FUNCTIONAL ACTIVATION DURING THE STROOP TASK IN NORMAL OLDER ADULTS & MCI

by

ANTONIO NICOLAS PUENTE

(Under the Direction of L. Stephen Miller)

ABSTRACT

The purpose of this study was to compare the neural activation of inhibition with functional Magnetic Resonance Imaging (fMRI) between normal and older adults with mild cognitive impairment (MCI). It was hypothesized that individuals with MCI have greater activation in specific brain regions. This hypothesis was not supported given there was no difference between groups in hypothesized regions or in post-hoc whole brain analyses with corrected thresholds. However, several measures from a neuropsychological battery were able to differentiate between normal and older adults with MCI. Results suggest traditional neuropsychological techniques may be superior to fMRI in detecting MCI.

INDEX WORDS: fMRI, older adults, MCI, inhibition, Stroop

FUNCTIONAL ACTIVATION DURING THE STROOP TASK IN NORMAL OLDER ADULTS & MCI

by

Antonio Nicolas Puente

B.A., Flagler College, 2007

A Thesis Submitted to the Graduate Faculty of The University of Georgia in Partial Fulfillment of the Requirements for the Degree

MASTER OF SCIENCE

ATHENS, GEORGIA

2012

© 2012

Antonio N. Puente

All Rights Reserved

FUNCTIONAL ACTIVATION DURING THE STROOP TASK IN NORMAL OLDER ADULTS & MCI

by

ANTONIO NICOLAS PUENTE

Major Professor: L. Stephen Miller

Committee: James MacKillop
Dean Sabatinelli

Electronic Version Approved:

Maureen Grasso
Dean of the Graduate School
The University of Georgia
May 2012

ACKNOWLEDGEMENTS

I would like to thank my advisor, Dr. L. Stephen Miller for his support and guidance while undergoing this project. I would also like to thank my committee, Dr. James MacKillop and Dr. Dean Sabatinelli for their insight. Members of my lab were also instrumental in providing feedback and assistance for this investigation. Kim Mason was also very helpful with data collection, and is thanked for her time and work provided for this project.

TABLE OF CONTENTS

ACKNOWLEDGEMENTS…………………………………………………………………...iv

LIST OF TABLES…………………………………………………………………………vi

LIST OF FIGURES……………………………………………………………………...vii

CHAPTER

1 INTRODUCTION…………………………………………………………......1

2 METHOD…………………………………………………………………..41

3 fMRI COMPARISION OF INHIBITION BETWEEN NORMAL AND OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT………………………...55

4 DISCUSSION……………………………………………………………...95

REFERENCES……………………………………………………………………………99

APPENDIX………………………………………………………………………………..122

LIST OF TABLES

Page

Table 1.1: The most common sets of diagnostic criteria for Alzheimer's disease summarized....53

Table 3.1: Group Demographics…………………………………………………………….....86

Table 3.2: Neuropsychological Performance………………………………………………….87

Table 3.3: Behavioral performance on Stroop task……………………………….…………..88

Table 3.4: Brain Regions activated to a greater degree by MCI – Normals ROI analyses.……..89

Table 3.5: Brain regions activated during inhibition across all participants; Incongruent >

Congruent WB analyses..………………………………………………………………90

LIST OF FIGURES

Page

Figure 2.1: Flow chart of recruitment…………………………………………………………...54

Figure 3.1: Example of Stroop task progression………………………………………………...91

Figure 3.2: Accuracy of both groups for all conditions…………………………………………92

Figure 3.3: Reaction time of both groups for all conditions……………………………………93

Figure 3.4: Brain regions activated during inhibition across all participants; Incongruent > Congruent WB analyses..…………………………………………………………....94

CHAPTER 1

INTRODUCTION

The number of older adults continues to grow at an unprecedented rate, as advances in medicine have greatly increased the average human lifespan. In 2008, it was estimated that older adults ($\geq$65) comprised seven percent of the world's population, and in 2040 it is expected that they will account for 14 percent of the world's population (Kinsella & He, 2009). Regrettably, as the number of older adults increases, so does the number of individuals affected by degenerative diseases and dementia (Alzheimer's Association, 2011; Alzheimer's Disease International, 2008).

Understanding the neurobiological processes underlying pathological aging is of great importance for individuals, caregivers, and the aggregate population. Frequently, neurodegenerative diseases result in dementia, which is associated with declines in functional ability: one's ability to carry out activities of daily living (ADLs). ADLs are comprised of instrumental activities of daily living (IADLs: laundry, managing finances, housekeeping) and basic activities of daily living (BADLs: bathing, dressing, toileting, eating; Marcotte, Scott, Kamat, & Heaton, 2010). Individuals with functional impairment are at an increased risk for a host of problems, such as car accidents (Lloyd et al., 2001), falls (van Doorn et al., 2003), and malnutrition (Wolf-Klein & Silverstone, 1994).

Due to functional impairment and the accompanied negative consequences, individuals with dementia are often dependent on others to function and complete ADLs. As a result, caregivers are also negatively affected by dementia and may suffer from increased rates of dementia also

impact the aggregate population, as the worldwide cost of dementia is estimated at 422 billion dollars (Wimo, Winblad, & Jönsson, 2010). Thus, as both the number of demented individuals and the impact of pathological aging continue to grow, more research is needed to understand and clarify these complex detrimental processes.

Normal Aging

Aging is an inevitable, gradual, and progressive process that increases the likelihood of disease and death (Harman, 1981). No single factor or process causes or can explain aging; rather, it is likely the result of extremely complex multifactorial processes (Weinert & Timiras, 2003). While there are several conceptualizations of normal aging, the current investigation defines it within a statistical framework. Thus, normal aging is a category that refers to a group of individuals representative of the typical aging process (Smith & Ivnick, 2003). Normally aging older adults usually have age-associated diseases and common medical conditions. These conditions are associated and may be due to biological changes that occur throughout the adult lifespan in the integumentary, vascular, respiratory, musculoskeletal, and sensory systems (Luggen, 2010; Saxon, Etten, & Perkins, 2010).

The most visible changes in aging occur in the integumentary system (i.e., skin, hair, nails, and glands). Older adults almost always have wrinkled skin, alopecia (i.e., hair loss), hair color loss, and brittle nails (Lindh, Pooler, Tamparo, & Dahl, 2009; Luggen, 2010). Although less physically noticeable, significant changes also occur in the vascular system in normal aging.

Older individuals are more likely to experience arteriosclerosis and atherosclerosis, have an increased heart weight, increased systolic blood pressure (i.e., blood pressure when active), and decreased diastolic blood pressure (i.e., blood pressure at rest; Larsen, 2009). Additionally,

older adults have diminished respiratory functioning and frequently experience difficulty breathing and shortness of breath (Lindh et al., 2009). Decreased effectiveness of the respiratory system is in part due to the decreased elasticity of the lungs, as well as the loss of the muscle structure in the respiratory system (Lindh et al., 2009).

Muscle changes are not limited to the respiratory system and also occur throughout the entire musculoskeletal system. During the adult lifespan, there is a gradual loss of muscle strength and muscle mass (i.e., sarcopenia; Roubenoff & Hughes, 2000), and this is accompanied by decreased bone density and mass (Saxon et al., 2010). Presumably, pervasive changes in bone and muscle are strongly associated with the diminished physical performance and mobility evident in old age (Saxon et al., 2010).

Age-related biological processes also adversely affect sensory systems, impacting older adults' vestibular sense, gustation, olfaction, tactile discrimination, audition, and vision (Lord & George, 2003; Woodruff-Pak, 1997). In old age, individuals commonly have difficulty identifying common substances by smell and experience a gradual loss of sweet and salty tastes. Decreased effectiveness in the gustatory and olfactory systems is accompanied by disturbances to the tactile system, and older adults require greater distances between two distinct points to identify simultaneous stimulation as separate locations (Woodruff-Pak, 1997).

Presbycusis (i.e., hearing loss) starts gradually in early adulthood and substantially increases in late adulthood, affecting the majority of adults 70 years or older (Gates & Mills, 2005; Lord & George, 2003). Hearing loss in old age is usually first evident as the decreased ability to understand speech with high frequency sounds in noisy environments. Subsequently, older adults are often unable to detect, localize, and identify sounds, and they experience comprehension problems (Gates & Mills, 2005).

Typically, changes in the visual system are first manifested as presbyopia, the inability to focus on close-up objects. Decreased visual acuity is another biological effect of aging and remains even when presbyopia is corrected with plus lenses (Gates & Mills, 2005). Furthermore, compared to young adults, older adults are more sensitive to glares, have difficulty discriminating between colors (e.g., yellow vs. blue), have reduced vision in low light conditions (e.g., dusk), and have decreased visual processing speed, visual scanning, and useful field of view (Jackson & Owsley, 2003).

These physical and sensory changes are notable, given that diminished functioning of these biological systems alters the everyday lives of normal older adults. For example, West et al. (2000) found poor performance on measures of vision (e.g., spatial vision & dark adaptation) was related to self-reported physical functioning. Similarly, Janssen, Heymsfield, and Ross (2002) documented that changes in the musculoskeletal system impact the lives of individuals, finding sarcopenia to be associated with diminished physical mobility.

Nonetheless, declines in these systems are usually gradual and can be remediated with adaptations in older adults' lives. Appollonio, Carabellese, Frattola, and Trabucchi (1996) examined the impact and remediation of sensory impairment on the lives of community dwelling older adults (i.e., 70-75). Older adults with compromised sensory functioning and without sensory aids (e.g., corrective lenses & hearing aids) have a substantially lower mean score on the IADL scale compared to older adults who used corrective devices to aid sensory functioning. Analyses also indicated that older adults with compromised sensory functioning who used sensory aids did not have a significantly different IADL score than individuals whom did not require sensory aids. Together, these findings support the perspective that declines in physical and sensory systems can be attenuated by adaptations (e.g, corrective devices) to their lives.

Cognition in Normal Aging

A less remediable consequence of aging, and associated factor of functional impairment, is cognitive decline. When age information processing slows, forgetfulness increases, and our ability to complete higher order complex cognitive processes declines. Compared to young adults, empirical evidence indicates older adults perform consistently worse on tasks measuring processing speed, memory, and executive functioning (EF; Christensen, 2001). These cognitive changes are related and possibly due to neuroanatomical (Eldkin-Thompson, Ballmaier, Hellemann, Pham, & Kumar, 2008; Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009; Newman, Trivedi, Bendlin, Ries, & Johnson, 2007) and neurofunctional age related changes (Cabeza, 2002; Davis, Dennis, Daselaar, Fleck, & Cabeza, 2007).

One noticeable change in old age is the ability to process information is slower and less efficient. Processing speed measures how quickly and efficiently an individual processes and acts upon information. As measured by reaction time, older adults are found to be consistently slower than younger adults on measures of processing speed (Cavanaugh & Blanchard-Fields, 2006). For example, Bashore, Ridderinkhof, and van der Molen (1997) compared the reaction times and event-related brain potentials between normal young and older adults during a choice reaction time task. Participants were presented with matrices containing the words “left” or “right” surrounded by randomly selected numbers or letters and instructed to respond with the appropriate button press. The authors reported that older adults had significantly longer mean reaction times, as well as a longer P300 latency. The authors concluded that slowed processing speed in older adults is due to inefficient response execution and not caused by slowed response selection.

In addition to being slower to process and act upon information, the ability to temporarily hold, process, and manipulate information (i.e., working memory) also becomes compromised with old age. Van der Linden, Brédart, and Beerten (1994) investigated list-length effects between 36 young and older adults using a running memory task. The authors reported no difference between groups when participants serially recalled four items, but they indicated significant age effects when adults recalled six consonants.

Although older adults usually have diminished capacity to hold information temporarily, working memory changes are most evident on tasks requiring mental manipulation. Dobbs and Rule (1989) administered six working memory measures to 228 adults to categorically separate tasks sensitive to changes in aging. They found older adults performed as well as young adults on tasks that did not require manipulation of information, but older adults were unable to provide as many correct responses on measures requiring mental manipulation. While older adults are usually unable to temporarily retain as much information as young adults, mental manipulation of temporarily held information is the most affected component of working memory in normal aging.

The most common and concerning cognitive complaint for older adults is diminished memory functioning. Older adults frequently report trouble-remembering names, misplacing household items (e.g., car keys), and word finding difficulties (Craik, 1994). Consistent with these subjective memory complaints, research commonly finds that older adults perform worse than young adults on memory measures.

While there are several different types of memory measures (i.e., implicit, semantic), a complete explanation on the effect of age on all types of memory is beyond the scope of this investigation. However, the effect of age on episodic memory, personally experienced past

events (Tulving, 1972), is typically the most pronounced and will be discussed. Episodic memory is traditionally measured with free and/or cued recall and recognition paradigms. Older adults typically recall less information than young adults, provide more intrusions, repeat more responses, and select more foils (Zacks, Hasher, & Li, 2000). Poor performance on measures of episodic memory is likely due to ineffective encoding and retrieval processes, rather than retention. When encoding and retrieval strategies are provided, older adults' performance increases and the differences between young and older adults become negligible or are attenuated (Balota, Dolan, & Duchek, 2000).

Despite necessitating minor adaptations, these aforementioned cognitive changes typically will not negatively impact the lives of normal older adults. In contrast, research has documented that declines in EF substantially affect the lives of older adults. EF is encompassed by many different cognitive functions that are considered "higher order" cognitive processes, including the ability to plan, initiate, inhibit, monitor, and perform behaviors. EF controls and regulates the majority of other cognitive abilities, allowing individuals to engage in socially responsible, appropriate, adaptive, and effective behaviors (Lezak, Howieson, & Loring, 2004).

One of the major components of EF, inhibition, becomes compromised with age. Older adults are more likely to fail to inhibit pre-potent responses and process task irrelevant stimuli (Lustig, Hasher, & Zacks, 2007; West & Alain, 2000). As a result, the lives of older adults are negatively impacted. Disturbances to inhibitory processes increase the likelihood one will engage in an alternative but irrelevant behavior (Grigsby, Kaye, & Robbins, 1995). Disinhibition could also cause socially inappropriate behaviors and lead to unsafe situations (American Bar Association/American Psychological Association Assessment of Capacity in Older Adults Project Working Group, 2008).

Probably the most common unsafe situation as a result of impaired inhibition for an older adult is while driving. Older adults are two to five times more likely than younger individuals to be involved in car accidents resulting in serious injury or fatality (Khan, 2009). While other factors likely attribute to the compromised driving ability of older adults (i.e., decreased vision), age related declines in inhibition increase the likelihood of unsafe driving.

Defective inhibition is manifested and impacts driving in several ways. For example, older adults frequently fail to inhibit the prepotent response when driving a vehicle that begins to skid (i.e., brake). They are also often unable to sufficiently brake/yield for emergency vehicles and changing stoplights (Potter, Grealy, & O'Connor, 2009). Furthermore, older adults are less likely to inhibit irrelevant information (e.g., storefronts & billboards) when driving (Sifrit, 2005).

Thus, as one may expect, deficits on measures of EF have been shown to diminish an individuals' ability to complete IADLs (Cahn-Weiner, Malloy, Boyle, Marran, & Salloway, 2000; Mitchell & Miller, 2008; Royall, Palmer, Chiodo, & Polk, 2004). For example, Cahn-Weiner et al. (2000) administered a comprehensive neuropsychological battery to community dwelling older adults to determine which cognitive ability is most associated with the successful completion of complex everyday activities. Compared to visuospatial, language, memory, and motor measures, the only measure that accounted for a significant proportion of variance in an older adult's ability to complete adaptive real-world behaviors was an EF composite score.

Two studies from our laboratory investigated the relationship between community dwelling older adults and functional ability (Lewis & Miller, 2007; Mitchell & Miller, 2008). Lewis and Miller (2007) compared the components of EF to determine which component best predicted functional ability. The EF components were derived from neuropsychological tests that measure specific constituents of EF (e.g., Tower of London, COWAT, WCST, & digit

span). Within a large range of EF ability in 83 older adults, working memory was most correlated with objective functional ability. However, simultaneous regression indicated the EF component most predictive of functional ability was planning.

Subsequent to this investigation, Mitchell and Miller (2008) examined the ability of four Delis Kaplan Executive Function System (D-KEFS) subtests and an EF composite score to account for observed functional ability in non-demented older adults ages 65 to 92 (i.e., performance on the Direct Assessment of Functional Status). While only a measure of planning and sequencing accounted for a significant amount of variance independently (i.e., DKEFS Trail Making Test 4), a hierarchical regression analysis revealed that the EF composite score accounted for 26% of the observed functional ability.

Traditionally, investigations of EF and functional status have been cross sectional designs, but Royall, Palmer, Chiodo, and Polk (2004) utilized a longitudinal paradigm to investigate this relationship. This study examined if declines in EF in 547 high functioning older adults predicted changes in functional status. Participants were evaluated annually over a three-year period, and decline on an EF measure (i.e., Exit-25) accounted for 57% of the decline on a self-reported measure of functional status. This finding remained significant after adjusting for age, baseline disability, level of care, and baseline EF performance.

Declines in EF and other cognitive functions (e.g., memory) in normal aging are associated with and may be due to normal age-related structural brain changes. Newman, Trevedi, Bendlin, Ries, and Johnson (2007) examined this perspective, and they found an inverse relationship between the time taken to complete an EF measure, Trail Making Test Part B, and the volume of gray matter within the left and right inferior frontal gyri. The authors also found a positive relationship between gray matter volume in the left and middle frontal gyri and number

of orally produced words. A subsequent investigation reported a positive correlation between the total volume in the anterior cingulate and performance on the Stroop interference test. Older adults with a smaller anterior cingulate required significantly more time to complete the task (Elderkin-Thompson et al., 2008).

Normal Aging Brain

With age, the overall volume of the brain declines (Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003), due to region specific decreases in gray (Jernigan et al., 2001; Raz et al., 2005) and white matter (Gunning-Dixon et al., 2009). There is also a decrease in the number and length of dendritic spines (Jacobs, Driscoll, & Schall, 1997), increases in ventricular volume (Resnick et al., 2003), increased number of white matter hyperintensities (Decarli et al., 2005), decreased gyral volume (Bigler, Andersob, & Blatter, 2002), and increased sulcal span (Liu et al., 2010).

Numerous cross-sectional investigations suggest that the total brain volume and other regional areas decrease throughout the human life span. Resnick et al. (2003) examined the volumetric changes in 92 non-demented older adults over a four-year time period to identify neuroanatomical changes due to the processes of normal aging. As predicted, global brain volume declined and ventricular volume increased (5.4 cm^3 decrease and 1.4 cm^3 annual increase, respectively). Region specific volumetric analyses revealed an annual total loss (i.e., gray and white matter together) of 2.58 cm^3, 1.58 cm^3, 1.00 cm^3 in the frontal, parietal, and temporal regions, respectively.

Similarly, Raz et al. (2005) analyzed regional brain changes in 72 healthy adults using a longitudinal design and found widespread non-uniform shrinkage in cerebral hemispheres and subcortical regions over a several year time period (i.e., 4.83 to 6.08 cm^3). They reported a mean

annual gray matter loss of 1.28 cm^3, 0.90 cm^3, 0.64 cm^3, 0.29 cm^3, 0.37 cm^3, 4.43 cm^3, in the prefrontal cortex, temporal lobe, inferior parietal lobule, hippocampus, caudate nucleus, and cerebellum, respectively. Analyses revealed age was negatively correlated with volumes in the prefrontal, hippocampus, caudate nucleus, and cerebellum.

Structural changes in normal aging are evidenced to alter neural activity of older adults. Persson et al. (2006) found a negative correlation between structural integrity and functional activations in the right prefrontal cortex during episodic memory encoding. Several modalities exist to measure the functional neural activity of older adults, including positron emission tomography (PET), single photon emission computed tomography (SPECT), electroencephalography (EEG), and functional magnetic resonance imaging (fMRI). While all these methods have utility, fMRI has potential advantages in studying pathological aging. It is non-invasive, repeatable, and relative to other neuroimaging measures, has a relatively good combination of temporal and spatial resolution (Dickerson & Sperling, 2008).

fMRI is an indirect measure of functional activity and is based on the principle that active neurons require oxygen. To provide the oxygen to these active neural areas, oxygen rich blood flows to the desired location, resulting in an increased amount of oxyhemoglobin compared to deoxyhemoglobin in active neural areas. Thus, functional activity in fMRI is measured by determining the ratio of oxyhemoglobin to deoxyhemoglobin in neural areas across specific time points.

Oxygenated hemoglobin (i.e., zero unpaired electrons) is diamagnetic, as it has zero magnetic moment and therefore causes no significant disturbances in the magnetic field. In contrast, deoxygenated hemoglobin (i.e., several unpaired electrons) is paramagnetic, as it is attracted to the magnetic field and causes disturbances to the magnetic field. Therefore, when

neural areas are active there is an increase in the ratio of oxygenated hemoglobin to deoxygenated hemoglobin at the active neural area, and the paramagnetic effects of the deoxygenated hemoglobin are decreased, resulting in an improved signal called the Blood Oxygen Level Contrast (BOLD; Huettel, Song, McCarthy, 2008).

Although dependent on several factors (e.g., cognitive task & measure of activation) older adults commonly exhibit altered patterns of activation (i.e., hyperactivation) compared to younger adults. For example Langenecker, Nielson, and Rao (2004) compared the neural activity between young and older adults in a block design paradigm during the Stroop task. Older adults engaged similar frontal regions to a greater degree than young adults. Nonetheless, the relationship of increased activation and aging is imperfect, and differences in analyses between investigations vary significantly. Some investigations use level or amount of activation (i.e., intensity) by examining the same brain regions in controls (e.g., young adults) and older adults, while others compare functional activity with extent of activation (i.e., number of voxels engaged). As a result, hyperactivation is often conflated as both increased magnitude and increased number of voxels in similar or different neural areas.

