mins): If you napped yesterday, how long did you nap, in minutes? | | *1 hr, 12 min* |
| **9. BEDTIME:** What time did you enter bed for the purpose of sleeping last night? | | *11:37 pm* |
| **10. TIME TO FALL ASLEEP** (mins): Counting from the time you wished to fall asleep, how many minutes did it take you to fall asleep? | | *20 min* |
| **11. AWAKENINGS**: How many times did you awaken during the night? | | *2* |
| **12. WAKE TIME** (middle of night): What is the total | | *30 min* |

| | | |
|---|---|---|
| number of minutes you were awake during the middle of the night once you fell asleep? *This does not include the time it took to fall asleep at the beginning of the night, or the time you spent awake in bed before getting out of bed in the morning.* | | |
| | | |
| **13. FINAL WAKE-UP:** What time did you wake up for the last time this morning? | | *7:13 am* |
| | | |
| **14. OUT OF BED:** What time did you actually get out of bed this morning? | | *7:23 am* |
| | | |
| **15. QUALITY RATING**: Pick ONE number to indicate your overall QUALITY RATING or satisfaction with your sleep. [1 = very poor; 2 = poor; 3 = fair; 4 = good; 5 = excellent] | | *3* |
| | | |
| **16. BEDTIME MEDICATION** (amount and time): List any sleep medication or alcohol taken at or near bedtime, and give the amount and time taken. | | *Ambien, 11:00 pm* |

APPENDIX D
FITNESS PHONE SCREEN

# Fitness phone screening for exercise, brain functions, and cognition study

Subject:_____ Date:_____ ID:_____

| **PAR-Q** | **Yes** | **No** |
|---|---|---|
| 1. Has your doctor ever said you have a heart condition and that you should only do physical activity recommended by a doctor | ☐ | ☐ |
| 2. Do you feel pain in your chest when you do physical activity | ☐ | ☐ |
| 3. In the past month, have you had chest pain when you were not doing physical activity | ☐ | ☐ |
| 4. Do you lose balance because of dizziness or do you ever lose consciousness | ☐ | ☐ |
| 5. Do you have a bone or joint problem that could be made worse by a change in your physical activity | ☐ | ☐ |
| 6. Is you doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition | ☐ | ☐ |
| 7. Do you know of any other reason why you should not do physical activity (If yes, please explain below) | ☐ | ☐ |
| | | |
| **Other health questions** | | |
| 1. Do you have diabetes? | ☐ | ☐ |
| 2. Do you have or had any of the following conditions: seizures, strokes, depression, or damage to the nerves of the legs? | ☐ | ☐ |
| 3. Have you smoked in the past 6 months? (If so, how many per day?) _____ | ☐ | ☐ |
| 4. Do you take testosterone or anabolic (growth hormone) replacements? | ☐ | ☐ |
| 5. Do you have asthma? | ☐ | ☐ |
| 6. Do you have lung disease? | ☐ | ☐ |

**Fitness assessment**

| | | |
|---|---|---|
| 1. Because of a health or physical problem, do you have any difficulty walking one mile? | ☐ | ☐ |
| 1a. If yes: How much difficulty do you have? (please circle one)<br>A little difficulty<br>Some difficulty<br>A lot of difficulty | ☐ | ☐ |
| 2. In the past 12 months did you do aerobic exercise (i.e. walking or speed walking)? | ☐ | ☐ |
| 2a. In the past 7 days did you do aerobic exercise? | ☐ | ☐ |
| 2b. What activities did you do?_____<br>_____<br>2c. In the past 7 days, about how much time did you spend doing aerobic exercise?<br>_____ | | |
| 3. In the past 12 months did you do high intensity exercise activities such as bicycling, swimming, jogging, racquet sports or using a stair-stepper, rowing or exercycle, at least 10 times? | ☐ | ☐ |
| 3a. In the past 7 days, did you do high intensity exercise? | ☐ | ☐ |
| 3b. What activities did you do?_____ | ☐ | ☐ |
| _____<br>3c. In the past 7 days, about how much time did you spend doing these activities?<br>_____ | | |
| 3d. Would you say that you do these activities with vigorous effort? | ☐ | ☐ |
| 4. Do you suffer from a physical condition that would prevent you from engaging in 12 continuous minutes of walking? | ☐ | ☐ |
| 5. Do you perform aerobic exercise at competitive levels? | ☐ | ☐ |

The above information is true to the best of my knowledge:

Name of patient: _____

Signature if patient: _____Date: _____

Name of person conducting the phone screen: _____

Signature of person conducting the phone screen: _____Date: _____

APPENDIX E
TMS SCREENING FORM

**Coded Name of TMS subject: _____**

Your head will be exposed to a magnetic pulse. To maximize safety, please answer the questions below. Please do NOT hesitate to ask any questions you may have regarding below.

Do you have, or have you ever had, any of the following? If YES, please explain on back.

**Y / N** Metallic hardware on the scalp?

**Y / N** Cardiac pacemaker?

**Y / N** Any history of heart disease or heart conditions?

**Y / N** Implanted medication pumps, intracardiac line, or central venous catheter?

**Y / N** History of cortical stroke or other cortical lesion such as brain tumor?

**Y / N** Prior diagnosis of seizure or epilepsy?

**Y / N** Previous brain neurosurgery?

**Y / N** Any chance you are pregnant? Date of last menstrual period _____

**Y / N** Any electrical, mechanical, or magnetic implants?

**Y / N** Migraine headaches- if YES, are they controlled? _____

**Y / N** List current medications on back of form (we are interested in medicines that Affect seizure threshold such as tricyclic antidepressants and neuroleptics)

**Y / N** Any problems swallowing or diagnosis of dysphagia?

**Y / N** Any history of cancer in your head or neck?

**Y / N** Unstable medical conditions? _____

**Y / N** Any body or clothing metal above your shoulders? If so, please remove.

**Y / N** Any metal on your body (i.e. watch or jewelry, hair holders or pins, eye glasses)

I have read and understand all questions in this document. My signature below indicates that I have accurately and completely answered all questions in this document.

SIGNATURE OF TMS SUBJECT: _____ DATE: _____
SIGNATURE OF INVESTIGATOR: _____ DATE: _____

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# BIOGRAPHICAL SKETCH

Keith Matthew McGregor graduated with honors from the College of the Holy Cross in Worcester, MA, with a B.A. in psychology. After working in the technology industry, he returned to graduate school in 2003 at the University of Florida entering the College of Liberal Arts and Science's program in Behavioral and Cognitive Neuroscience within the Department of Psychology. In 2006, he earned a Master of Science degree and began his doctoral program shortly thereafter. In 2008, Keith obtained a predoctoral fellowship from the United States Department of Veteran's Affairs Office of Academic Affairs Initiative for Rehabilitation Research. He is married to Kristi Stahnke and has two children: Liam and Leah. After graduation, Keith will accept a Career Development Award from the United States Department of Veteran's Affairs.