Hyperactivation, defined as a greater number of voxels recruited to a greater degree sometimes occurs in homologous contralateral areas typically engaged by younger adults to successfully complete cognitive processes (Cabeza, Anderson, Locantore, & McIntosh, 2002). For example, on episodic encoding tasks younger adults typically activate left lateralized neural areas (e.g., prefrontal cortex & hippocampus), while older adults generally display bilateral activity. In support of these findings, Cabeza proposed a Hemispheric Asymmetry Reduction in Older Adults model (HAROLD; Cabeza, 2002). The HAROLD model suggests the origin of greater bilateral activation in numerous cognitive tasks is caused by either altered neural

structures (i.e., neurogenic view) and/or altered cognitive processes (i.e., psychogenic view). Regardless of origin, less asymmetrical activation is thought to enhance/preserve cognitive functioning (i.e., the compensatory view) or is a mere by-product of aging indicative of decreasing differentiation of cognitive functions, and it either serves no specific function or it benefits cognition (i.e., the dedifferentiation view).

While the altered patterns of activation in older adults (i.e., hyperactivation and reduced asymmetry) remains to be fully understood, preliminary evidence suggests the recruitment of more voxels, often bilaterally, is to compensate for the decreased effectiveness of neural areas and preserve cognitive function that would be otherwise compromised (e.g., DLPFC; Reuter-Lorenz & Cappell, 2008). The compensation perspective is supported by several findings, including the finding that within groups of individuals with declining cognitive performance (e.g., older adults), hyperactivated areas were positively correlated with behavioral performance (Milham et al., 2002; Persson et al., 2006). Additional support for the compensation view is the finding that individuals likely with neuropathology (e.g., MCI & apolipoprotein epsilon allele 4 carriers) frequently display increased patterns of activation and indistinguishable behavioral performance when compared to individuals free of pathology (Bondi, Houston, Eyler, & Brown, 2005; Braak et al., 1999; Han, Bangen, & Bondi, 2009).

Altered functional activation and neuroanatomical changes accompany the process of aging, and they are associated with and likely account for the cognitive decline that occurs in aging. While it is not the focus of this investigation, these changes are also probably related to the physical and sensory changes in aging, and they may be partly the result of the same or a very similar multifactorial complex process. This inevitable and intricate process affects all individuals and impacts their daily life by limiting their mobility, perceptions, and cognition. As

a result of these numerous changes, some normal aging older adults experience declines in their functional ability (Cahn-Weiner et al., 2000). The ability of older adults to perform IADLs is compromised when there are declines in EF (Mitchell & Miller, 2008; Royall et al., 2004), and changes in one component of EF, inhibition, appear to be particularly important given its negative impact when compromised (Potter et al. 2009; Sifrit 2005). Despite these deleterious effects of normal aging, normal older adults have much less if any functional impairment compared to pathological aging older adults (Marcotte et al., 2010).

Pathological Aging

Theoretical disagreements and complexities inherent to aging have prevented a clear definition of pathological aging. However, given that normal aging refers to a group of individuals representative of the typical aging process, pathologically aging adults are those who experience an atypical aging process. These individual have diseases and conditions that are not typical or frequent in normal aging older adults. Thus, the pathological aging process is often understood through investigations of neurodegenerative diseases, which are defined as neurological diseases characterized by progressive declines in the structure, activity, and function of the brain (Rodgers, 2009). Types of neurodegenerative diseases include Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (e.g., ALS or Lou Geherig's Disease), frontotemporal dementia, Lewy body dementia, prion diseases, and Alzheimer's disease (AD; Bertram & Tanzi, 2005).

As the second most common neurodegenerative disease, Parkinson's disease is defined by the significant loss of dopaminergic neurons in the substantia nigra and significant motor impairment (Bertram & Tanzi, 2005). While the preliminary and typical presenting symptoms of Parkinson's disease are motor dysfunction (i.e., tremor at rest, motor rigidity, akinesia, postural

instability, flexed posture, and freezing), dementia commonly occurs as a result of underlying histological changes and pathology (Jankovic, 2008). Approximately half of non-demented Parkinson's disease patients will develop dementia in four years, and the majority will develop dementia in eight years (Caballol, Martí, & Tolosa, 2007). Dementia due to Parkinson's disease is traditionally characterized by EF impairment but is also frequently accompanied by deficits in attention, memory and visuospatial functioning (Emre, 2003).

Similar to Parkinson's disease, severe motor impairments are also the hallmark of two other neurodegenerative diseases, Huntington's disease and ALS. Huntington's disease is an autosomal genetic disorder that destroys neurons within the caudate nucleus and putamen, and it is hallmarked by uncontrollable, random, and jerky movements (e.g., chorea). This rare neurodegenerative disorder results in death 15 to 20 years after the initial symptoms, but is usually preceded by dementia (Naarding, Kremer, & Zitman, 2001). Dementia due Huntington's disease is often classified as subcortical dementia, and it is marked by deficits in attention, processing speed, EF, visuospatial abilities and, to a lesser degree, memory (Peavy et al., 2010).

ALS is characterized by destruction of motor neurons in the cortex, brain stem, and spinal cord, which leads to widespread muscle degeneration and usually results in death 1 to 20 years after onset (Rowland & Shneider, 2001). The relationship between ALS and dementia is nebulous, as dementia often occurs before the symptoms of ALS appear (Ichikawa et al., 2008). Ichikawa et al. (2008) note, when neuropsychological testing can be completed, the characteristics of the dementia are very similar to frontotemporal dementia.

Frontotemporal dementia is yet another neurodegenerative disorder characterized by significant behavior and cognitive changes, with an onset typically between 45 – 65 and a mean illness duration of 8 years (Snowden, Neary, & Mann, 2002). Adults affected by frontotemporal

dementia commonly exhibit apathy, socially inappropriate and/or socially withdrawn behavior, disinhibition, attention deficits, reduced spontaneous speech, impaired word comprehension, word finding difficulties, and anosognosia (Ichikawa et al., 2008; Snowden et al., 2002).

Lewy body dementia is a debilitating degenerative disorder that affects older adults, and it has a variable clinical presentation due to abnormal neurofilament proteins and senile plaques in cortical and subcortical structures. Despite its heterogeneous makeup, the typical presenting clinical symptom of Lewy body dementia is severe memory impairment that impairs daily functioning. Additionally, individuals with Lewy body dementia experience fluctuating cognition and consciousness, auditory and visual hallucinations, and Parkinson like motor symptoms (McKeith, 2002).

Alzheimer's disease

Comparable to the clinical presentation of Lewy body dementia, the most common neurodegenerative disorder and type of dementia is Alzheimer's disease (AD). Characterized by memory deficits and progressive cognitive decline, AD affects an individuals' ability to function independently and is currently estimated to affect 5.4 million Americans, of which the vast majority are 65 or older (Alzheimer's Association, 2011). In addition to preferentially affecting older adults, others factors are associated with the development of AD, including: gender (Letenneur, Gilleron, Commenges, Helmer, Orgogozo, & Dartigues, 1999), education (Launer et al., 1999), cognitive reserve (Stern, 2006), socio-economic status (Fratiglioni, Winblad, & Vonstrauss, 2007), occupation (Fratiglioni et al., 2007), smoking (Launer et al., 1999), alcohol consumption (Launer et al., 1999), familial history ("The Canadian Study of Health and Aging: risk factors for Alzheimer's disease in Canada," 1994), genetic status (Bertram & Tanzi, 2005), head injury (Launer et al., 1999), and hypertension (Skoog & Gustafson, 2006).

Findings from epidemiological investigations indicate that the single greatest risk factor for AD is age (Plassman et al., 2007). For example, an epidemiological study comprised of 1,236 participants estimated the incidence rate to be 0.08% per year for individuals 60-65, while it was reported that the rate was 6.48% for individuals older than 85 (Kawas et al., 1997). Similarly, Launer et al. (1999) found that incidence of AD significantly increased between groups of older adults, from 1.2 per 1,000 for adults between 65-69 and 63.5 per 1,000 for individuals 90 years of age or older. As these investigations suggest the incidence of AD increases significantly after middle adult hood, with the highest incidence occurring in the last decades of life; this supports the widely accepted perspective that age is the strongest risk factor for AD.

Female gender is found to increase the likelihood an individual will develop AD, as women have a higher prevalence and incidence of AD (Letenneur et al., 1999). Evidence from a large dataset of Swedish older adults (≥75) supports this perspective (Fratiglioni et al., 2007). Although this finding is consistently found in population-based studies, the relationship between gender and AD is not fully understood but may be due to survival differences and/or biological factors.

An interaction analyses conducted with 2,881 French older adults (>65) found an effect between age and gender, such that the incidence rate of AD was significantly greater in women only after age 80, and it was concluded that an increased lifespan may explain the relationship between AD and gender (Letenneur et al., 1999). Biological factors, however, may further explain this relationship, with a prospective study indicating incidence differences between two groups of pre and post-menopausal women whom either did or did not receive estrogen replacement therapy (Kawas et al., 1997). A Cox proportional hazards regression analysis

calculated the relative risk while accounting for age and education, and found the relative risk for estrogen replacement users to non-users was 0.457 indicating non-users have increased risk for developing AD. Moreover, out of 34 women who were diagnosed, only 9 estrogen replacement users developed AD over a 16-year period, whereas 25 who did not receive estrogen replacement developed AD.

Increased incidence and prevalence of AD in women may mostly be due to biological differences, but it is possible education may contribute to gender differences through non-discernible complex mechanisms (Letenneur et al., 1999). Launer et al. (1999) pooled a sample of 528 older adults and out of 328 diagnosed AD cases, 315 had less than 12 years of education. The relationship between education and AD may in part be due to cognitive reserve (Stern, 2006).

The cognitive reserve model suggests the brain copes with brain damage by using existing cognitive processes or recruits additional resources to maintain cognition (Stern, 2003, 2006). The amount of cognitive reserve varies between individuals, and those with greater cognitive reserve are able to better sustain brain damage. An individual with more cognitive reserve usually have more education and would show less functional deficits than an adult with less cognitive reserve but the same amount of brain damage. The cognitive reserve model also suggests two older adults may look very similar clinically but may have very different levels of underlying neuropathology (Stern, 2006). Individuals with greater cognitive reserve have further to fall and require a greater amount of neuropathology to exhibit clinical symptoms (Stern, 2003). Even though it is plausible the cognitive reserve model may at least in part account for the relationship between education and AD, it may additionally be accounted for by socio-economic status.

The relative risk for an older adult with low socio-economic status was substantially greater than individuals with a high status (Fratiglioni et al., 2007). However, adults with high educational attainment and low socio-economic status were not at a higher risk for dementia, but individuals with low educational attainment were at a higher risk regardless of past or current socio-economic status. Thus, although low socio-economic status is an independent risk factor for AD, this relationship is may be better explained by educational attainment (Fratiglioni et al., 2007).

There also appears to be a genetic risk for AD. Results from the Canadian Study of Health and Aging indicated persons with first-degree relatives diagnosed with AD have an increased predisposition for AD ("The Canadian Study of Health and Aging: risk factors for Alzheimer's disease in Canada," 1994). The authors found individuals with a family history of dementia had an odds ratio of 2.62 and thus were two to three times more likely to develop dementia compared to individuals without a familial history. Although this relationship may be explained by environmental factors, it is more likely that genetic factors explain this association.

Bertram and Tanzi (2005) conducted an extensive review on the genetic underpinnings of neurodegenerative diseases, noting three genes: ß-amyloid precusor protein (APP), presenilin 1, and presenilin 2 cause Early-onset AD, and one genetic factor, apolipoprotein epsilon allele 4 (APOE ε-4), increases the probability an individual will develop Late-onset AD (i.e., >65). Early-onset, familial AD, accounts for less than 5% of AD cases and is identified as the onset of dementia due to AD before 65 (American Psychiatric Association, 2004). Early-onset AD is due to 160 mutations in APP, presenilin 1 and presenilin 2, and although these genetic abnormalities all have different molecular effects, the end result of mutations on these three genes is the same: increased number of amyloid-ß 42 peptide, $Aß_{42}$. This is associated with neuronal death and

typically dementia (Bertram & Tanzi, 2008). APP is estimated to account for 10 to 15 percent of Early-onset, familial AD (<65), while presenilin 1 is estimated to account for 30 to 70 percent, and presenilin 2 is thought to account for less than five percent (Bird, 2009). APP mutations are located on chromosome 21, while presenilin 1 and presenilin 2 mutations are located on chromosomes 14 and 1, respectively (Bertram & Tanzi, 2005).

In contrast to Early-onset AD, only one genetic factor has been consistently associated with the large majority of late-onset AD cases (Bertram & Tanzi, 2005). The APOE ε-4 gene increases the prevalence and incidence of Late-onset AD (i.e., sporadic AD), but it is not necessary or sufficient to cause AD. The relative risk of an older adult with one copy of the APOE allele ε-4 compared to an individual without is 1.4, whereas the relative risk for one with two copies is 3.1 (Fratiglioni et al., 2007). Thus, compared to non-carriers, individuals with one APOE allele ε-4 are at a heightened risk, while carriers of two APOE ε-4 allele are 3 times as likely to develop AD.

High blood pressure and hypertension may increase the probability an individual will develop AD. For example, Llewellyn et al. (2010) followed 856 adults, fifty years or older, revealing adults with untreated hypertension were one and a half times more likely to develop AD. Similarly, data from the Kungsholmen project suggest adults with high blood pressure are more likely to develop AD (Fratiglioni et al., 2007). Nonetheless, the relationship between AD and hypertension is equivocal, as other investigations have found no association (e.g., Qiu, Winblad, & Fratiglioni, 2005). One possible explanation is that hypertension causes vascular changes (e.g., arterial stiffness) and cerebrovascular lesions thereby increasing the likelihood an individual with AD pathology will be diagnosed with dementia of the Alzheimer’s type, despite having mixed pathology (Skoog & Gustafson, 2006).

Diagnosing Pathological Aging

Currently, a definitive diagnosis of AD is not possible until autopsy, as there are no biomarkers that provide definitive diagnoses (O'Brien, 2007). Therefore, antemortem diagnoses of AD are made by a specific set of clinical criteria (Storey, Slavin, & Kinsella, 2002). At least four separate sets of diagnostic criteria have been established with the goal to identify individuals with AD as early and accurately as possible (Table 1.1). Commonly used sets of criteria include the International Classification of Diseases and related health problems, 10th Revision (ICD-10; World Health Organization, 1992) Diagnostic and Statistical Manual, 4th edition, Text Revision (DSM-IV-TR; American Psychiatric Association, 2004) and National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA; McKhann et al., 1984), which was recently revised by National Institute of Aging - Alzheimer's Association workgroups (NIA-AA; McKhann et al., 2011).

Although operationally different, one can conclude that these sets of criteria are relatively similar. The DSM-IV-TR, ICD-10 and NINCDS-ADRDA require the presence of a memory impairment accompanied by an additional cognitive deficit. The DSM-IV requires the presence of aphasia, apraxia, agnosia, or EF impairment, while the ICD-10 requires the deterioration in judgment and thinking in addition to memory. The NINCDS-ADRDA calls for deterioration in any additional unrelated cognitive domain. In contrast the NIA-AA does not require memory to be impaired but does mandate two cognitive domains are compromised.

Only NINCDS-ADRDA requires cognitive deficits to be confirmed by neuropsychological testing. The NIA-AA guidelines do not require neuropsychological testing, given not all have access, but suggest it should be completed when self/collateral report and mental status examination don't provide a "confident diagnosis" (McKhann et al., 2011, p 265).

The ICD-10 requires obtaining information from an informant and suggests when feasible to confirm cognitive impairments with neuropsychological testing. The DSM-IV-TR neither requires nor suggests acquiring supplemental data for confirmation.

A commonality between all the sets of criteria is the description of the course, as all indicate the onset is not sudden and is followed by gradual deterioration after onset. All also require the presence of functional impairment for a diagnosis to be given. Finally, all sets exclude any diagnoses be given if the symptoms are in the presence of another disorder.

Despite their frequency of use, these diagnostic criteria sets have numerous limitations. Cummings (2006) noted these diagnostic sets of criteria are not operationalized and it is unclear how to determine the presence of an abnormality and how severe the deficit has to be. Therefore, this makes a diagnosis very dependent on clinical judgment, which is documented to lead to error and inaccurate diagnoses (Cummings, 2006). To determine the validity, accuracy, and clinical utility of these sets of diagnostic criteria several investigations have compared clinical diagnoses with postmortem diagnoses and confirmation.

An early paper by Rocca, Amaducci, and Schoenberg (1986) reviewed several investigations that compared clinical diagnoses made with the NINCDS-ADRDA criteria to neuropathological findings on autopsy. The authors noted the sensitivity to be approximately 70%, and the ability to limit diagnoses to individuals with AD pathology using a positive predictive value ranged from 55 to 82%. Kukull et al. (1990) compared the sensitivity and specificity of the NINCDS-ADRDA with the DSM-III, finding the NINCDS-ADRDA criteria to have better sensitivity, 92%, but inferior specificity, 65%, as the DSM-III had an 80% specificity and 76% sensitivity. Tierney et al. (1988) explored the accuracy of the NINCDS-ADRDA criteria in 57 subjects, 22 of whom had a clinical AD diagnoses, and they found the accuracy rate

was dependent on the applied neuropathological criteria, as the confirmation rate varied from 64 to 86%.

Thus, the evidence indicates accuracy and precision of diagnostic criteria sets is less than outstanding. To assist clinicians in distinguishing dementia from normal and early pathological aging accurately, Hughes et al. (1982) developed the clinical dementia rating scale (CDR). The CDR is a global staging dementia instrument that includes semi-structured interviews of the patient and informant to rate the patient's cognitive performance in six domains -- memory, orientation, judgment and problem solving, community affairs, homes and hobbies, and personal care (Morris, 1993). The CDR is found to reliably identify pathological aging earlier than it may be possible with neuropsychological tests, as it is less impacted by 'ceiling' and 'floor' effects (Morris, 1997, p. 173). The CDR is also able to distinguish individuals with dementia due to AD, as Morris, McKeel, Fulling, Torack, and Berg (1988) reported that 26 individuals' postmortem pathological diagnoses were all identified as demented (i.e., >1 CDR).

Cognition in Pathological Aging

While neuropathology likely occurs years or decades before changes in cognition are evident, AD is characterized by specific progressive cognitive changes (Braak et al., 1999). Memory impairment is the hallmark of AD and is frequently the presenting symptom for individuals with AD (Storey et al., 2002). Nonetheless, other significant cognitive domains are negatively impacted by AD, including: language, visuospatial functioning, attention, and EF.

Storey et al. (2002) conducted a review of the cognitive changes that occur in AD, noting declines in personal memories specific to location and time are the first cognitive changes detected by neuropsychological measures. However, not all aspects of episodic memory are equally impacted, as retrograde episodic memories (i.e., formed before clinical AD symptoms)

are initially preserved, but anterograde (i.e., formed after clinical AD symptoms) are typically evident first. Measures of verbal memory (e.g., list-learning and story recall) are found to be sensitive measures for AD, as individuals in the beginning clinical or pre-clinical stages of AD can be reliably detected and separated from normal adults by their performance on these measures (e.g., CVLT; Storey et al., 2002).

Greene, Baddeley, and Hodges (1995) investigated the relationship between episodic memory and minimal (i.e., 24-30 Mini-Mental Status Exam; MMSE) and mild AD (i.e., 17-23 MMSE) in sixty-three older adults with four anterograde episodic memory measures. As expected, immediate and delayed recall scaled scores on logical memory were significantly worse in both patient groups (i.e., minimal & mild). Patients' immediate recall, delayed recall, and recognition on the Consortium to Establish a Register in Alzheimer's Disease (CERAD) word list was also worse compared to controls. Raw scores revealed patient groups recalled an average of approximately four words on the final trial for immediate recall and only provided one word on average on delayed recall. Poor performance was attributed to impaired learning. Serial position curves revealed patient groups recalled items at the end of the ten-item list at a higher frequency (i.e., recency effect), and component analyses indicated no benefit to patient groups' secondary memory with repeated exposure, as they displayed a flat learning curve. Together, this evidence suggests patient groups relied on short-term memory (i.e., primary memory) for performance and the majority of information was not encoded into long-term memory (i.e., secondary memory) and therefore not recalled. Nonetheless, AD individuals were able to recognize on average nine out of ten items on recognition trials, which suggests with assistance they are able to accurately retrieve information. Thus, both deficient encoding and

retrieval processes likely play a role in the anterograde episodic memory deficits seen in early AD.

Historically, semantic deficits are believed to occur in early AD, but are not as sensitive in detecting very mild AD. To investigate this perspective, Hodges and Patterson (1995) administered a neuropsychological memory battery to normal older adults and three groups of individuals in presumably different stages of AD (i.e., minimal, mild, and moderate). On average, individuals from the minimal group (i.e., MMSE > 23) were impaired on three out seven semantic memory measures and, as a group, were significantly worse on four out of six semantic memory measures compared to normal older adults. However, there was a large amount of variability in the results, as several individuals in this group were consistently impaired on all semantic memory measures, while others were only impaired on a couple tests and some performed in the normal range. In contrast, almost all minimally affected individuals were impaired on two measures of episodic memory (i.e., logical memory and the Rey complex figure test). Thus, deficits on measures of semantic memory do not appear universal in early AD, and they are only impacted in some individuals in the early stages of the disease, but are likely to be affected as the disease progresses.

Often in parallel or subsequent to semantic memory deficits, individuals in the early stages of AD display language impairments. Specifically, it is found that they exhibit impoverished vocabulary and dysnomia (Appell, Kertesz, & Fisman, 1982; Storey et al., 2002). In order to compensate for dysnomia, patients often engage in circuitous speech, using circumlocutions, generic, and neighboring terms to attenuate the word finding difficulties (Appell et al., 1982). However, in this stage syntax and prosody (i.e., rhythmic aspects of speech) are largely intact, and comprehension is relatively preserved. As AD progresses,

impaired receptive language abilities become evident, and auditory and reading comprehension are defective. Speech becomes filled with phonemic and semantic paraphasias and empty content (Storey et al., 2002). Towards the end of disease, the ability to produce intelligible speech is devoid, as verbal output is restricted to echolalia or mutism (Appell et al., 1982; Storey et al., 2002).

Despite mixed evidence regarding the temporal sequence, changes in visuospatial abilities almost always succeed the preliminary memory changes and may accompany language changes in AD (Uhlhaas et al., 2008). Visuospatial processing involves identifying objects by accurate perception of the components and attributes, as well as the perception and interpretation of spatial relationships (Carlson, 2010). With the progression of typical AD, deficits in visuospatial processing become evident as individuals often develop visual agnosia (i.e., inability to combine visual perceptions into complete patterns) and apraxia (i.e., loss of a skilled movement that is not accounted for by muscle weakness, abnormal muscle tone or posture, intellectual deterioration, poor comprehension, or other disorders of movement; Kolb & Wishaw, 2009; Storey et al., 2002; Uhlhaas et al., 2008). Neuropsychological investigations have found deficits in object recognition, facial recognition, color and pattern processing, as well as spatial processing, visuo-motor coordination, and motion perception. Compared to dorsal stream processes (i.e., motion perception, distance perception, etc.), deficits in ventral stream processes (i.e., object recognition, facial recognition, etc.) are found impaired earlier in the course of AD, and more frequently and severely impaired (Kirby, Bandelow, & Hogervorst, 2010).

Binetti et al. (1998) measured visuospatial abilities in twenty-one demented patients over time who were in the early stages of AD at baseline. Compared to normal older adults at baseline, demented individuals were impaired on visual object measures (e.g., Incomplete letters

& Silhouettes), but they were not significantly different on any spatial perception measures. However, over an eight-month period patients declined on measures of spatial perception (e.g., Rey Copy), while performance on visual object measures did not change. Collectively, AD patients first experience deficits on visuospatial measures of objects and, subsequently, have impairments on visuospatial measures of spatial perception. The authors suggest that deficits in visual object perception may occur first due to already compromised semantic memory processes, as these visuospatial measures require retrieval of information.

In the preliminary stages of AD, cognitive changes are often manifested as memory disturbances and followed by changes in visuospatial abilities, language and EF (Storey et al., 2002). After amnestic changes, and before visuospatial and language declines, changes in EF usually become evident in the everyday lives of affected AD individuals. These changes are typically recognized in novel situations that require the ability to plan, initiate, monitor, and adapt behavior to successfully carry out goal directed actions, as well as on neuropsychological measures of EF in clinical settings (Perry & Hodges, 1999).

For example, twenty older adults with AD performed substantially worse on four measures of EF (e.g., Trail Making Test & Controlled Word Association Test, COWAT) and a measure of memory, the CERAD word list-learning task (Lafleche & Albert, 1995). Similarly, Baudic et al. (2006) administered a neuropsychological battery to thirty-six AD patients whom were divided into two groups based on their MMSE score, very mild (i.e., >24) and mild (i.e., 20-23), and seventeen normal controls. Scheffé test of means revealed differences between very mild AD individuals and normal controls on measures of spatial and episodic memory recall and EF. However, there was no difference on measures of language and visuospatial abilities.

As evidence suggests, deficits in EF occur in the early stages of AD, even though they are often overlooked in clinical settings (Boyle, 2004). Collette, Van der Linden, and Salmon (1999) found that AD individuals perform worse on measures of EF compared to normal controls. In contrast to other studies the authors investigated which domains of EF (e.g., inhibition, planning, monitoring, etc.) could account for these observed deficits on EF measures. Principal component analysis indicated inhibition and the coordination between storage and processing functions explains deficits on numerous EF measures. However, upon further investigation it appears the first component (i.e., inhibition) accounts for poor performance on traditional measures of EF (e.g., Phonemic Fluency Task & Hayling Inhibition task), while the second component (i.e., storage and processing functions) accounts for measures that may be better categorized as measures of working memory (e.g., Self-ordered Pointing Task & Alpha-span Task) and not as EF.

All together, evidence indicates individuals with the most common neurodegenerative disease, AD, experience changes in episodic and semantic memory, language, visuospatial ability and EF. As a result of these cognitive changes patients lose the ability to perform IADLs, and subsequently basic ADLs (Galasko et al., 2005). The relationship between cognition and functional impairment is of great importance, as it is not only a major diagnostic difference between pathological (i.e., AD) and normal aging, but is likely the most significant impact of pathological aging. Functional impairment is associated with diminished quality of life, increase in caregiver stress, overuse of health care services, and is the leading cause of nursing home placements (Boyle, 2004).

To explore the relationship between cognition and functional impairment Cahn-Weiner, Ready, and Malloy (2003) administered a neuropsychological battery, including a measure of

memory, EF, language, visuospatial ability, and an ADL and memory questionnaire to twenty-four mildly demented AD individuals. A stepwise multiple regression was conducted with the collateral report ADL questionnaire (i.e., Lawton and Brody ADL questionnaire) as the dependent variable and the four neuropsychological measures as the independent variables. As predicted the EF measure (e.g., COWAT) was the only neuropsychological measure significantly related to the ADL questionnaire and accounted for 41% of the observed variance.

In a related study, Chen et al. (1998) found significant correlations between measures of EF (i.e., COWAT, Mattis Dementia Rating Scale Conceptualization and Initiation, Wisconsin Card Sorting Test (WCST), and a caregiver-rated ADL questionnaire (i.e., Blessed Dementia Activities subscale). One EF measure, the WCST, accounted for 67% of the variance on the Blessed Dementia activities subscale without accounting for global cognition (i.e., MMSE) and 34% of it while including the MMSE.

Thus, EF is strongly related to functional impairment in AD, impacting an individual's ability to complete ADLs and is therefore of particular interest. Moreover, results from several studies indicate that functional impairment due to compromised EF may be due to specific components of EF (Collette, Vanderlinden, & Salmon, 1999; Lewis & Miller, 2007). Jefferson, Paul, Ozonoff, and Cohen (2006) compared inhibition (i.e., DKEFS Color-Word Interference Test), planning (i.e., Tower Test), sequencing (i.e., Trail Making Test), verbal (i.e., COWAT) and nonverbal generation (i.e., Ruff Figure Fluency Test), and working memory (i.e, Paced Auditory Serial Addition Task), as predictors of IADLs in seventy-two patients "at risk for future cognitive and functional decline" (p. 317). Logistic regression indicated that the single significant predictor of an individual's ability to complete IADLs was a measure of inhibition. It

is therefore plausible to infer deficits in inhibition may compromise an older adult's ability to complete ADLs and IADLs.

The Pathological Aging Brain

Cognitive and functional decline in AD is presumably due to substantial synapse loss and neuronal degeneration likely initiated by either or both senile plaques and neurofibrillary tangles (NFTs; Schönheit, Zarski, & Ohm, 2004). While evidence indicates both senile plaques and NFTs frequently lead to cell death, controversy exists regarding the temporal sequence of these cellular pathologies. Hardy and Higgins (1992) proposed the amyloid cascade hypothesis suggesting senile plaques with amyloid ß cause the formation of NFTs, cell loss, vascular damage, and eventual cognitive and functional impairment.

The main and core constituent of senile plaques is Aß, a peptide product from amyloid precursor protein (APP) and is derived by sequential cleavages by two enzymes (Golde, Eckman, & Younkin, 2000). APP is first cleaved by a membrane enzyme, ß-secretase, into a large protein derivative, which is secreted from the cellular membrane into the extracellular fluid. The remaining portion of the APP, carboxyl-terminal fragment is cleaved by γ-secretase, generating Aß proteins with 39-42 amino acids (Golde, 2003; Hardy & Higgins, 1992). Although $Aß_{42}$ is documented to more readily accumulate, both $Aß_{42}$ and $Aß_{40}$ are believed to be significant components of the pathological processes associated with Aß (Golde et al., 2000). Hardy and Higgins (1992) suggest Aß is neurotoxic and causes NFTs and cell death, but indicate the exact mechanisms of this process are still unclear. Nonetheless, they suggest that Aß initiates cell death by increasing intraneuronal calcium homeostasis, which increases tau phosphorylation, leading to the formation of paired helical filaments, NFTs, and disrupting normal cellular processes (e.g., cellular transport).

In contrast to the amyloid cascade hypothesis, others suggest the beginning of the degenerating process in AD is the formation of NFTs and neuropil threads (NTs; i.e., an additional abnormally phosphorylated tau protein; Braak et al., 1999). The authors propose the formation of NFTs and NTs evolve independently from the Aß in six predictable and reliable stages. Unlike Aß plaques that first form in the neocortex, NFTs first appear in limbic structures (Price & Morris, 1999), where only a few projection cells are impacted in the trans-entorhinal area, while lesions are found in the first Ammon's horn sector and the entorhinal proper in the second stage. In stage three, there is severe damage seen in the trans-entorhinal and entorhinal regions, and preliminary lesions are seen in the hippocampus, temporal and insular areas. Stage four is characterized with expansion of NFTs into neocortical areas, and with these changes in stages three and four some individuals begin to exhibit mental deterioration and slight personality alterations; however, patients are not typically diagnosed with AD until the final phase, stages five and six. In stage five, there is widespread deterioration of the neocortex and in the final stage, stage six, NFTs are found in primary motor and sensory areas.

While there is disagreement as to what pathology occurs first, there is agreement that both Aß and abnormally phosphorylated tau proteins are associated with neuronal death. Consistent with the pattern of NFTs and NTs, gray matter loss is found to occur in phases throughout the course of AD (i.e., ≈ 2.1 years). Individuals with mild AD have substantial gray matter deficits (i.e., < 15%) in medial temporal and parietal regions, while only having mild deficits in the frontal cortex (i.e., 6-10%) and very minimal loss in sensory and motor areas (i.e., 0-5%; Thompson et al., 2003). Over time, AD individuals progressed from mildly to moderately demented (i.e., average MMSE 12.9), displaying an approximately 5% annual decrease of total gray matter in the right and left hemisphere, while age matched controls had <1% annual gray

matter loss (Thompson et al., 2003). In addition, participants with AD had significantly greater total cerebral volume loss: 5.22%, compared to normal older adults' .88%, although analyses indicated no difference of total white matter loss.

While volumetric loss in normal aging is attributed to neuronal shrinkage, decrease in the length and number of dendritic spines, and white matter degradation, volume loss in AD is mainly due to gray matter declines that results from neuronal loss (Gómez-Isla et al., 1997). Consistent with these findings, a meta-analysis comprised of one hundred and twenty-one neuroimaging investigations concluded individuals with mild AD are able to be reliably distinguished from normal older adults by comparison of superior temporal lobes, amygdala, thalamus, temporal horns, left temporoparietal cortices, and the hippocampi. However, in the very early stages of AD, only the hippocampus reliably discriminated between normal and AD patients, specifically noting loss within CA1 and subiculum within the hippocampal formation (Zakzanis, Graham, & Campbell, 2003). These findings are consistent with both the sequence of clinical symptoms and neuropathology, as NFTs and NTs are found to affect structures within medial temporal structures (Braak et al., 1999; Storey et al., 2002).

This pathological loss of neurons negatively affects cognitive functioning as investigations have documented significant correlations between anatomical structures and domains of cognitive functioning, such as memory and EF (Elgh et al., 2006; Meguro et al., 2003, 2004). Similar to normal aging, changes to neural structures in pathological aging also impact functional neural activity. For example, Dickerson and Sperling (2008) note there is a positive correlation between extent of hippocampal atrophy and amount of activation in the medial temporal regions during a memory task, as activation increased with amount of atrophy.

In addition to functional abnormalities evident in memory functions, compared to normal older adults pathologically aging participants commonly display differential functional activation while performing measures of visuospatial (Prvulovic et al., 2002), language (Grossman et al., 2003), and EF (Li, Zheng, Wang, Gui, & Li, 2009). Prvulovic et al. (2002) administered an angle discrimination task to fourteen mild to moderate AD patients and fourteen age-matched controls, reporting AD individuals recruited more voxels in the occipitotemporal junction, but controls activated regions within the superior parietal lobule to a greater extent. Differences in activation were partially accounted for by amount of atrophy, as AD patients had a greater amount of atrophy in the superior parietal lobule. The authors proposed that these patients recruited the occipitotemporal junction to a greater extent to compensate for parietal dysfunction. During language functions, AD patients recruited relatively similar areas compared to normal older adults during the processing of verbs. Both groups activated posterolateral temporal and inferior frontal regions, but older adults with AD displayed less activation (i.e., hypoactivation) in these neural areas (Grossman et al., 2003).

Li et al. (2009) explored the differences between normal older adults, mild cognitive impairment (MCI), and AD with a measure of EF, the Stroop task. Presented in a block design format, participants randomly viewed the colors red, blue, or green displayed in a conflicting color (e.g., blue printed in red) for 350 ms. The presentation of the stimulus was immediately followed by a 650 ms rest period, and the sequence was repeated three consecutive times. For imaging analyses, regions of interest (ROIs) were defined, and a chi-square test revealed that compared to normal older adults, participants with AD had decreased amplitude of activation in the anterior cingulate, bilateral middle and inferior frontal gyri, bilateral inferior parietal lobule,

and bilateral insula. In contrast, when comparing MCI and normal aging adults, participants with MCI activated all the aforementioned regions to a greater extent than controls.

Mild Cognitive Impairment

To understand pathological aging, identifying individuals between normal and pathological aging is critical. MCI is a stage between normal and pathological aging that was developed to identify individuals in the pre-dementia phase in order to intervene and potentially slow the neurodegenerative processes (Petersen, 2004). This state is best conceptualized on a continuum, overlapping with normal and pathological aging (Petersen, 2003). Although by definition these individuals will likely not have significant functional impairment, this construct is of particular importance due to the fact that many of these individuals will progress into dementia, mainly AD, at an exponentially increased rate (Petersen, 2004).

Historically, an individual with MCI had memory impairment beyond expected normal age related declines, but other cognitive domains were unaffected (Petersen, 2004). Petersen et al. (1999) developed the original MCI criteria, and to receive a diagnosis, individuals were required to have: 1. Memory complaint, preferably corroborated by an informant, 2. Objective memory impairment for age and education, 3. Largely intact general cognitive function, 4. Intact activities of daily living, 5. Not demented.

While the majority of MCI literature refers to individuals who have memory impairment greater than expected for normal aging, the concept has evolved due to a considerable amount of disagreement between empirical investigations of MCI (Winblad et al., 2004). The most recent development of this construct was by a workgroup formed by the National Institute on Aging-Alzheimer's Association (Albert et al., 2011). In contrast to the original criteria (Petersen et al., 1999), Albert et al. (2011) do not require memory impairment for diagnosis but suggest one must

have objective cognitive impairment in one or more domains. To meet criteria, it must additionally be determined that there is a concern of cognitive decline as reported by the client, informant or a clinician, and functional abilities are intact and the individual is not demented. In addition to these requirements other causes (i.e., vascular or medical) of cognitive decline besides the AD pathophysiological process who rule out an individual from receiving a diagnosis (Albert et al., 2011).

Epidemiological studies report that individuals without MCI progress into AD at 1 to 2% annually; whereas, the rate of progression of individuals with MCI is estimated at 10 to 15% annually (Petersen et al., 2001). Nonetheless, conversion rates of MCI to AD across studies have not been consistent, varying from 0 to 34% and are likely due to sample characteristics (e.g., sample source, subtype ratio). This variability is likely due to varying diagnostic criteria (i.e., definition of impairment) and other factors such as age of population (Fischer et al., 2007; Petersen et al., 2009; Visser & Verhey, 2007). For example, clinic-referred samples typically have a higher conversion rate (Petersen et al., 2009), usually reporting an annual conversion rate of 10-15%, compared to 5-10% rate for community based epidemiological studies (DeCarli, 2003). This difference may be due to a higher ratio of amnestic to nonamnestic MCI in clinic-referred samples, as amnestic MCI individuals are more likely to convert to AD compared to non-amnestic. For example, a prospective investigation followed 141 MCI individuals for 2.5 years, and found 49% and 27% of amnestic and non-amnestic participants converted, respectively (Fischer et al., 2007).

Similar to AD, the criteria for MCI is subjective and clinical judgment is necessary to make a diagnosis, therefore a standardized technique such as the CDR may improve identifying individuals in the prodromal stages of pathological aging. While some suggest CDR 0.5 is

equivalent to MCI, others disagree (Petersen, 2003). Nonetheless, it is widely accepted that a CDR of 0.5 represents questionable dementia, as these persons display neuropsychological deficits greater than expected for age or education and progress into dementia at similar rate as those diagnosed with MCI (e.g., 12%; Nourhashémi et al., 2008; Petersen, 2004). Given the subjectivity and lack of operationalization, identifying the prodromal stage of pathological aging may best accomplished with CDR, especially when several investigators are assessing for dementia.

For example, Marin et al. (2001) explored the inter-rater reliability of the CDR with 62 mildly demented chronic care residents and four separate raters. The authors found excellent inter-rater reliability with all six domains and reported intra-class correlation coefficients of .95 to .98 and .99 for the global CDR rating. Similarly, Chaves et al. (2007) found high inter-rater reliability for global CDR rating for 90 normal, questionable, or demented individuals (e.g., 85%) between four raters. In contrast, an investigation with twenty-four medical professionals (i.e., physicians & nurses) reported moderate overall inter-rater reliability (Rockwood, Strang, MacKnight, Downer, & Morris, 2000). Nonetheless, these findings all together support the perspective that individuals are reliably identified as being normal or having questionable, mild, moderate, or severe dementia.

Examining Pathological Aging with fMRI

As discussed previously, fMRI investigations have compared differences in neural activity during cognitive performance between normal older adults and pathologically aging adults. In general, the majority of these investigations have used measures of memory and found significantly increased activity in memory regions during encoding and retrieval processes in MCI compared to normal aging (Dickerson & Sperling, 2008; Sperling et al., 2010). Dickerson

et al. (2005) investigated the functional activity in memory regions between normal controls, MCI and AD with a face-name encoding paradigm. Despite indistinguishable behavioral performance from normal controls, MCI subjects recruited significantly more neural areas within the hippocampus. In contrast, participants with AD displayed significantly less activation and performed worse on the memory task. Hämäläinen et al. (2007) also found MCI participants to have greater activation in the hippocampal formation, parahippocampal gyus, and fusiform cortex, while engaged in memory encoding processes. Putcha et al. (2011) reported hyperactivation of the hippocampus during encoding of face-name pairs in MCI compared to normal. The authors additionally found hippocampal activation was negatively correlated with cortical thinning in characteristic AD cerebral areas.

Dickerson and Sperling (2008) suggest these frequent findings of increased activation during memory processes in MCI could be a compensatory response to neuropathology, as pathogenic processes are documented to occur decades before clinical diagnosis of AD (Braak et al., 1999). However, there are likely other reasons for the observed hyperactivation with the hippocampus and surrounding memory regions. Putcha et al. (2011) found memory performance was not improved by increased hippocampal activation, and concluded hyperactivation could be indicative of attempted but failed compensation, inadequate encoding and neuronal excitotoxicity. Furthermore, the finding of hyperactivation during memory processes in MCI compared to controls is not universal, as some have found no difference and/or hypoactivation (Mandzia, McAndrews, Grady, Graham, & Black, 2009; Sperling et al., 2010). Inconsistent findings could be due to memory load (de Rover et al., 2011) or type of encoding (deep vs. superficial; Trivedi et al. 2011). Regardless, functional activation within “memory” regions

during memory processes in MCI is only beginning to be understood, but one potential explanation of hyperactivation in MCI compared to normal older adults is compensation.

In contrast to fMRI investigations of memory between normal controls and MCI, there are only a few studies of EF comparing differences in functional activation between these groups. One of these explored the difference in neural activity between normal aging and MCI with the numerical Stroop task (Kaufmann et al., 2008). The task was presented in a block design format, and each participant was required to indicate which number was larger, physically and numerically, in three different conditions: maximally incongruent, minimally incongruent, and neutral for ninety-six separate trials. Whole brain group uncorrected analyses (i.e., $p < .01$) indicated MCI patients engaged more neural areas including, the inferior frontal gyrus, orbitofrontal cortex, inferior parietal lobe, middle/superior temporal gyrus, cerebellum and visual processing areas at greater intensity than controls in the interference contrast.

In another EF fMRI study, Rosano et al. (2005) examined functional activation differences in an event related paradigm during a task that required individuals to inhibit a pre-potent response. Activation was evaluated in three distinct regions of interest, the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), and posterior parietal cortex (PPC). Despite indistinguishable behavior performance, group analyses of percent signal change indicated older adults with MCI displayed significantly greater engagement of the DLPFC and PPC, but not the ACC.

In contrast to Kaufmann et al. (2008) and Rosano et al. (2005), a recent investigation did not find individuals with MCI displayed greater activation during EF (Staffen et al., 2011). Normal and MCI older adults were administered an oddball task during functional imaging, and group whole brain comparisons revealed normal older adults displayed greater activation while

inhibiting a response to various stimuli. Normal and MCI older adults were behaviorally equivalent on the oddball task.

Laine et al. (2009) also compared the functional correlates of EF with requiring participants to attend and respond to separate sources of stimuli during PET scans. Similar to Staffen et al. (2011), normal older adults recruited prefrontal cortex regions of interest to a greater degree than MCI individuals. However, the sample was small, 6 controls and 6 MCI, and participants were behaviorally different. Taken together functional activation differences between normal and MCI older adults during EF are inconsistent.

Several investigations have found MCI older adults display greater BOLD response during EF compare to normal controls (Kaufmann et al., 2008; Li et al., 2009; Rosano et al., 2005), while two recent studies report normal older adults exhibit greater functional activation compared to MCI participants when performing an EF task (Laine et al., 2009; Staffen et al., 2011). Inconsistent results may be due to task, sample, and/or analyses differences. Both Laine et al. (2009) and Staffen et al. (2011) MCI samples were the amnestic subtype, whereas Kaufmann et al. (2008) and Rosano et al. (2005) included the nonamnestic subtype as well. Future research is needed to clarify this relationship.

Aims of Current Study

Given the association of EF and functional impairment, and the limited amount of investigations of functional activation during EF between normal older adults and MCI, the aim of this study were to contrast neural activity during inhibition between these two groups. More specifically, the primary aim of this study was to compare the magnitude of activation between two groups of older adults, normal (CDR = 0) and mild cognitive impairment (CDR = 0.5) during inhibition in predefined regions of interest (ROIs; i.e., OFC, DLPFC, ACC, PPC). The

secondary aim of this investigation was to compare accuracy and reaction time on a modified Stroop task (Stroop, 1938). A measure of inhibition, was used due to its relationship with functional impairment (Jefferson, Paul, Ozonoff, & Cohen, 2006), and ability to account for impairments on other neuropsychological measures of EF (Collette et al., 1999).

Based on the perspective that individuals with MCI have underlying neuropathology (Morris et al., 2001), it was hypothesized that these adults would display greater magnitude of activation in all ROIs during inhibition as an attempt to attenuate the effects of the neuropathology and preserve cognitive functioning. Moreover, the hypotheses were based on Dickerson and Sperling's (2008) suggestion that activation during cognitive performance would roughly follow an inverted U shape, depending on level of neuropathology. Although hyperactivation may aid participants with MCI performance, it was hypothesized older adults with MCI would be as less accurate and slower during inhibition compared to normal controls. It is hoped that evidence from this investigation will be used with future studies to reliably identify individuals at-risk for functional impairment.

CHAPTER 2

METHOD

Participants

Power Analysis. The comparisons for the proposed study were the functional activation differences between normal older adults and MCI. To determine the amount of individuals required to yield interpretable findings, effect sizes for each ROI from results of previous investigations were computed. To determine the average effect size for all ROIs for the comparisons of interest, the results from two investigations were used (Kaufmann et al., 2008; Rosano et al., 2005). From the reported t and z values, an average effect size was computed through several steps.

First, the reported statistic (i.e., t or z) was converted into an effect size, pearson r, using transformations specified by Rosenthal (1991; $r = \sqrt{t^2/ t^2+df}$; $r=Z/\sqrt{N}$). Since the sampling distribution of Pearson r's is not normal, all transformed r values were transformed into Fisher z's (Zr) using the Fisher transformation (i.e., $z' = .5[\ln(1+r) - \ln(1-r)]$). After the r values were converted to Fisher's z values, it was necessary to account for the influence of the number of individual observations, using the formula $\sum(N-3)(Zr)(/\sum(N-3)$. Thus, the Zr values were weighted according to the number of individual observations per investigation. Finally, all weighted Fisher's z values were averaged and converted back to an r value.

The resulting average effect size for all ROIs, .58, was converted to a Cohen's d in order be inputted into G-Power*3 (Faul, Erdfelder, Lang, & Buchner, 2007). The specifications for

the power analysis while assuming independent samples were: one tailed, p = .05 level, Cohen's d = 1.4, and power = .80. The analysis yielded a sample of 12 for each group, 24 total for this

comparison (i.e., Normal vs. MCI). However more participants were collected for each group given the original proposal was between three groups of 12, yielding 36 total participants.

Recruitment/ Exclusionary Criteria. One hundred and sixty four participants from the surrounding Athens area community were contacted regarding participation. "Brain Health" talks were given to all local assisted living facilities, caregiver support groups, Osher Lifelong Learning Institute, Athens-Clarke county public library, and a local church regional event. Announcements were made at dementia caregiver workshop, as well as at a local Alzheimer's Association chapter meeting. Following the completion of numerous talks and in person announcements, newspaper advertisements were made in the Athens Banner Herald newspaper at the beginning of every month for six months. Participants were included if they were compatible with the magnetic resonance imaging (MRI) environment, between 65 – 85, had a reliable collateral, literate, not demented or have history of a neurological disorder (e.g., Multiple Sclerosis, Lupus), completed modified Stroop task at above chance levels, and had all necessary MRI data (e.g., fieldmaps). First, participants were screened over the phone, and they were subsequently screened upon the first scheduled session. In total 52 participants were recruited and run; however, only 43 participants were included in final analyses (Figure 2.1). Upon completion, all were given $100 for participation and if the participant or collateral requested,

they were provided with the contact information for referral sources (e.g., memory clinic, local neurologist).

Measures

Participants and informants were interviewed with the CDR. The CDR is a semi-structured interview that obtains information from the participant and informant and rates the individual's cognitive performance for six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care (Hughes et al., 1982). Each domain is scored individually on a five-point scale (i.e., 0.0 none, 0.5 questionable, 1.0 mild, 2.0 moderate, 3.0 severe), except personal care, which is scored on a four-point scale (i.e., 0.0 none, 1.0 mild, 2.0 moderate, 3.0 severe). The score indicates level of impairment caused by cognitive decline and not by physical or other non-cognitive factors for each domain. A global CDR score is obtained through an algorithm based on each domain's rating, where memory is a primary category and all others are secondary categories. Specific guidelines are in Morris (1993), while a computerized scoring algorithm provided by Washington University Alzheimer's Disease Research Center can be found at http://www.biostat.wustl.edu/~adrc/cdrpgm/index.html. Similar to each individual domain score, the global scale score is on a 5 point scale where 0.0 indicates no dementia, 0.5 questionable, 1.0 mild, 2.0 moderate, and 3.0 severe dementia (Morris, 1997). A global CDR score of 0 was considered normal, and 0.5 was representative of MCI.

In addition to the CDR, participants were administered the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh,1975), the Repeatable Battery for the Assessment for Neuropsychological Status (RBANS; Randolph, 1998), Delis-Kaplan Executive Function System Trail Making Test (DKEFS-TMT; Delis, Kaplan & Kramer, 2001), the

Geriatric Depression Scale (GDS; Yesavage et al., 1983), and Short Battery of Physical Performance (SPPB; Guralnik et al., 1994). The MMSE is a 30-item test of general cognitive functioning that measures an individual's orientation, registration (i.e., ability to repeat words), attention and calculation, memory recall and language. This measure has a total possible score of 30, and is often used in primary care settings as a screener for cognitive impairment and dementia, where a score of 24 or below is considered to be indicative of cognitive impairment (Folstein et al., 1975). The MMSE was used to determine global cognitive functioning of all participants.

To compare cognitive functioning in several domains between groups the RBANS was administered across all participants. Specifically, overall ability, memory, attention, language and visual spatial ability were quantitatively examined with RBANS. The RBANS is a "comprehensive screener" administered individually and is normed on individuals between the ages of 20 – 89. This measure is a standalone measure that takes approximately 30 minutes to complete and can be administered to individuals with a variety of neurological conditions. There are 12 separate subtests, which make up 6 different indices. Raw scores on the individual subtests and participants age were used to derive age-based scaled and standard scores from a United States population based normative sample. The 6 indices are immediate memory, visuospatial/constructional, language, attention, delayed memory and total scale.

Two of five conditions of the DKEFS-TMT were administered (i.e., number-letter switching and motor speed). Number letter switching requires the participant to connect and switch between numbers and letters in ascending order (Delis et al., 2001). This test is a measure of mental flexibility, but also requires visual scanning, number and letter sequencing, and processing speed (Delis et al., 2001). On the motor speed condition the individual traces a dotted

line as neatly and quickly as possible without errors, and touches every circle along the correct route (Delis et al., 2001). Motor speed is a measure of visuomotor processing speed. Number-letter switching was used to determine EF outside of the MRI on a standardized measure. Motor speed examined processing speed between groups.

Depressive symptomology was measured by a self-report scale developed to measure depression geriatric samples, the GDS (Yesavage et al., 1983). Unlike other self-report depression scales, somatic symptoms of depression are deemphasized given they are associated with the normal aging process and not due to depression. The yes-no format of this questionnaire is another benefit of this measure. It is also found to have good psychometric properties, as well as sensitivity and specificity for depression (Peach, Koob, & Kraus, 2001). The GDS also ensured there were no participants experiencing severe levels of depressive symptomology.

To determine physical functioning lower body, the SPPB was used. The SPPB is a brief physical performance test that measures balance, gait, strength, and endurance in lower extremities. The SPPB measures how long an individual remains standing, their stance, time required to walk 8 feet, and how quickly an adult stands from a sitting position five consecutive times (Guralnik et al., 1994).

fMRI task and experimental design

Before entering the scanning environment, participants completed three practice trials of a modified Stroop task designed in E-prime 2.0. (Psychology Software Tools, Inc., 2007). The task was administered in a separate office at the Bioimaging Research Center (BIRC) on a computer monitor, and participants used the keyboard to respond. To facilitate participants' task comprehension and ensure adequate task performance, three separate practice trials were

completed. At times participants were provided with feedback during practice trials if they misunderstood task instructions.

The first practice trial consisted of 36 trials, and presented the stimuli for four and half seconds with a half second inter-stimulus interval (ISI). This allowed the participant five seconds to respond. The second trial also had 36 trials, but it presented the stimuli for three and a half seconds with a half second ISI, allowing the participant four seconds to respond. The third and final practice trial there was 96 stimuli presented. The stimuli were presented as they were in the scanner, presenting the word or XXXX's 2.5 seconds with a half second ISI. The participant had 3 seconds to respond. Performance on the final practice trial was analyzed to determine if participants could complete the task with a minimum accuracy level of 50% for the incongruent condition. After completion of practice trials participants were placed in the MRI machine.

All conditions were counterbalanced, although the selection of the stimuli within each condition was random. For the congruent condition four-color words were randomly presented in ink consistent with the semantic meaning; whereas during the incongruent condition four-color words were randomly presented in a color inconsistent with the meaning of the word. The neutral condition consisted of four capital X's randomly presented in one of the four possible colors (see Figure 3.1).

The experimental stimuli were presented to participants through MRI compatible goggles (Resonance Technology, Inc.). If required, MRI compatible corrective lenses were placed in the goggles. Participants responded with a button press from the respective response pad with the left middle, left index, right index, or right middle finger to indicate the color of the presented stimulus, while disregarding the meaning of the word. Instructions were given verbally and visually before they began the task even though the participants completed all practice trials

before entering into the MRI. Green, yellow, red, and blue corresponded to the left middle, left index, right index, and right middle, respectively. In addition to practice trials and verbal and visual instructions presented at the beginning of the task, a color bar was positioned at the bottom of the visual field throughout the task to help participants remember the corresponding button presses for each of the four-colors and attenuate errors due to memory impairments.

Participants responded with the appropriate button press after the onset of the current stimulus, but before the onset of subsequent trials. Every stimulus was presented for 2.5 seconds with a 0.5 second ISI, thereby allowing participants 3.0 seconds to respond. Responses made during the presentation of the word or during the inter-stimulus interval were recorded, and analyzed for accuracy and reaction time.

The paradigm was an event related design, and was jittered specific to the number of conditions and maximal detection of brain activation. Specifically, this design was structured to maximally account for variations in the hemodynamic response function (HRF) given a 3 second epoch, 2 second repetition time (TR) and three conditions (i.e., two active and one baseline). To achieve the most efficient design and greatest likelihood of detection, 93%, there were 192 total events, 64 trials per condition. This model assumed second-order polynomial drift and the hemodynamic response function (HRF) followed the canonical HRF of Statistical Parametric Mapping version 2.0 (i.e., double gamma; SPM 2.0; London, UK; http://www.fil.ion.ucl.ac.uk/spm). The jittering algorithm was based on the procedures outline by Kao, Mandal, Lazar, and Stufken (2009). Thus, to maximize detection this event related paradigm included 64 trials per condition, 192 total trials, and lasted 576 seconds (i.e., 9 minutes and 36 seconds).

Image Acquisition

Structural and functional images were acquired at the University of Georgia's Bioimaging Research Center (BIRC). A fast spoiled gradient recall (FSPGR) protocol was used to acquire the structural scans (TE = min full, TR = 7.8ms, flip angle = 20°, slice thickness = 1.2 mm, acquisition matrix = 256 x 256 mm). The FSPGR protocol covered the top of the head to the brain stem, collected 176 images and lasted 418 seconds (i.e., 6 minutes and 58 seconds).

Functional images were acquired as T2* images using an echo planar imaging (EPI) sequence. This EPI sequence lasted 9 minutes and 36 seconds and collected 288 volumes with 30 slices (TE = 25 ms, TR = 2000 ms, 90° RF pulse, spacing = 0 mm, slice thickness = 4 mm, acquisition matrix = 64 x 64, FOV = 22 x 22 cm).

Procedure

The proposed study was a portion of a larger investigation that was conducted in the University of Georgia Neuropsychological and Memory Assessment Laboratory and the UGA Bioimaging Research Center. As a result, the administered measures and experimental paradigm were within an extensive behavioral and neuroimaging protocol, and this investigation included only a portion of the measures and procedures completed by participants. Potential participants were screened through an initial telephone screen to assess their eligibility for the study. After determining eligibility, participants were scheduled for two separate sessions.

The first session took approximately 3 hours and encompassed cognitive, behavioral and psychological testing. Before the research protocol was initiated, participants and collaterals were met in the psychology clinic parking lot and given a parking pass. They were then escorted to the University of Georgia Neuropsychological and Memory Assessment Laboratory and consented. After consenting to participate in the study, participants completed the MRI compatibility screening form, the GDS, the NEO Five Factor Inventory 3 and a demographics

questionnaire. While participants completed these self-report measures, informed collaterals underwent a semi-structured interview by a CDR-certified examiner. After the administration of CDR to the collateral was completed, the examiner then interviewed the participant with the CDR. If the participant did not finish the questionnaires while their collateral was being interviewed, they completed them after the CDR interview.

Following the CDR, the MMSE, RBANS, and DKEFS-TMT were administered. After cognitive testing, the participants were administered the Direct Assessment of Functional Status (DAFS) and SPPB. All cognitive and behavioral testing was completed in the University of Georgia Neuropsychological and Memory Assessment Laboratory, room 415 of the Psychology building.

The second data collection session was conducted at the BIRC in the Coverdell building, and lasted approximately 3 hours. During the first hour, the participant became acquainted and practiced the Stroop and a working memory task. After practice trials for both tasks were completed, a small sample of blood was collected through a finger stick by a certified phlebotomist. Participants were then further screened by the MRI technician and removed all metal items and placed them along with personal items in a designated locker. Participants were then placed and remained in the MRI for approximately 90 minutes, even though the scan time was only 66 minutes. Participants underwent structural, functional, and diffusion imaging procedures.

The FSPGR protocol was initiated first, and was followed by the collection of three runs of functional images during a working memory task and the EPI sequence for the Stroop. Phase and magnitude images, and resting state functional images were subsequently collected. After fMRI was complete, diffusion tensor images were acquired. Only the structural and functional

images obtained during the Stroop were used for the current study. Subsequent to the completion of the diffusion tensor imaging, participants were removed from the scanner environment, thanked and reminded of their third and final day of participation that was completed with the UGA Vision Laboratory (not a part of this specific study).

Preprocessing

fMRI data was preprocessed with SPM version 8.0 (Wellcome Department of Cognitive Neurology, London, UK) through Matlab (The Math Works, Natick, MA) using the aforementioned parameters and an interleaved bottom up slice collection. Images were first converted from GE DICOM format to NIFTI using the dcm2nii conversion tool (Rorden, 2007). Functional images were first corrected for slice timing using the median slice within the interleaved bottom-up sequence (i.e., #29) as the reference image. This is necessary since SPM assumes all slices are collected at the same time unless otherwise indicated. Following slice timing, the first volume from the Stroop and the source structural scan was aligned to the anterior commissure for improved coregistration. A fieldmap was then created using the fieldmap toolbox in SPM8 with both phase and magnitude images. Slice time corrected images were then realigned and unwarped to adjust for any potential distortion from magnetic field inhomogeneities and incidental movement during the scan. The fieldmap (i.e., voxel displacement map) was used in this step to assist with adjusting for distortions in the EPI images. Subsequently, the source anatomical was co-registered with the first functional image produced by realigning and unwarping. Then the co-registered image, 3D, and all functional images were co-registered to Montreal Neurological Institute (MNI) stereotaxic space via the MNI-152 template. Thus, during coregistration SPM aligns the T-1 image with the first functional image through computational processes that rotate and translate the source anatomical image into the

space of the first functional image. This process is then repeated for the co-registered and all functional images to standard space, the MNI-152 template.

Following co-registration, the transformed anatomical image was further divided into GM, WM, CSF, bone, soft tissue and air via the New Segment SPM subroutine. From this step a deformation field is created and is applied to all functional images to spatially normalize images to MNI space. The last step of pre-processing involves smoothing the images to de-emphasize random noise and increase the signal-to-noise ratio, by placing a 6.875_{mm} x 6.875_{mm} x 8.0_{mm} full width half maximum Gaussian kernel on every voxel.

Data analysis

Independent samples t-tests were used to analyze the behavioral data in Predictive Analytics Software (PASW) version 18.0. Dependent variables for the t-tests were the Stroop Effect reaction time (i.e., Inc - Con) and the percentage correct for each condition. Neuropsychological measures were compared with one-way between groups analysis of covariance (ANCOVA). Given the education difference between groups, it was entered as a covariate in the ANCOVAs. To control for type one-error, Bonferroni corrections were applied. A correction of 5 comparisons to p-value .05 was made for the number individual analyses between groups with the separate neuropsychological measures. An additional correction was made for RBANS indices. Corrections were applied separately given the correlation and inherent interrelatedness of the RBANS and its indices.

Following pre-processing, conditions and timing of the event related paradigm were specified through 1st level analyses. A Matlab file (i.e., .mat) was used to identify the events of interest in seconds. Given that Kaufmann et al. (2008) suggested increased activation during inhibitory processes in MCI could be due to increased errors, only trials associated with accurate

responses were specified. The data were then estimated with the classical SPM method, Restricted Maximum Likelihood, and contrasts were defined to compare conditions within subjects. To determine activation due to inhibition within groups, a t-test compared activation between the incongruent and congruent condition with the defined contrast 1 -1, as the neutral condition is an active baseline and is coded as an implicit variable.

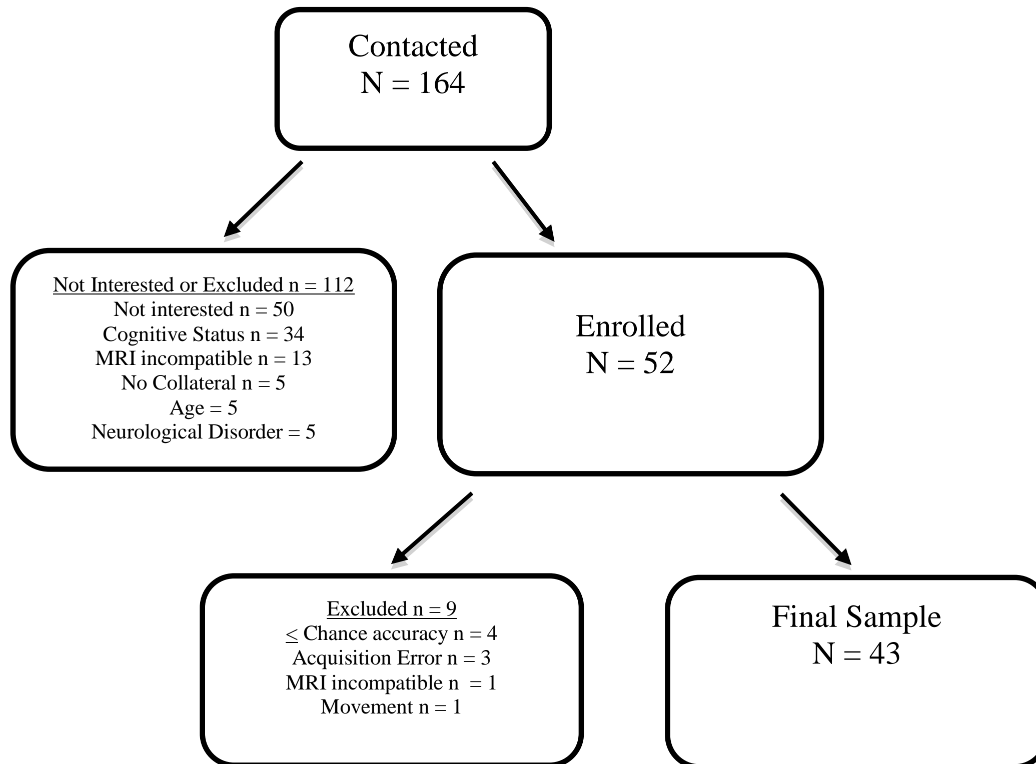
After the contrast file of interest was created, a 2nd analysis within SPM8 compared contrasts of interest between groups using an independent samples t-test (i.e., MCI-Normal). An additional 2nd level analysis combined contrasted .mat images for all participants in each group (i.e., normal, MCI) by uploading the specific con_000*.img files and compared activation within groups and across all participants with a one sample t-test. Both second level analyses first analyzed the BOLD response within the ROIs (VMPFC, DLPFC, ACC, and PPC) with a mask created in the WFU: PickAtlas, and subsequently as whole brain.

Table 1.1 The most common sets of diagnostic criteria for Alzheimer's disease summarized

	DSM-IV-TR	ICD-10	NINCDS-ADRDA	NIA-AA
Cognitive Deficits	Memory Impairment accompanied by either, aphasia, apraxia, agnosia, EF impairment	Memory impairment accompanied by decline in other abilities, which is characterized by deterioration in judgment and thinking	Impairment in memory and another cognitive function	Impairment in at least two of the following cognitive domains: memory, visuospatial ability, language and EF.
Supportive Evidence	---	Collateral Report	Neuropsychological Testing	Self and collateral report and objective cognitive assessment, either mental status exam or neuropsychological testing.
Functional Impairment	Impairment in social or occupational functioning from previous level of functioning	Impairment in ADLs	Impaired ADLs and altered patterns of behavior	Impairment in ability to work or usual activities
Course	Gradual onset and continual decline	Gradual onset and slow deterioration	Progressive decline without a sudden onset	Gradual onset, and progressive decline from previous levels of functioning
Exclusions	Not due to psychological (e.g., MDD), medical (e.g., Cerebrovascular), or systemic (Vitamin B_{12} deficiency) conditions or substance abuse	Not due to other medical (e.g., HD) or systemic conditions (e.g., hypothyrodism), or substance abuse	Age of onset <40 or >90; no other diseases or disorders can account for the cognitive changes	Symptoms are not explained by delirium, medication, PD, another neurological or non-neurological disease . Substantial concomitant cerebrovascular disease or presence of multiple and extensive infarcts or severe whit matter hyperintensity burden. Core features of DLB, bv-FTD, sv-PPA or na-PPA are present.

Abbreviations: DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders; EF, Executive Functioning; MDD, Major Depressive Disorder; ICD-10, International Classification of Diseases; ADLs Activities of Daily Living; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NIA-AA, National Institute of Aging-Alzheimer's Association; HD, Huntington's Disease; PD, Psychiatric Disorder, DLB, Dementia with Lewy Bodies; bv-FTD, Behavioral Variant Frontotemporal Dementia; sv-PPP, Semantic Variant Primary Progressive Aphasia; na-PPA, Nonfluent/Agrammatic variant Primary Progressive Aphasia

Figure 2.1 Flow chart of recruitment



CHAPTER 3

FMRI COMPARISION OF INHIBITION BETWEEN NORMAL AND OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT

[1]Puente, A.N., & Miller, L.S. To be submitted to the Journal of the International Neuropsychological Society

Abstract

This investigation compared the neural correlates of inhibition in normal older adults (OA) and OA with mild cognitive impairment (MCI). It was hypothesized OA with MCI would recruit a greater amount of resources for inhibition, and therefore display greater functional activation in specific regions of interest (ROIs). During inhibition, there were no functional Magnetic Resonance Imaging (fMRI) between group differences in apriori specified ROIs or post-hoc whole brain analyses with corrected thresholds. However, a neuropsychological screening battery found differences between groups. The results of this study suggest fMRI with inhibition may not reliably identify MCI, and this condition may be best detected by traditional neuropsychological techniques.

Introduction

With the exponential growth of older adults (OA), the number of individuals with dementia is drastically increasing (Alzheimer's Association, 2011). Dementia dramatically changes the lives of OA (Marcotte, Scott, Kamat, & Heaton, 2010), their caregivers (Schulz & Beach, 1999), and impacts society as a whole (Wimo, Winblad, & Jönsson, 2010). Petersen et al. (1999) suggested MCI is a transitional stage between normal and pathological aging. Individuals with MCI are at an increased risk for Alzheimer's Disease (AD) compared to OA without MCI (Fischer et al., 2007; Petersen et al., 2009). The criteria and conceptualization of MCI has evolved with research findings, and MCI is no longer considered a "transitional state" but still represents an individual that is neither normal nor demented (Albert et al., 2011). Given a potential cause of cognitive changes leading to MCI is neurodegenerative disease (Wilson, Leurgans, Boyle, & Bennett, 2011), this clinical syndrome provides clinicians a possibility to intervene and potentially slow underlying neurodegenerative processes (e.g., Alzheimer's disease; AD).

Individuals with MCI, by definition, do not have severe global cognitive deficits, but they do have deficits in specific cognitive domains (Albert et al., 2011; Winblad et al., 2004). One cognitive ability that is impaired in MCI is EF (Brandt et al., 2009; Crowell, Luis,Vanderploeg, Jchinka, & Mullan, 2002; Nordlund, Rolstad, Hellström, Sjögren, Hansen, & Wallin, 2005; Petersen, 2004; Rainville, Lepage, Gauthier, Kergoat, & Belleville, 2012). EF is a heterogeneous construct encompassed by many "higher order" cognitive processes including the ability to plan, initiate, inhibit, monitor and perform behaviors. These abilities allow individuals to engage in socially responsible, appropriate, adaptive, and effective behaviors (Lezak, Howieson, & Loring, 2004). When EF is compromised it negatively impacts the ability to complete activities of daily

living and increases the likelihood of conversion to dementia from MCI (Cahn-Weiner, Ready, & Malloy, 2003; Lewis & Miller, 2007; Mitchell & Miller, 2008; Pereira, Yassuda, Oliveira, & Forlenza, 2008; Tabert et al., 2006). Inhibition is one component of EF found to be compromised in MCI (Belanger, Belleville, & Gautheir, 2010; Irish, Lawlor, Coen, & O'Mara, 2011; Kramer et al., 2006; Traykov et al., 2007; Wylie, Ridderinkhof, Eckerle, & Manning, 2007) and is predictive of functional ability in OA (Jefferson, Paul, Ozonoff, & Cohen, 2006). Successful inhibition is particularly helpful in novel or unexpected situations where stopping an automatic response such as pressing the brake while skidding, could be life threating.

Functional neuroimaging studies have reported a number of brain regions are involved with inhibition. In general, these are frontal and parietal regions, including the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC) and posterior parietal cortex (PCC); (Banich et al., 2000; Lui, Banich, Jacobson & Tanabe, 2004; Mostofsky et al., 2003; Nee, Wager, & Jonides, 2007). The neural correlates in OA are similar, but fMRI investigations comparing young and OA typically find older adults display greater activation in the same and different brain regions such as the left inferior frontal gyrus (Langenecker, Nielson, & Rao, 2004; Milham et al., 2002). In contrast to fMRI studies of inhibition in normal adults, there is a very limited amount of small investigations comparing normal OA and OA with MCI. These studies have a small number of participants, used liberal statistical procedures, included data not representative of inhibition (e.g., failed inhibition) or did not report behavioral data (Kaufmann et al., 2008; Li, Zheng, Wang, Gui & Li, 2009; Rosano et al., 2005). Despite these shortcomings, the these fMRI investigations report OA with MCI have greater functional activation compared to normal OA during inhibition similar to the finding that normal OA in

general have greater activation compared to young adults (Kaufmann et al., 2008; Li, Zheng, Wang, Gui & Li, 2009; Rosano et al., 2005).

The first investigation to examine this relationship found OA with MCI have greater functional activation during inhibition in the DLPFC and PPC (Rosano et al., 2005). Kaufmann et al. (2008) compared functional activity with whole brain analyses, and they found OA with MCI had greater activation in several areas including the orbitofrontal cortex (OFC) and the PPC. Another comparison of inhibitory neural activity between OA with MCI and normal OA revealed greater activation in the DLFPC, ACC, PPC, the basal ganglia, and inferior frontal regions (Li et al., 2009).

One explanation of greater activation by OA with MCI is to overcome neuropathology and maintain cognitive performance (Dickerson & Sperling, 2008; Sperling et al., 2010). Neuropathology occurs in MCI many years before clinical symptoms of dementia are present (Braak, Griffing, Arai, Bohl, Bratzke, & Braak, 1999; Markesbery, 2010; Markesbery, Schmitt, Kryscio, Davis, Smith, & Wekstein, 2006). To overcome the effects of the pathology and preserve premorbid abilities, OA with MCI may recruit additional resources and therefore have greater functional activation compared to normal controls.

The objective of this fMRI investigation was to compare OA with MCI and normal OA during inhibition. Even though there have been several studies comparing the neural activity differences between OA with MCI and normal OA, the literature is limited and this investigation attempts to clarify the relationship of inhibitory neural activity between these groups. It was hypothesized OA with MCI would have greater activation in the orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), & posterior parietal cortex (PPC). Greater activation may support inhibitory control, and permit OA with MCI to

perform as well as normal OA on the task of inhibition. However, it was hypothesized OA with MCI will be less accurate and slower during inhibition.

Method

Participants

OA with and without cognitive impairment between ages 65 – 85 were recruited from the local community of Athens, GA, through community engagement and newspaper advertisements. Potential participants were first screened over the phone and included if they were compatible with the magnetic resonance imaging (MRI) environment, between 65 – 85, had a reliable collateral, were literate by self-report, and were not demented or did not have history of a neurological disorder (e.g., Multiple Sclerosis, Lupus). Participants were provided with monetary compensation for their time.

Fifty-two older adults were enrolled in the study. However, due to less than chance performance on the task during fMRI (n=4), incomplete data acquisition (n=3), excess movement (n=1) and MRI incompatibility (n=1) the final sample included in analyses was 43. Participants were grouped according to global Clinical Dementia Rating scale (CDR; Hughes et al., 1982) score. A global CDR score of 0 was considered normal, and 0.5 was representative of MCI. In the final sample there were 26 normal OA and 17 with MCI. Despite uneven group sizes the groups did not differ in age, gender, handedness, diabetes, family history of AD or balance, gait or strength of their lower extremities. Groups did however differ with respect to education (Table 3.1).

Procedures

After determining eligibility, participants were scheduled for two separate sessions. The first session took approximately three hours and encompassed informed consent, interviewing,

questionnaires, and neuropsychological testing. Participants completed an MRI compatibility screening form, the Geriatric Depression Scale (GDS; Yesavage et al., 1983), demographics questionnaire and two additional self-report questionnaires not used for the present investigation. While participants completed self-report measures, informed collaterals were interviewed with the CDR by a CDR-certified examiner. The participant was then interviewed with the CDR by a CDR-certified examiner. Following the CDR, the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh,1975), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998), Delis-Kaplan Executive Function System Trail Making Test (DKEFS-TMT; Delis, Kaplan & Kramer, 2001), and Short Battery of Physical Performance (SPPB; Guralnik et al., 1994) were administered.

The second data collection session was conducted at the Bioimaging Research Center (BIRC) at the University of Georgia and lasted approximately 3 hours. First, participants were acquainted and practiced a modified Stroop paradigm and another task not relevant to this current study on a computer in a separate room from the MRI. Participants were then placed and remained in the MRI for approximately an hour. Structural images were collected first, followed by the sequence for the modified Stroop task, and phase and magnitude images.

Measures

Neuropsychological. To obtain participants' overall general cognitive functioning the MMSE was administered. The MMSE is a 30-item test of general cognitive functioning that measures an individual's orientation, registration (i.e., ability to repeat words), attention and calculation, memory recall and language. This measure has a total possible score of 30, and is often used in primary care settings as a screener for cognitive impairment and dementia, where a

score of 24 or below is considered to be indicative of cognitive impairment (Folstein et al., 1975).

To compare memory, attention, language and visual spatial functioning between groups the RBANS was administered to all participants. The RBANS is a standalone measure that takes approximately 30 minutes, is normed on individuals between the ages of 20 – 89 and can be administered to individuals with a variety of neurological conditions (Randolph, 1998). There are 12 separate subtests, which make up 6 different indices. Raw score on the individual subtests and participants age were used to derive age-based scaled and standard scores from a United States population based normative sample. The six indices are immediate memory, visuospatial/constructional, language, attention, delayed memory and total scale.

Two of five conditions of the DKEFS-TMT, number-letter switching and motor speed, were administered to examine EF and visuomotor processing speed. Number letter switching requires the participant to connect and switch between numbers and letters in ascending order (Delis et al., 2001). This test is a measure of mental flexibility, but also requires visual scanning, number and letter sequencing, and processing speed (Delis et al., 2001). On the motor speed condition the individual traces a dotted line as neatly and quickly as possible without errors, and touches every circle along the correct route (Delis et al., 2001).

Depressive symptomology was measured by a self-report scale developed to measure depression in geriatric samples, the GDS (Yesavage et al., 1983). Unlike other self-report depression scales, somatic symptoms of depression are deemphasized given they are associated with the normal aging process and not necessarily related to depression in this population. It is also found to have good psychometric properties and is a valid measure of geriatric depression (Peach, Koob, & Kraus, 2001).

To determine lower body physical functioning, the SPPB was used. The SPPB is a brief physical performance test that measures balance, gait, strength, and endurance in lower extremities. The SPPB measures how long an individual remains standing, their stance, time required to walk 8 feet, and how quickly an adult stands from a sitting position five consecutive times (Guralnik et al., 1994).

Neuroimaging

Task. The task presented during fMRI was a modified Stroop task designed in E-prime 2.0 (Psychology Software Tools, Inc., 2007). All conditions were counterbalanced, although the selection of the stimuli within each condition was random. For the congruent condition four-color words were randomly presented in ink consistent with the semantic meaning; whereas during the incongruent condition four-color words were randomly presented in a color inconsistent with the meaning of the word. The neutral condition consisted of four capital X's randomly presented in one of the four possible colors (see Figure 1).

The experimental stimuli were presented to participants through MRI compatible goggles, and, if required, MRI compatible corrective lenses were placed in the goggles. Participants responded with a button press from two response pads with select fingers indicating the color of the presented stimulus. Green, yellow, red, and blue corresponded to the left middle, left index, right index, and right middle, respectively. In addition to the practice, instructions were given verbally and visually before participants began the task. To decrease errors due to memory, a color bar was positioned at the bottom of the visual field throughout the task to help participants remember the corresponding button presses for each of the four-colors.

Participants responded with the appropriate button press after the onset of the current stimulus, but before the onset of subsequent trials. Every stimulus was presented for 2.5 seconds

with a 0.5 second ISI, thereby allowing participants 3.0 seconds to respond. Responses made during the presentation of the word or during the inter-stimulus interval were recorded, and analyzed for accuracy and reaction time.

The paradigm was an event related design, and was jittered to maximize detection of brain activation. Specifically, this design was structured to maximally account for variations in the hemodynamic response function (HRF) given a 3 second epoch, 2 second repetition time (TR) and three conditions (i.e., two active and one baseline). To achieve the most efficient design and greatest likelihood of detection, 93%, there were 192 total events. This model assumed second-order polynomial drift and the HRF was the convolution of a 3 second epoch and the canonical HRF of Statistical Parametric Mapping version 2.0 (i.e., double gamma; SPM; London, UK; http://www.fil.ion.ucl.ac.uk/spm). The jittering algorithm was based on procedures outline by Kao, Mandal, Lazar, and Stufken (2009). Thus, to maximize detection this event related paradigm included 64 trials per condition, and lasted 576 seconds (i.e., 9 minutes and 36 seconds).

Sequences. A fast spoiled gradient recall (FSPGR) protocol was used to acquire the structural scans (TE = min full, TR = 7.8ms, flip angle = 20°, slice thickness = 1.2 mm, acquisition matrix = 256 x 256 mm). The FSPGR protocol covered the top of the head to the brain stem, collected 176 images and lasted 418 seconds (i.e., 6 minutes and 58 seconds). Functional images were acquired as T2* images using an echo planar imaging (EPI) sequence. This EPI sequence lasted 9 minutes and 36 seconds and collected 288 volumes with 30 slices, and covered from the top of the head to the top of the cerebellum (TE = 25 ms, TR = 2000 ms, 90° RF pulse, spacing = 0 mm, slice thickness = 4 mm, acquisition matrix = 64 x 64, FOV = 22 x 22 cm).

Analyses

FMRI data was preprocessed with SPM version 8.0 (Wellcome Department of Cognitive Neurology, London, UK) through Matlab (The Math Works, Natick, MA) using the aforementioned parameters and an interleaved bottom up slice collection. Images were first converted from GE DICOM format to NIFTI using the dcm2nii conversion tool (Rorden, 2007). Functional images were first corrected for slice timing using the median slice within the interleaved bottom-up sequence (i.e., #29) as the reference image. Following slice timing the center of all EPI and the source structural was aligned to the anterior commissure for improved coregistration. A fieldmap was then created using the fieldmap toolbox in SPM8 with phase and magnitude images, and slice time corrected images were then realigned and unwarped. The fieldmap (i.e., voxel displacement map) was used in this step to assist with adjusting for distortions in the EPI images. The source anatomical was then co-registered with the first functional image produced by realigning and unwarping. Then the co-registered image, 3D, and all functional images were co-registered to the Montreal Neurological Institute (MNI) 152 T1 template. Following co-registration, the transformed anatomical image was divided into GM, WM, CSF, bone, non-brain soft tissue and air in New Segment. From this step a deformation field was created and applied to all functional images to spatially normalize images to MNI stereotaxic space. The last step of pre-processing was smoothing the images with a 6.875_{mm} x 6.875_{mm} x 8.0_{mm} full width half maximum Gaussian kernel on every voxel.

After pre-processing, conditions and timing of the event related paradigm were specified through 1st level analyses. Only conditions associated with accurate responses were specified for each condition, while conditions answered incorrectly were specified in a separate column in the design matrix. The data were then estimated with the classical SPM method, Restricted

Maximum Likelihood and contrasts of interest were defined 1-1 (Incongruent – Congruent) as the neutral condition was an active baseline and coded as an implicit variable. To compare group differences 2nd level analysis was completed within SPM8 and compared contrasts of interest (i.e., incongruent – congruent) between groups using an independent samples t-test (i.e., MCI-Normal). An additional 2nd level analysis was completed to determine activation due to inhibition within groups with a one-sample t-test with the specific con_000* .img files comparing incongruent – congruent. Both second level analyses first analyzed the BOLD response within the ROIs (VMPFC, DLPFC, ACC, and PPC) with a mask created in the WFU: PickAtlas (Maldjian, Laurienti, Kraft, & Burdette, 2003) using the automated anatomical labeling atlas (AAL; Tzourio-Mazoyer et al., 2002), and subsequently as whole brain.

Behavioral

Independent samples T-tests were used to analyze the behavioral data from the fMRI task in Predictive Analytics Software (PASW) version 18.0. Dependent variables for the T-tests were reaction time and percentage correct for each condition as well as the Stroop Effect (i.e., Inc RT – Con RT). Neuropsychological measures were compared with one-way between groups analysis of covariance (ANCOVA). Given the education difference between groups, it was entered as a covariate in the ANCOVAs. To control for type one-error Bonferroni corrections were applied. A correction of 5 comparisons was made for the number between group individual analyses of separate neuropsychological measures. An additional correction was made for analyses with the RBANS indices. Corrections were applied separately given the correlation and inherent interrelatedness of the RBANS and its indices.

Results

Neuropsychological

ANCOVAs revealed differences on several neuropsychological measures (Table 3.2). OA with MCI had an average raw score of approximately 26 on the MMSE, which was worse than normal OA [F (1, 40) = 9.350, p = .004]. As a result of worse performance on three out of five indices, OA with MCI overall ability (RBANS TS) was less than controls [F (1, 40) = 14.827 p = .000]. The three indices OA with MCI were worse on were the immediate memory index [F (1, 40) = 8.337, p = .006], delayed memory [F (1, 40) = 8.888, p = .005], and language [F (1, 40) = 12.446, p = .001]. OA with MCI were not significantly different than normal OA on visuospatial/constructional and attention despite overall lower means [F (1, 40) = 5.192 p = .028; F (1, 40) = 4.435, p = .042]. OA with MCI were additionally not statistically worse on a measure of EF [DKEFS#4; F (1, 38) = 6.474, p = .015] after multiple testing correction was applied (p.01). There were also no differences on visuomotor processing speed [DKEFS#5; F (1, 40) = 3.899, p = .055].

fMRI task

Independent t-test analyses suggested no differences in accuracy between groups for congruent [*t* (41) = 1.115, p = .271], neutral [*t* (22.591) = 2.390, p = .026], or incongruent [*t* (19.994) = 1.8, p value = .087; Table 3.2 & Figure 3.2] tasks. Similarly there were no group differences for reaction time during congruent [*t* (41) = -.58, p value = .553], neutral [*t* (23.121) = -1.027, p value = .310], or incongruent tasks [*t* (22.145) = -.995, p value = .331; Table 3.2 & Figure 3.3]. Paired sample t-test revealed there was a Stroop Effect for normal [*t* (25) = 12.448, p = .000] and OA with MCI [*t* (16) = 6.502, p = .000], as both groups were slower to respond during the incongruent compared to the congruent condition. Normal OA [*t* (25) = 2.637, p =

.014] and OA with MCI [t (16) = 2.448, p = .026] were less accurate during the incongruent compared to congruent condition.

fMRI

There were no activation differences between OA with MCI and normal OA from ROI analyses using a family wise error (FWE) corrected $p < .01$. To explore potential between group differences in ROIs, a liberal threshold, uncorrected $p < .01$, was used. This threshold revealed OA with MCI recruited the right middle and superior frontal gyri, and the opercular part of the left inferior frontal gyrus (Table 3.4). Normal controls did not exhibit greater activation at the same threshold.

Because between group differences were not found in ROI analyses with corrected threshold of $p < .01$, within group whole brain (WB) analyses were completed across all participants. Twelve clusters passed a threshold of $p < .01$, FWE corrected, minimum of 8 contiguous voxels (Table 3.5 & Figure 3.4). The largest cluster's local maxima [Z = 6.66] was in the left precentral gyrus. From the left precentral gyrus this cluster extended rostrally to the orbital frontal parts of the middle and inferior frontal gyri, and inferiorly to the left insula. This cluster also included triangular and opercular parts of the inferior frontal gyrus, which together had the greatest number of voxels within this cluster. The second cluster's local maxima [Z = 6.44] was located in the left inferior parietal lobule. This cluster ranged from the lateral to medial sections of parietal cortex, and stretched caudally to the middle occipital gyrus. The third cluster was located in the frontal cortex, with the vast majority of voxels surrounding the local maxima in the left supplementary motor area (SMA) [Z = 6.11]. This cluster also included right SMA and extended inferiorly and included the left and right middle cingulate gyrus. The fourth cluster was located in subcortical regions, and included the left thalamus and left caudate

nucleus. The next largest cluster in terms of number voxels activated was circumscribed to the prefrontal cortex including the right superior and right middle frontal gyri. The sixth cluster stretched from the right insula superiorly to the rolandic operculum, and included the right superior temporal pole and right inferior frontal gyrus opercular part. The seventh and eleventh cluster included the left thalamus and left lenticular nucleus, specifically the pallidum and putamen sections. Activation in the remaining clusters was located in the right inferior frontal gyrus triangular part, other prefrontal regions, PPC and visual regions.

Specific to OA with MCI, four clusters passed the threshold of $p < .05$, FWE corrected, minimum 8 contiguous voxels (Table 3.5). The largest peak activated voxel [$Z = 5.61$] was located in second largest cluster, which was in the inferior occipital and temporal gyrus. An additional cluster also was found in the inferior occipital gyrus. This analysis also yielded activation of the superior parietal gyrus and in the opercular and triangular parts of the left inferior frontal gyrus.

Within group analyses of normal OA indicated several areas were recruited for inhibition. The largest cluster spanned from the left and right SMA to the left superior frontal gyrus laterally as well as the left and right middle cingulum and left superior medial frontal gyrus. The second largest cluster was also located in the frontal cortex, and included the left precentral gyrus, left middle frontal gyrus and the opercular part of the left inferior frontal gyrus. Additional clusters were located in the frontal cortex. One cluster had a peak voxel within the left precentral gyrus, and included the left middle and superior frontal gyri and the left SMA. Another cluster was circumscribed to the left inferior frontal gyrus triangular part. Parietal areas, the left precuneus, left inferior parietal lobule and left superior parietal gyrus, were also involved during inhibition. Additionally, a small cluster of voxels was found in the thalamus.

Discussion

The aim of this investigation was to examine the functional activation differences between normal OA and OA with MCI during inhibition. The limited extant literature suggested OA with MCI would display greater activation than normal controls during inhibition (Li et al., 2009; Kaufmann et al., 2005; Rosano et al., 2005). In contrast to the literature and our hypothesis, there were no differences in neural activity during inhibition between groups at $p < .01$, corrected.

However, between group post-hoc analyses with liberal thresholds ($p < .01$ uncorrected) revealed MCI group had greater activation than controls. Specifically, two clusters in the prefrontal cortex were activated more by OA with MCI. However, there was no behavior differences between groups on the fMRI task as individuals with MCI were just as accurate and just as quick during all conditions. These results are parallel with the perspective that OA with MCI may perform as well as normal OA behaviorally but display a greater level of neural activity. These between group differences, however, should be viewed with substantial caution due to the lack of correction. Thresholds without correction have substantial chance for type I error given the large number of comparisons and multiple testing problem (Bennett, Baird, Miller, & Wolford, 2009; Bennett, Wolford, Miller, & 2009).

Methodological differences may account for why greater activation in MCI was found in previous fMRI studies of inhibition but not in the present investigation (Kaufmann et al., 2008; Li et al., 2009; Rosano et al., 2005). For example, Li et al. (2009) did not report behavioral responses during fMRI acquisition therefore it is difficult to be sure participants were actively engaged in the task. Furthermore, an extremely liberal threshold (i.e., $p < .01$, uncorrected) was used to compare functional activation between groups. Similarly, Kaufmann et al. (2008) used

the same liberal threshold vulnerable to type 1 error (Bennett et al., 2009; Bennett et al., 2009). Both Kaufmann et al. (2008) and Li et al. (2009) also used block designs, which present numerous incongruent stimuli sequentially. This allows participants to prepare to inhibit as they begin to expect these trials and, as a result, the cognitive load on inhibitory control is reduced and may not be as representative of the inhibition process.

Rosano et al. (2005) extracted peak activations (i.e., maxima) from all ROIs in every OA, and completed t-tests comparing normal and MCI groups. Maxima may not be the best representation of the data as it represents only one observation, and these are not typically normally distributed, making the use of t-tests problematic. Additionally, their analyses included functional data associated with both correct responding and errors. Data acquired during error trials may not be indicative of the inhibition process and may have influenced final results. Thus, increased activation observed in OA with MCI in Kaufmann et al. (2008), Li et al. (2009), and Rosano et al. (2005) may be confounded with cognitive processes other than inhibition, uncorrected thresholds, and nontraditional neuroimaging statistical procedures.

Given there were no between group differences, within group analyses were completed to ensure reliable neural activity was occurring during inhibition. Expected areas for inhibition were found across all participants as well as within each group in whole brain analyses (Table 3.5 & Figure 3.4). Within group analyses across all participants found significant activation in inferior and superior prefrontal regions. Specifically, robust activation in prefrontal regions was found bilaterally in the DLPFC, OFC and PPC. Additional activation across all participants was found in the motor and subcortical regions associated with successful inhibition. These regions have been found in fMRI investigations of inhibition with the Stroop task in studies of normal OA (Bowes Stroman, & Garcia, 2011; Langenecker, Nielsen & Rao, 2004; Milham et al., 2002).

Thus, activation across all participants suggests successful performance required traditional areas involved with inhibition.

Behavioral data from the fMRI task also suggests participants were engaged in inhibition given both groups were slower to respond during the incongruent compared to the congruent condition. Similar to the functional data, there were no between group differences during inhibition and the study's hypothesis about between group behavioral performance was not supported. However, on all measures (i.e., reaction time and accuracy) of the modified Stroop task, there was a trend of OA with MCI to perform worse (Table 3.3, Figure 3.2 & 3.3). Our lack of differences on the Stroop Task, therefore, may be due to power, given the number of participants needed for a strictly behavioral investigation is typically larger.

In contrast to fMRI, neuropsychological measures detected differences between normal and OA with MCI. Neuropsychological results were as expected and consistent with the extant literature. MMSE scores of approximately 26 are common for MCI (Pozueta et al., 2011). Similarly, a score of < 27 but > 23/24 on the MMSE is often used as scores for identifying MCI (Hoops et al., 2009; Mitchell, 2009; Nasreddine et al., 2005). Poorer performance on memory measures involving learning, storage, and recall (i.e., RBANS IM & RM) is common and typically the characteristic problem of individuals with MCI (Albert et al., 2011; Petersen et al., 1999). Decreased language ability is also found among OA with MCI (Carter, Caine, Burns, Herholz, & Lambon Ralph, 2011; Nordlund, Rolstad, Hellström, Sjögren, Hansen, & Wallin, 2005). The overall ability of OA with MCI is also worse overall. Duff, Hobson, Beglinger, and O'Bryant (2010) found the same results in their investigation of RBANS performance in normal OA and OA with MCI, where the MCI group was worse on the RBANS TS, IM, DM and language indices.

Finding group differences with outside of the scanner cognitive measures but not fMRI, suggests that at least as compared to a functional inhibition task like the Stroop, OA with MCI may be better detected by traditional neuropsychological techniques. This is consistent with the perspective of Marcotte, Scott, Kamat, and Heaton (2010), who suggest neuroimaging lacks specificity and is not always helpful for diagnosing different neurological conditions such as beginning stages of neurodegenerative diseases (e.g., MCI). Furthermore, fMRI is not yet well validated as a biomarker and requires more research to be able to reliably detect OA with MCI (Albert et al., 2011). Although neuroimaging is extremely valuable given in some instances it can detect abnormal neurological conditions before behavior changes are apparent (Dickerson et al., 2005; Dickerson & Sperling, 2008; Zamrini, Santi, & Tolar, 2004), more data is required to determine if fMRI of inhibition can reliably identify OA with MCI.

Future fMRI investigations are needed to determine the reliability of these findings. Additional functional neuroimaging studies should use appropriate thresholds and statistical techniques with various EF tasks to best understand this relationship. It is also recommended future research use equal sample sizes, which were not used and may be viewed as a limitation of this study (i.e., Normal = 26; MCI = 17). The completion of practice sessions prior to scanning could also be viewed as a limitation given there are practice effects related to executive tasks (Basso, Bornstein, & Lang, 1999) and the Stroop task in general (MacLeod, 1998). However, Stroop practice effects typically require practice over several hours (MacLeod, 1998). Additionally, the behavioral data from the current study documents a Stroop Effect such that participants were significantly slower to respond during the incongruent than the congruent condition. All together this suggests practice sessions likely familiarized participants to the task but did not decrease the prepotent response.

An additional potential limitation is specific to the study's paradigm design. Event related designs are associated with decreased signal-to-noise ratio (Bandettini & Cox, 2000; Miezin, Maccotta, Ollinger, Petersen, & Buckner, 2000). Event-related designs with short epochs may be particularly problematic given the time required for the HRF may cause saturation of the signal such that when deconvolving the fMRI signal, trials/conditions (e.g., baseline) not associated with the signal response show an increased response and the signal associated with the event is truncated (Bandettini & Cox, 2000). It is therefore, not surprising then that block design paradigms have greater percent signal change compared to event related designs.

However, the use of an event related design could be viewed as a strength given it provides an ecological measure of inhibition. Block designs present stimuli requiring inhibition consecutively, which decreases the "load" on the pre-potent response and allows participants to prepare to inhibit and over time habituate to the pre-potent response. In contrast, an event related design allows for the presentation of stimuli requiring inhibition in an unpredictable sequence, which eliminates the ability to prepare to inhibit.

There were several additional strengths of our current investigation. The number of participants (N = 43) is larger than any of the other previous investigations of inhibition with normal OA and OA with MCI (Kaufmann et al., 2008; Li et al., 2009; Rosano et al., 2005; Staffen et al., 2011). An additional strength is use of the traditional color word Stroop task and recording of behavioral responses during scanning, which to our knowledge is the only study to have done so. Additionally, in contrast to Kaufmann et al. (2008) and Rosano et al. (2005) data associated with errors were not included in analyses ensuring activation was due to successful

and not failed inhibitory control. Additional strengths were the use of an event related design, corrected thresholds, and fieldmaps during preprocessing.

fMRI is a valuable tool that has the potential to aid clinicians with detecting pathological aging before clinical symptoms are present (Bondi, Houston, Eyler, & Brown, 2005; Bookheimer et al., 2000; Filippini et al., 2009; Han et al., 2007). However, currently the fMRI literature of inhibition in OA with MCI is inconclusive and limited. The overall literature and present data suggests fMRI of inhibition does not provide clinicians with a reliable method to identify OA with MCI. It is hoped this along with other investigations will motivate future research that will further our knowledge and ability to detect preclinical stages of neurodegenerative diseases and, ultimately, decrease the substantial impact of these diseases.

References

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., . . . Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia, 7, 270-279. doi: 10.1016/j.jalz.2011.03.008

Alzheimer's Association (2011). Alzheimer's disease facts and figures. *Alzheimer's and Dementia, 7*, 208-244. doi: 10.1016/j.jalz.2011.02.004

Bandettini, P. A., & Cox, R. W. (2000). Event-related fMRI contrast when using constant interstimulus interval: theory and experiment. *Magnetic Resonance in Medicine, 43,* 440-548.

Banich, M. T., Milham, M. P., Atchley, R., Cohen, N. J., Webb, A., Wszalek, T., & Magin, R. (2000). fMRI Studies of Stroop Tasks Reveal Unique Roles of Anterior and Posterior Brain Systems in Attentional Selection. *Journal of Cognitive Neuroscience, 12,* 988-1000.

Basso, M. R., Bornstein, R. A., & Lang, J. M. (1999). Practice effects on commonly used measures of executive function across twelve months. *The Clinical Neuropsychologist, 13,* 283-292.

Bélanger, S., Belleville, S., & Gauthier, S. (2010). Inhibition impairments in Alzheimer's disease, mild cognitive impairment and healthy aging: Effect of congruency proportion in a Stroop task. *Neuropsychologia, 48,* 581-590.

Bennett, C. M., Baird, A. A., Miller, M. B., & Wolford, G. L. (2009) *Neural correlates of interspecies perspective taking the post-mortem Atlantic Salmon: An argument for*

multiple comparisons correction. Poster session presented at the 15th Annual Meeting of the Organization for Human Brain Mapping, San Francisco, CA.

Bennett, C. M., Wolford, G. L., & Miller, M. B. (2009). The principled control of false positives in neuroimaging. *Scan, 4,* 417-422. doi 10.1093/scan/nsp053

Bondi, M. W., Houston, W. S., Eyler, L. T., & Brown, G. G. (2005). fMRI evidence of compensatory mechanisms in older adults at genetic risk for Alzheimer disease. *Neurology, 64*, 501-508. doi: 10.1212/01.wnl.0000150885.00929.7e

Bookheimer, S. Y., Strojwas, M. H., Cohen, M. S., Saunders, A. M., Pericak-Vance, M. A., Mazzoitta, J. C., & Small, G. W. (2000). Patterns of Brain Activation in People at Risk for Alzheimer's Disease. *New England Journal of Medicine, 343,* 450-456. doi:10.1056/NEJM200008173430704

Bowes, J. R., Stroman, P., & Garcias, A. (2011). Neural correlates of focused attention in cognitively normal older adults. *World Journal of Neuroscience, 1,* 19-27. doi:10.4236/wjns.2011.12003

Braak, E., Griffing, K., Arai, K., Bohl, J., Bratzke, H., & Braak, H. (1999). Neuropathology of Alzheimer's disease: what is new since A. Alzheimer? *European Archives of Psychiatry and Clinical Neuroscience, 249*(9), 14-22.

Brandt, J., Aretouli, E., Nejistrom, E., Samek, J., Manning, K., Albert, M. S., & Bandeen-Roche, K. (2009). Selectivity of Executive Function Deficits in Mild Cognitive Impairment. *Neuropsychology, 23,* 607-618. doi:10.1037/a0015851.

Cahn-Weiner, D. A., Ready, R. E., & Malloy, P. F. (2003). Neuropsychological predictors of everyday memory and everyday functioning in patients with mild Alzheimer's disease. *Journal of Geriatric Psychiatry & Neurology, 16*, 84–89.

Carter, S. F., Caine, D., Burns, A., Herholz, K., & Ralph, M. A. L. (2011). Staging of the cognitive decline in Alzheimer's disease: insights from a detailed neuropsychological investigation of mild cognitive impairment and mild Alzheimer's disease. *International Journal of Geriatric Psychiatry.* Advance online publication. doi: 10.1002/gps.2738

Crowell, T. A., Luis, C. A., Vanderploeg, R. D., Schinka, J. A., & Mullan, M. (2002). Memory Patterns and Executive Functioning in Mild Cognitive Impairment and Alzheimer's Disease. *Aging, Neuropsychology, and Cognition, 9,* 288-297.

Delis, D., Kaplan, E., & Kramer, J. (2001). Delis-Kaplan Executive Function System. The Psychological Corporation, San Antonio, TX: Harcourt Brace & Company.

Dickerson, B. C., & Sperling, R. A. (2008). Functional abnormalities of the medial temporal lobe memory system in mild cognitive impairment and Alzheimer's disease: Insights from functional MRI studies. *Neuropsychologia, 46,* 1624-1635.

Dickerson, B. C., Salat, D. H., Greve, D. N., Chua, E.F., Rand-Giovannetti, E., Rentz, D. M., … Sperling, R. A. (2005). Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. *Neurology, 65*, 404–411

Duff, K., Hobson, V. L., Beglinger, L. J., & O'Bryant, S. E. (2010). Diagnostic Accuracy of the RBANS in Mild Cognitive Impairment: Limitations on Assessing Milder Impairments. *Archives of Clinical Neuropsychology, 25,* 429-441. doi:10.1093/arclin/acq045

Fischer, P., Jungwirth, S., Zehetmayer, S., Weissgram, S., Hoenigschnabl, S., Gelpi, E., . . . Tragl, K. H. (2007). Conversion from subtypes of mild cognitive impairment to Alzheimer dementia. *Neurology, 68*, 288-291. doi:10.1212/01.wnl.0000252358.03285.9d

Filippini, N., MacIntosh, B. J., Hough, M. G., Goodwin, G. M., Frisoni, G. B., Smith, S. M., . . . Mackay, C. E. (2009). Distinct patterns of brain activity in young carriers of the APOE ε-

4 allele. *Proceedings of the National Academy of Sciences of the United States of America, 106,* 7209-7214.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*, 189-198.

Guralnik, J. M., Simonsick, E. M., Ferrucci, L., Glynn, R. J., Berkman, L. F., Blazer, D. G., & Wallace, R. B. (1994). *Journal of Gerontology, 49,* M85-M94.

Han, S. D., Houston, W. S., Jak, A. J., Eyler, L. T., Nagel, B. J., Fleisher, A. S., . . . Bondi, M. W. (2007). Verbal paired-associate learning by APOE genotype in nondemented older adults: fMRI evidence of a right hemispheric compensatory response. *Neurobiology of Aging, 28,* 238-247. doi: 10.1016/j.neurobiolaging.2005.12.013

Hoops, S., Nazem, S., Siderowf, A. D., Duda, J. E., Xie, S. X., Stern, M. B., & Weintraub, D. (2009). Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkison disease. *Neurology, 73,* 1738-1745. doi: 10.1212/WNL.0b013e3181c34b47

Hughes, C. P, Berg, L, Danziger, W. L, Coben, L. A, & Martin, R. L. (1982). A new clinical scale for the staging of dementia. *The British Journal of Psychiatry, 140*, 566-572. doi: 10.1192/bjp.140.6.566

Irish, M., Lawlor, B. A., Coen, R. F., & O’Mara, S. M. (2011). Everyday episodic memory in amnestic mild cognitive impairment: a preliminary investigation. *BMC Neuroscience, 12*(80), 1-13. doi:10.1186/1471-2202-12-80

Jefferson, A., Paul, R., Ozonoff, A., & Cohen, R. (2006). Evaluating elements of executive functioning as predictors of instrumental activities of daily living (IADLs). *Archives of Clinical Neuropsychology, 21*, 311-320. doi: 10.1016/j.acn.2006.03.007

Kaufmann, L., Ischebeck, A., Weiss, E., Koppelstaetter, F., Siedentopf, C., Vogel, S. E., . . . Wood, G. (2008). An fMRI study of the numerical Stroop task in individuals with and without minimal cognitive impairment. *Cortex, 44*, 1248-1255. doi: 10.1016/j.cortex.2007.11.009

Kramer, J. H., Nelson, A., Johnson, J. K., Yaffe, K., Glenn, S., Rosen, H. J., & Miller, B. (2006). Multiple Cognitive Deficits in Amnestic Mild Cogntive Impairment. *Dementia and geriatric cognitive disorders, 22,* 306-311. doi: 10.1159/000095303

Kukull, W. A., Larson, E. B., Reifler, B. V., Lampe, T. H., Yerby, M. S., & Hughes, J. P. (1990). The validity of 3 clinical diagnostic criteria for Alzheimer's disease. *Neurology, 40,* 1364-1369.

Langenecker, S. A., Nielson, K. A., & Rao, S. M. (2004). fMRI of healthy older aduls during Stroop intereference. *Neuroimage, 21,* 192-200.

Lewis, M., & Miller, L. S. (2007). Executive Control Functioning and Functional Ability in Older Adults. *The Clinical Neuropsychologist, 21*, 274-285. doi: 10.1080/13854040500519752

Lezak, M., Howieson, D. B., & Loring, D. W. (2004). *Neuropsychological Assessment* (4th ed.). New York, NY: Oxford University Press.

Li, C., Zheng, J., Wang, J., Gui, L., & Li, C. (2009). An fMRI Stroop Task Study of Prefrontal Cortical Function in Normal Aging, Mild Cognitive Impairment, and Alzheimer's Disease. *Current Alzheimer Research, 6*, 525-530. doi: 10.2174/156720509790147142

Liu, X., Banich, M. T., Jacobson, B. L., & Tanabe, J. L. (2004). Common and distinct neural substrates of attentional control in an integrated Simon and spatial Stroop as assessed by event-related fMRI. *Neuroimage, 22*, 1097-1106. doi:10.1016/j.neuroimage.2004.02.033

MacLeod, C. M. (1998). Training on integrated versus separated Stroop tasks: The porgression of intereference and facilitation. *Memory & Cognition, 26,* 201-211.

Maldjian, J. A., Laurienti, P. J., Kraft, R. A., & Burdette, J. H. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage, 19,* 1233-1239. doi:10.1016/S1053-8119(03)00169-1

Marcotte, T. D., Scott, J. C., Kamat, R., & Heaton, R. (2010). Neuropsychology and the Prediction of Everyday Functioning. In T. D. Marcotte & I.Grant (Ed.), *Neuropsychology of Everyday Functioning* (pp. 5-39). New York, NY: Guilford Press.

Markesbery, W. R. (2010). Neuropathologic Alterations in Mild Cognitive Impairment: A Review. *Journal of Alzheimer's Disease, 19,* 221-228. doi: 10.3233/JAD-2010-1220

Markesbery, W. R., Schmitt, F. A., Kryscio, R. J., Davis, D. G., Smith, C. D., & Wekstein, D. R. (2006). Neuropathologic Substrate of Mild Cognitive Impairment. *Archives of Neurology, 63,* 38-46.

Miezin, F. M., Maccotta, L., Ollinger, J. M., Petersen, S. E., & Buckner, R. L. (2000). Characterising the hemodynamic response: effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing. *Neuroimage, 11,* 735-759.

Milham, M. P., Erickson, K. I., Banich, M. T., Kramer, A. F., Webb, A., Wszalek, T., & Cohen, N. J. (2002). Attentional Control in the Aging Brain: Insights from an fMRI Study of the Stroop Task. *Brain and Cognition, 49,* 277-296.

Mitchell, A. (2009). A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. *Journal of Psychiatric Research, 43,* 411-431. doi:10.1016/j.jpsychires.2008.04.014

Mitchell, M., & Miller, L. S. (2008). Executive Functioning and Observed Versus Self-Reported Measures of Functional Ability. *The Clinical Neuropsychologist, 22*, 471 - 479.

Mostofsky, S. H., Schafer, J. G. B., Abrams, M. T., Goldberg, M. C., Flower, A. A., Boyce, A., . . . Pekar, J. J. (2003). fMRI evidence that the neural basis of response inhibition is task-dependent. *Cognitive Brain Research, 17,* 419-430.

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., . . . Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. *Journal of the American Geriatrics Society, 53,* 695-699. doi: 10.1111/j.1532-5415.2005.53221.x

Nee, D. E., Wager, T. D., & Jonides, J. (2007). Interference resolution: Insights from a meta-analysis of neuroimaging tasks. *Cognitive, Affective, & Behavioral, 7*, 1-17.

Nordlund, A., Rolstad, S., Hellström, P., Sjögren, M., Hansen, S., & Wallin, A. (2005). The Goteborg MCI study: mild cognitive impairment is a heterogenous condition. *Journal of Neurology, Neurosurgery, & Psychiatry with Practical Neurology, 76,* 1485-1490. doi: 10.1136/jnnp.2004.050385

Peach, J., Koob, J. J., & Kraus, M. J. (2001). Psychometric evaluation of the Geriatric Depression Scale (GDS): Supporting its use in health care settings. *Clinical Gerontologist, 23*, 57–68.

Pereira, F. S., Yassuda, M. S., Oliveira, A. M., & Forlenza, O. V. (2008). Executive dysfunction correlates with impaired functional status in older adults with varying degrees of cognitive impairment. *International Psychogeriatrics, 20,* 1104-1115. doi:10.1017/S1041610208007631

Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine, 256*, 183-194. doi: 10.1111/j.1365-2796.2004.01388.x

Petersen, R. C., Roberts, R. O., Knopman, D. S., Boeve, B. F., Geda, Y. E., Ivnik, R. J., . . . Jack, C. R. (2009). Mild Cognitive Impairment: Ten Years Later. *Archives of Neurology, 66*, 1447-1455. doi: 10.1001/archneurol.2009.266

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild Cognitive Impairment Clinical Characterization and Outcome. *Archives of Neurology, 56,* 303-308.

Pozueta, A., Rodríguez-Rodríguez, E., Vazquez-Higuera, J. L., Mateo, I., Sánchez-Juan, P., González-Perez, S., . . . Combarros, O. (2011). Detection of early Alzherimer's disease in MCI patients by the combination of MMSE and an episodic memory test. *BMC Neurology, 11,* 78-82. doi:10.1186/1471-2377-11-78

Predictive Analytics Software, 2002. Predictive Analytics Software (version 18.0). Chicago, IL: SPSS Inc.

Psychology Software Tools. 2006. E-Prime (Version 2.0). Pittsburgh, PA: Psychology Software Tools.

Rainville, C., Lepage, E., Gautheir, S., Kergoat, M. J., & Belleville, S. (2012). Executive function deficits in persons with mild cognitive impairment: A study with a Tower of London task. *Journal of Clinical and Experimental Neuropsychology, 34,* 306-324. http://dx.doi.org/10.1080/13803395.2011.639298

Randolph, C. (1998). Repeatable battery for the assessment of neuropsychological status. San Antonio, TX: The Psychological Corporation.

Rorden, C. (2007). Dcm2nii to NIFTI convertor.

Rosano, C., Aizenstein, H. J., Cochran, J. L., Saxton, J. A., De Kosky, S. T., Newman, A. B., …Carter, C. S. (2005). Event-related functional magnetic resonance imaging investigation of executive control in very old individuals with mild cognitive impairment. *Biological Psychiatry, 57*, 761-767. doi: 10.1016/j.biopsych.2004.12.031

Sperling, R. A., Dickerson, B. C., Pihlajamaki, M., Vannini, P, LaViolette, P. S., Vitolo, O. V., . . . Johnson, K. A. (2010). Functional Alterations in Memory Networks in Early Alzheimer's Disease. *NeuroMolecular Medicine, 12,* 27-43.

Staffen, W., Ladurner, G., Holler, Y, Bergmann, J., Alchhorn, M., Golaszewski, S., & Kronbichler, M. (in press). Brain activation disturbance for target detection in patients with mild cognitive impairment: an fMRI study. *Neurobiology of Aging.*

Tabert, M. H., Manly, J. J., Liu, X., Pelton, G., H., Roseblum, S., Jacobs, M., . . . Devanan, D. P. (2006). Neuropsychological Prediction of Conversion to Alzheimer Disease in Patients with Mild Cognitive Impairment. *Archives of General Psychiatry, 63,* 916-924.

Traykov, L., Raoux, N., Latour, F., Gallo, L., Hanon, O., Baudic, S., . . . Rigaud, A. S. (2007). Executive Functions Deficit in Mild Cognitive Impairment. *Cognitive and Behavioral Neurology, 20,* 219-224.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., . . . Joliot, M. (2002). Automated Anatomical Labeling of Activations in SPM Using a Macroscropic Anatomical Parcellation of the MNI MRI Single – Subject Brain. *Neuroimage, 15,* 273-289.

Wilson, R. S., Leurgans, S. E., Boyle, P. A., & Bennett, D. A. (2011). Cognitive Decline in Prodromal Alzheimer Disease and Mild Cognitive Impairment. *Archives of Neurology, 68*, 351-356. doi: 10.1001/archneurol.2011.31

Wimo, A., Winblad, B., & Jönsson, L. (2010). The worldwide societal costs of dementia: Estimates for 2009. *Alzheimer's and Dementia, 6*, 98-103. doi: 10.1016/j.jalz.2010.01.010

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L. O., . . . Petersen, R. C. (2004). Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *Journal of Internal Medicine, 256*, 240-246.

Wylie, S. A., Ridderinkhof, K. R., Eckerle, M. K., & Manning, C. A. (2007). Inefficient response inhibition in individuals with mild cognitive impairment. *Neuropsychologia, 45,* 1408-1419. doi: :10.1016/j.neuropsychologia.2006.11.00

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., & Leirer, V. O. (1983). Development and Validation of a Geriatric Depression Screening Scale: A Preliminary Report. *Journal of Psychiatric Research, 17,* 37-49.

Zamrini, E., Santi, S. D., & Tolar, M. (2004). Imaging is superior to cognitive testing for early diagnosis of Alzheimer’s diesase. *Neurobiology of Aging, 25,* 685-691. doi:10.1016/j.neurobiolaging.2004.02.009

Table 3.1 Group Demographics

	Normal Controls (N = 26)	MCI (N=17)
Age	74 (5.5)	75 (6.3)
Years of Education*	17 (2.3)	14.4 (3.4)
Gender (M, FM)	10, 16	7, 10
Handedness (R, L)	23, 3	17
Hx of Diabetes	1	3
Family Hx of AD	8	4
GDS	6.4 (5)	6.4 (4.2)
SPPB	8.9 (2.5)	9.7 (2.3)

Hx = History; AD = Alzheimer's Disease; GDS = Geriatric Depression Scale; SPPB = Short Battery of Physical Performance
*Significant group differences between groups $p < .05$

Table 3.2 Neuropsychological Performance

Measure	Normal Controls	MCI	P-Value
MMSE*	28.0 (2; 23-30)	25.9 (2.4; 19-30)	.004
DKEFS#4	10.0 (3.1; 1-15)	7.3 (4.3; 1-13)	.015
DKEFS#5	10.0 (3.2; 1-14)	7.9 (3.5; 1-12)	.055
RBANS*	103.5 (14.4; 82-145)	86.9 (14.6; 59-120)	.000
*IM**	103.2 (17.5; 61-132)	86.05 (14.9; 57-109)	.006
VS	103.9 (11; 84-126)	95.5 (17.3; 64-126)	.028
*LA**	102.5 (10; 88-125)	89.3 (17.3; 40-117)	.001
ATN	107.5 (17.2; 79-138)	95 (13.4; 64-115)	.042
*DM**	103.5 (13.3; 75-137)	86.9 (19.9; 44-110)	.005

MMSE = Mini-Mental State Examination; DKEFS #4 = Delis-Kaplan Executive Function System Trail Making Test Condition 4; DKEFS #5 = Delis-Kaplan Executive Function System Trail Making Test Condition 5; RBANS = Repeatable Battery for the Assessment for Neuropsychological Status; IM = Immediate Memory; VS = Visuospatial/constructional ability; LA = Language; ATN = Attention; DM = Delayed Memory
RBANS Index scales are italicized.
MMSE values are raw scores, and have a minimum of 0 and maximum of 30.
DKEFS#4 and #5 values are scaled scores with a mean of 10 and standard deviation of 3.
RBANS indices values are standard scores with a mean of 100 and standard deviation of 15.
Values are mean & (SD; range)
* Significant group differences between groups $p < .01$

Table 3.3 Behavioral performance on Stroop task

Condition		Normal	MCI	P-Value
Congruent	ACC	.99 (.12)	.98 (.03)	.271
	RT	837.5 (131.1)	864.8 (167.9)	.553
Neutral	ACC	.99 (.01)	.98 (.02)	.026
	RT	851.7 (100.8)	894.6 (173.5)	.310
Incongruent	ACC	.97 (.05)	.92 (.11)	.087
	RT	1084.6 (182)*	1173.5 (337.7)*	.331

ACC = Accuracy; RT = Reaction Time
Accuracy values are in percentiles.
Reaction time values are in milliseconds.
Values are mean & (SD)
* Significant differences between Inc & Con RT within groups $p < .01$

Table 3.4
Brain Regions activated to a greater degree by MCI – Normals ROI analyses

Cluster	Maxima X	Y	Z	Region	Extent	Mean T
1	36	11	61	R Middle Frontal Gyrus	43	2.7
				R Superior Frontal Gyrus	5	2.6
2	-45	17	15	L Inferior Frontal Gyrus Opercular	19	2.6

Threshold was P < .01, extent ≥ 8 voxels

Table 3.5 Brain regions activated during inhibition across all participants; Incongruent > Congruent WB analyses

Group	Cluster	Maxima X	Y	Z	Regions	Extent	Mean T
All Participants	1	-44	2	36	L Precentral Gyrus	1844	6.6
					L Inferior Frontal Gyrus Triangular	1678	6.6
					L Inferior Frontal Gyrus Opercular	764	6.4
					L Middle Frontal Gyrus	268	6.0
					L Rolandic Operculum	114	6.0
					L Superior Temporal Pole	91	6.0
					L Superior Frontal Gyrus	21	5.8
					L Insula	17	5.8
					L Middle Frontal Gyrus Orbital	4	5.8
					L Inferior Frontal Gyrus Orbital	1	5.8
					L Temporal Superior Gyrus	1	5.8
	2	-32	-53	47	L Inferior Parietal lobule	1376	6.7
					L Superior Parietal Gyrus	895	6.5
					L Precuneus	539	6.6
					L Middle Occiptal Gyrus	264	6.0
					L Angular Gyrus	42	6.4
					L Supramarginal Gyrus	32	6.0
					R Superior Parietal Gyrus	2	5.8
	3	-2	14	44	L Supplementary Motor Area	635	6.3
					R Supplementary Motor Area	125	6.0
					R Middle Cingulate Gyrus	84	6.0
					L Middle Cingulate Gyrus	82	6.2
					L Superior Medial Frontal Gyrus	38	6.3
					R Superior Medial Frontal Gyrus	2	5.7
	4	-15	-14	18	L Thalamus	139	6.2
					L Caudate Nucleus	76	6.2
	5	35	-2	63	R Superior Frontal Gyrus	26	5.9
					R Middle Frontal Gyrus	26	6.1
	6	48	14	-6	R Insula	36	6.0
					R Inferior Frontal Gyrus Opercular	12	5.8
					R Superior Temporal Pole	6	5.6
					R Rolandic Operculum	3	5.7
					R Inferior Frontal Gyrus Orbital	2	5.8
	7	23	-14	6	R Thalamus	5	5.7
	8	42	30	29	R Inferior Frontal Gyrus Triangular	68	5.8
					R Middle Frontal Gyrus	52	5.9
	8	-39	-83	2	L Middle Occipital Gyrus	72	5.9
					L Inferior Occipital Gyrus	16	5.8
	10	24	-71	50	R Superior Parietal Gyrus	70	5.8
	11	-23	-11	3	L Lenticular Nucleus Pallidum	19	5.8
					L Lenticular Nucleus Putamen	2	5.7
					L Thalamus	2	5.8
	12	-41	32	35	L Middle Frontal Gyrus	15	5.8
Normal OA	1	-2	14	44	L Supplementary Motor Area	874	6.5
					R Supplementary Motor Area	227	6.4
					R Middle Cingulum	104	6.4
					L Middle Cingulum	58	6.3
					L Superior Medial Frontal Gyrus	32	6.3
					L Superior Frontal Gyrus	27	6.0
	2	-44	0	35	L Precentral Gyrus	567	6.6
					L Middle Frontal Gyrus	14	6.0
					L Inferior Frontal Gyrus Opercular	6	5.9
	3	-6	-72	53	L Precuneus	176	6.3
	4	-38	-3	51	L Precentral Gyrus	255	6.2
					L Middle Frontal Gyrus	100	6.1
					L Superior Frontal Gyrus	27	6.0
					L Supplementary Motor Area	5	5.8
	5	-32	-54	47	L Inferior Parietal Lobule	177	6.1
					L Superior Parietal Gyrus	26	5.8
	6	-48	38	9	L Inferior Frontal Gyrus Triangular	161	5.9
	7	-14	-14	17	L Thalamus	10	5.8
MCI	1	-51	-70	-11	L Inferior Occipital Gyrus	37	8.2
					L Inferior Temporal Gyrus	10	7.8
	2	-44	-77	-5	L Inferior Occipital Gyrus	51	7.6
	3	-23	-59	44	L Superior Parietal Gyrus	13	7.3
					L Middle Occipital Gyrus	1	7.1
	4	-44	18	15	L Inferior Frontal Gyrus Triangular	4	7.1
					L Inferior Frontal Gyrus Opercular	9	7.2

Threshold for all participants was $P < .01$, FWE corrected. For Normal and MCI groups $P < .05$, FWE corrected. Both had minimum number of voxels ≥ 8. Regions were identified with the AAL atlas in MNI space. Clusters are in descending order according to peak activation level of maxima.

Figure 3.1. Example of Stroop task progression. Each experimental condition, neutral, congruent, and incongruent presents randomly selected stimuli for 2.5s, and is followed by a blank screen without experimental stimuli and a space separator for 0.5s. There was a total of 192 3s events.

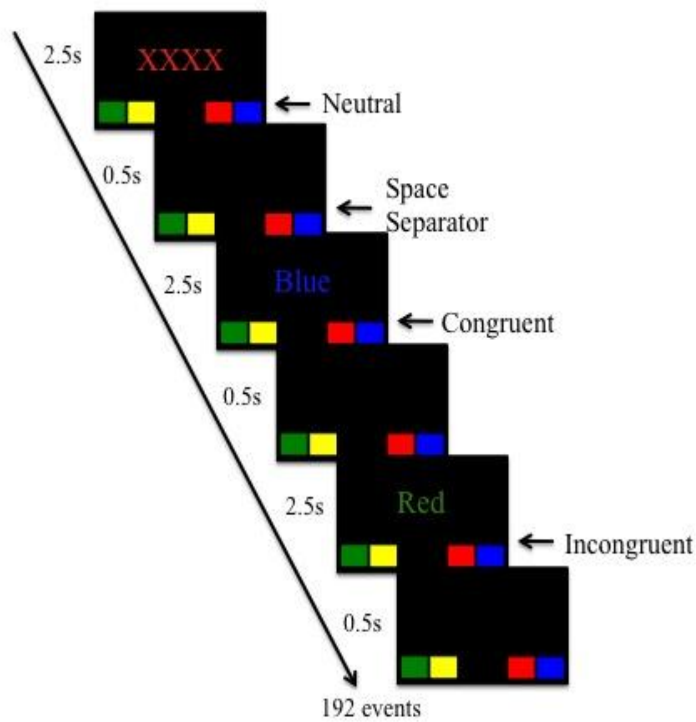


Figure 3.2
Accuracy of both groups for all conditions

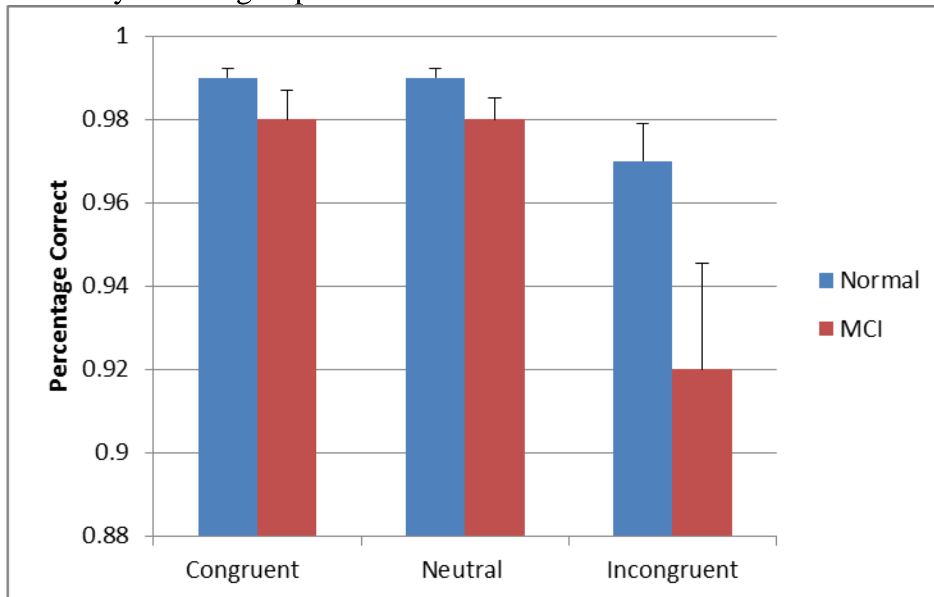


Figure 3.3
Reaction time of both groups for all conditions

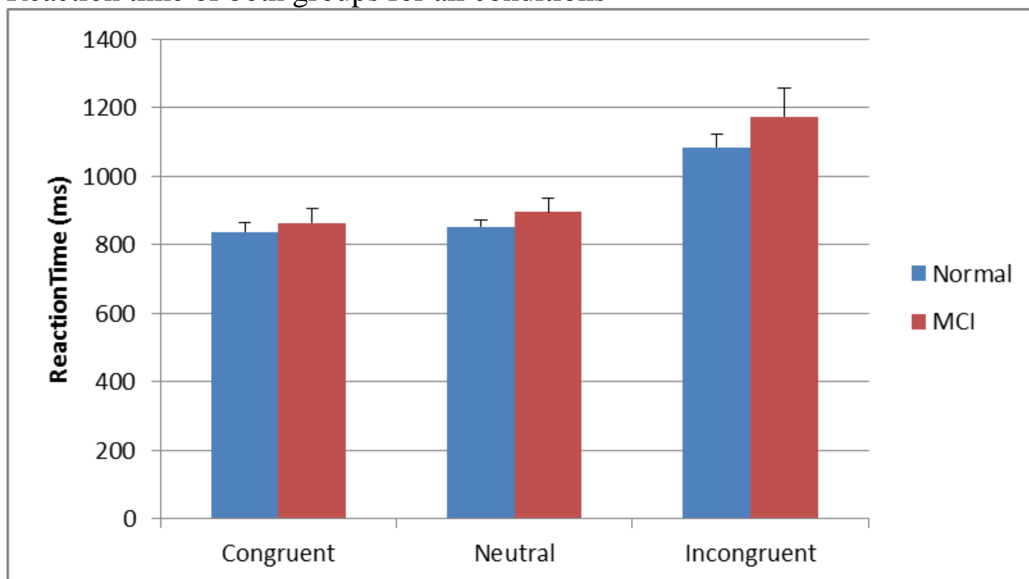
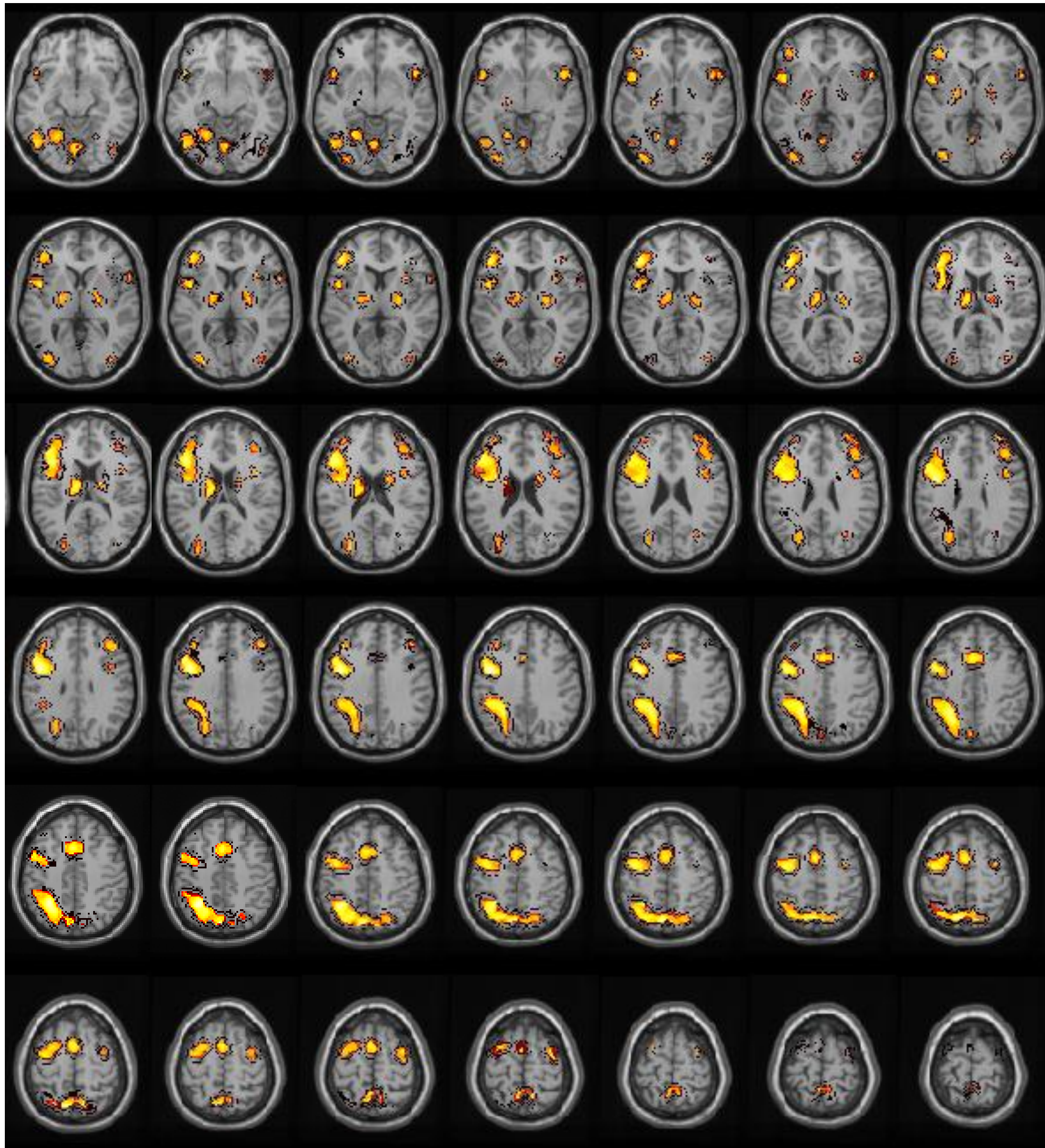


Figure 3.4
Brain regions activated during inhibition across all participants; Incongruent > Congruent WB analyses



CHAPTER 4

DISCUSSION

The aim of this thesis was to compare functional activation during inhibition in normal older adults (OA) and OA with mild cognitive impairment (MCI). Even though there is a substantial amount of evidence suggesting inhibition is compromised in OA with MCI (Belanger, Belleville, & Gautheir, 2010; Irish, Lawlor, Coen, & O'Mara, 2011; Kramer et al., 2006; Traykov et al., 2007; Wylie, Ridderinkhof, Eckerle, & Manning, 2007), there are only a limited amount of small investigations examining functional activation differences during inhibition between OA with MCI and normal OA (Kaufmann et al., 2008; Li et al., 2009; Rosano et al., 2005; Staffen et al., 2011). Besides one study (i.e., Staffen et al., 2011) all reported greater activation in OA with MCI compared to normal OA. Despite limitations associated with these studies including: small sample sizes and liberal statistical procedures it was hypothesized OA with MCI would have greater activation in ROIs.

Results did not support the hypothesis, and there were no between group differences with multiple test corrected threshold (i.e., FWE). However, post-hoc analyses with uncorrected thresholds indicated the MCI group had greater activation in two clusters in the prefrontal cortex. These results are parallel with the perspective that greater activation in OA with MCI may aid performance (Dickerson & Sperling, 2008). These between group findings, however, should be viewed with substantial caution due to the lack of correction.

The interpretation of uncorrected thresholds is likely one of the reasons accounting for the discrepancy between this investigation’s conclusion and previous fMRI studies. All studies

that found greater activation in MCI during inhibition did not use corrected thresholds for between group comparisons. Other methodological differences between studies may also account for different conclusions. These differences include analyzing data associated with processes other than inhibition, type of experimental design and statistical analyses. Li et al. (2009) did not report behavioral data during scanning, and Kaufmann et al. (2008) and Rosano et al. (2005) included functional data associated with failed inhibition in final analyses. Additionally, Li et al. (2009) and Kaufmann et al. (2008) used a block design, which decreases an individuals prepotent response (i.e., read the color word) and thus less representative of inhibition. Greater functional activation in MCI during inhibition may also be due to between group comparisons with local maxima in ROI instead of the mean magnitude from these areas (Rosano et al., 2005).

To ensure reliable neural activity was occurring during inhibition, and null results were not due to a lack of activation during inhibition, within group analyses were completed. Across all participants functional activation was found in areas typically engaged in inhibition in OA including the DLPFC, OFC and PPC as well as motor and visual regions. This suggests the contrast of interest (i.e., incongruent – congruent) required participants to engage in inhibition.

Behavioral performance on the fMRI task also suggested participants were engaged in inhibition. Both groups were slower to respond during the incongruent compared to the congruent condition. However, similar to functional data there was no behavioral differences between groups on the fMRI task, and the study’s hypothesis about behavioral performance was not supported. However, there was a trend in all conditions of the Stroop task for OA with MCI to be less accurate and slower. Thus, no between group differences on the Stroop Task, may be

due to power given the number of participants (N = 43) included is relatively small for a behavioral investigation.

In contrast to fMRI results, OA with MCI performed significantly worse on several neuropsychological measures, including ones of global cognition, memory, and language. These findings are consistent with the literature, supporting the perspective that MCI is reliably identified by neuropsychological measures. Taken together with fMRI results, these findings suggest OA with MCI are best detected by traditional neuropsychological techniques.

More research will be necessary to examine the relationship between functional activation in OA with MCI and normal OA. Future research should use equal sample sizes, which were not used in this study and is a limitation. The use of an event related design could also be considered a limitation as they are associated with decreased signal-to-noise ratio (Bandettini & Cox, 2000; Miezin, Maccotta, Ollinger, Petersen, & Buckner, 2000). The decreased signal to noise ratio is likely related to the fact that when deconvolving the fMRI in event related designs trials/conditions (e.g., baseline) not associated with the signal response show an increased response and the signal associated with the event is truncated (Bandettini & Cox, 2000). It is therefore, not surprising then that block design paradigms have greater percent signal change compared to event related designs.

At the same time the use of an event related design could be viewed as a strength given it provides an ecological measure of inhibition. In contrast, block designs present stimuli requiring inhibition consecutively, which decreases the “load” on the pre-potent response and allows participants to prepare to inhibit and over time habituate to the pre-potent response.

There were several additional strengths of this study, including the number of participants, which is greater than all previous fMRI investigations of inhibition comparing OA

with MCI and normal OA. An additional strength was that functional data associated with errors was not included, ensuring activation was due to successful and not failed inhibition.

Neuroimaging has the potential to aid clinicians with detecting pathological aging before clinical symptoms are present (Bondi, Houston, Eyler, & Brown, 2005; Bookheimer et al., 2000; Filippini et al., 2009; Han et al., 2007). However, fMRI of inhibition was not able to distinguish OA with MCI, but neuropsychological measures were able to identify OA with MCI. This finding is consistent with the perspective that neuroimaging is not always sensitive to detecting the beginning stages of neurodegenerative diseases and is not a biomarker (Albert et al., 2011; Marcotte, Scott, Kamat, & Heaton, 2010). Future fMRI investigations are required to clarify the relationship between functional activation due to inhibition in OA with MCI and determine if fMRI as a tool in general can reliably identify this valuable clinical syndrome.

REFERENCES

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., . . . Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's and Dementia, 7*, 270-279. doi: 10.1016/j.jalz.2011.03.008

Alzheimer's Association (2011). Alzheimer's disease facts and figures. *Alzheimer's and Dementia, 7*, 208-244. doi: 10.1016/j.jalz.2011.02.004

American Bar Association/American Psychological Association Assessment of Capacity in Older Adults Project Working Group. (2008). *Assessment of Older Adults with Diminished Capacity: A Handbook for Psychologists.* Retrieved from http://www.apa.org/pi/aging/programs/assessment/capacitypsychologist handbook.pdf

Alzheimer's Disease International. (2008, December). *The prevalence of dementia worldwide.* Retrieved from http://www.alz.co.uk/adi/pdf/prevalence.pdf.

American Psychiatric Association. (2004). *Diagnostic and Statistical Manual of Mental Disorders Text Revision* (4th ed.). Arlington, VA: American Psychiatric Publishing, Inc.

Appell, J., Kertesz, A., & Fisman, M. (1982). A study of language functioning in Alzheimer patients. *Brain and Language, 17*, 73-91. doi: 10.1016/0093-934x(82)90006-2

Appollonio, I., Carabellese, C., Fratolla, L. F., & Trabucchi, M. (1996). Effects of Sensory Aids on the Quality of Life and Mortality of Elderly People: A Multivariate Analysis. *Age and Aging, 25,* 89-96. doi: 10.1093/ageing/25.2.89

Balota, D. A., Dolan, P. O., & Duchek, J. M. (2000). Memory changes in healthy older adults. In E. Tulving & F. I. M. Craik (Eds.), *The Oxford hanbook of memory*. New York, NY: Oxford University Press.

Bandettini, P. A., & Cox, R. W. (2000). Event-related fMRI contrast when using constant interstimulus interval: theory and experiment. *Magnetic Resonance in Medicine, 43,* 440-548.

Bashore, T., Ridderinkhof, K. R., & van der Molen, M. W. (1997). The Decline of Cognitive Processing Speed in Old Age. *Current Directions in Psychological Science, 6,* 163-169. doi: 10.1111/1467-8721.ep10772944

Baudic, S., Barba, G. D., Thibaudet, M. C., Smagghe, A., Remy, P., & Traykov L. (2006). Executive function deficits in early Alzheimer's disease and their relations with episodic memory. *Archives of Clinical Neuropsychology, 21*, 15–21.

Bertram, L., & Tanzi, R. E. (2005). The genetic epidemiology of neurodegenerative disease. *The Journal of Clinical Investigation, 115*, 1449-1457.

Bertram, L., & Tanzi, R. E. (2008). Thirty years of Alzheimer's disease genetics: the implications of systematic meta-analyses. *Nature Reviews Neuroscience, 9*, 768-778. doi: 10.1038/nrn2494

Bigler, E. D., Andersob, C. V., & Blatter, D. D. (2002). Temporal Lobe Morphology in Normal Aging and Traumatic Brain Injury. *American Journal of Neuroradiology 23*, 255-266.

Binetti, G., Cappa, S., F., Magni, E., Padovani, A., Bianchetti, A., & Trabucchi, M. (1998). Visual and spatial perception in the early phase of Alzheimer's diease. *Neuropsychology, 12,* 29-33. doi: 10.1037/0894-4105.12.1.29

Bondi, M. W., Houston, W. S., Eyler, L. T., & Brown, G. G. (2005). fMRI evidence of compensatory mechanisms in older adults at genetic risk for Alzheimer disease. *Neurology, 64*, 501-508. doi: 10.1212/01.wnl.0000150885.00929.7e

Boyle, P. (2004). Assessing and predicting functional impairment in Alzheimer's disease: The emerging role of frontal system dysfunction. *Current Psychiatry Reports, 6*, 20-24. doi: 10.1007/s11920-004-0033-9

Braak, E., Griffing, K., Arai, K., Bohl, J., Bratzke, H., & Braak, H. (1999). Neuropathology of Alzheimer's disease: what is new since A. Alzheimer? *European Archives of Psychiatry and Clinical Neuroscience, 249*, 14-22.

Caballol, N., Martí, M. J., & Tolosa, E. (2007). Cognitive dysfunction and dementia in Parkinson disease. *Movement Disorders, 22*, 358-366. doi: 10.1002/mds.21677

Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: The HAROLD model. *Psychology and Aging, 17*, 85-100. doi: 10.1037/0882-7974.17.1.85

Cabeza, R., Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging Gracefully: Compensatory Brain Activity in High-Performing Older Adults. *NeuroImage, 17*, 1394-1402. doi: 10.1006/nimg.2002.1280

Cahn-Weiner, D. A., Malloy, P. F., Boyle, P. A., Marran, M., & Salloway, S. (2000). Prediction of functional status from neuropsychological tests in community-dwelling elderly individuals. *The Clinical Neuropsychologist, 14*, 187-195.

Cahn-Weiner, D. A., Ready, R. E., & Malloy, P. F. (2003). Neuropsychological predictors of everyday memory and everyday functioning in patients with mild Alzheimer's disease. *Journal of Geriatric Psychiatry & Neurology, 16*, 84–89.

Carlson, N. (2010). *Physiology of Behavior* (10th ed.). Boston, MA: Allyn & Bacon.

Cavanaugh, J. C., & Blanchard-Fields, F. (2006). *Adult development and aging*. Belmont, NJ: Thomson Wadsworth.

Chaves, M. L., Camozzato, A. L., Godinho, C., Kockhann, R., Schuh A., & de Almeida, V. L. (2007). Validity of the Clinical Dementia Rating Scale for the Detection and Staging of Dementia in Brazilian Patients. *Alzheimer Disease & Associated Disorders, 21*, 210-217.

Chen, S. T., Sultzer, D. L., Hinkin, C. H., Mahler, M. E., & Cummings, J. L. (1998) Executive Dysfunction in Alzheimer's Disease: Association With Neuropsychiatric Symptoms and Functional Impairment. *Journal of Neuropsychiatry & Clinical Neurosciences, 10*, 426-432.

Christensen, H. (2001). What cognitive changes can be expected with normal ageing? *The Australian and New Zealand Journal of Psychiatry, 35,* 768-775. doi

Collette, F., Vanderlinden, M., & Salmon, E. (1999). Executive Dysfunction in Alzheimer's Disease. *Cortex, 35*, 57-72. doi: 10.1016/s0010-9452(08)70785-8

Craik, F. I. M. (1994). Memory Changes in Normal Aging. *Current Directions in Psychological Science 3*, 155-158. doi: 10.1111/1467-8721.ep10770653

Cummings, J. L. (2006). Definitions and diagnostic criteria. In S. Gauthier (Ed.), *Clinical Diagnosis and Management of Alzheimer's Disease* (3rd ed., pp. 3-14). London, UK: Informa Healthcare.

Davis, S. W., Dennis, N. A., Daselaar, S. M., Fleck, M. S., & Cabeza, R. (2007). Que PASA? The Posterior-Anterior Shift in Aging. *Cerebral Cortex, 18*, 1201-1209. doi: 10.1093/cercor/bhm155

de Rover, M., Pironti, V. A., McCabe, J. A., Acosta-Cabronero, J., Arana, F. S., Morein-Zamir, S, . . . Sahakian, B. J. (2011). Hippocampal dysfunction in patients with mild cognitive

impairment: A functional neuroimaging study of a visuospatial paried associates learning task. *Neuropsychologia, 49,* 2060-2070.

DeCarli, C. (2003). Mild cognitive impairment: prevalence, prognosis, aetiology, and treatment. *The Lancet Neurology, 2*, 15-21. doi: 10.1016/s1474-4422(03)00262-x

Decarli, C., Massaro, J., Harvey, D., Hald, J., Tullberg, M., Au, R., . . . Wolf, P. (2005). Measures of brain morphology and infarction in the framingham heart study: establishing what is normal. *Neurobiology of Aging, 26*, 491-510. doi: 10.1016/j.neurobiolaging.2004.05.004

Delis, D., Kaplan, E., & Kramer, J. (2001). Delis-Kaplan Executive Function System. The Psychological Corporation, San Antonio, TX: Harcourt Brace & Company.

Dickerson, B. C., Salat, D. H., Greve, D. N., Chua, E.F., Rand-Giovannetti, E., Rentz, D. M., … Sperling, R. A. (2005). Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. *Neurology, 65*, 404–411

Dickerson, B., & Sperling, R. (2008). Functional abnormalities of the medial temporal lobe memory system in mild cognitive impairment and Alzheimer's disease: Insights from functional MRI studies. *Neuropsychologia, 46*, 1624-1635. doi: 10.1016/j.neuropsychologia.2007.11.030

Dobbs, A. R., & Rule, B. G. (1989). Adult age differences in working memory. *Psychology and Aging, 4*, 500-503. doi: 10.1037/0882-7974.4.4.500

Dura, J. R., Stukenberg, K. W., & Kiecolt-Glaser, J. K. (1991). Anxiety and depressive disorders in adult children caring for demented parents. *Psychology and Aging, 6*, 467-473. doi: 10.1037/0882-7974.6.3.467

Elderkin-Thompson, V., Ballmaier, M., Hellemann, G., Pham, D., & Kumar, A. (2008). Executive function and MRI prefrontal volumes among healthy older adults. *Neuropsychology, 22*, 626-637. doi: 10.1037/0894-4105.22.5.626

Elgh, E., Lindqvist Åstot, A., Fagerlund, M., Eriksson, S., Olsson, T., & Näsman, B. (2006). Cognitive Dysfunction, Hippocampal Atrophy and Glucocorticoid Feedback in Alzheimer's Disease. *Biological Psychiatry, 59*, 155-161. doi: 10.1016/j.biopsych.2005.06.017

Emre, M. (2003). Dementia associated with Parkinson's disease. *The Lancet Neurology, 2*, 229-237. doi: 10.1016/s1474-4422(03)00351-x

Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G*power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods, 39*, 175-191.

Filippini, N., MacIntosh, B. J., Hough, M. G., Goodwin, G. M., Frisoni, G. B., Smith, S. M., . . . Mackay, C. E. (2009). Distinct patterns of brain activity in young carriers of the APOE ε-4 allele. *Proceedings of the National Academy of Sciences of the United States of America, 106,* 7209-7214.

Fischer, P., Jungwirth, S., Zehetmayer, S., Weissgram, S., Hoenigschnabl, S., Gelpi, E., . . . Tragl, K. H. (2007). Conversion from subtypes of mild cognitive impairment to Alzheimer dementia. *Neurology, 68*, 288-291. doi:10.1212/01.wnl.0000252358.03285.9d

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*, 189-198.

Fratiglioni, L., Winblad, B., & Vonstrauss, E. (2007). Prevention of Alzheimer's disease and dementia. Major findings from the Kungsholmen Project. *Physiology & Behavior, 92*, 98-104. doi: 10.1016/j.physbeh.2007.05.059

Galasko, D. , Schmitt, F., Thomas, R., Jin, S., Bennett, D., & Ferris, S. (2005). Detailed assessment of activities of daily living in moderate to severe Alzheimer's disease. *Journal of the International Neuropsychological Society, 11*, 446-453. doi: 10.1017/S1355617705050502

Gates, G., & Mills, J. (2005). Presbycusis. *The Lancet, 366*, 1111-1120. doi: 10.1016/s0140-6736(05)67423-5

Golde, T. E. (2003). Alzheimer disease therapy: Can the amyloid cascade be halted? *Journal of Clinical Investigation, 111*, 11-18. doi: 10.1172/jci200317527

Golde, T. E., Eckman, C. B., & Younkin, S. G. (2000). Biochemical detection of Abeta isoforms: implications for pathogenesis, diagnosis, and treatment of Alzheimer's disease. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1502*, 172-187. doi: 10.1016/s0925-4439(00)00043-0

Gómez-Isla, T., Hollister, R., West, H., Mui, S., Growdon, J. H., Petersen, R. C., . . . Hyman, B. T. (1997). Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. *Annals of Neurology, 41*, 17-24. doi: 10.1002/ana.410410106

Greene, J. D. W., Hodges, J. R., & Baddeley, A. D. (1995). Autobiographical memory and executive function in early dementia of Alzheimer type. *Neuropsychologia, 33,* 1647-1670. doi: 10.1016/0028-3932(95)00046-1

Grigsby, J., Kaye, K., & Robbins, L. J. (1995). Behavioral disturbance and impairment of executive functions among the elderly. *Archives of Gerontology Geriatrics, 21*, 167-177. doi: 016749439500636Y

Grossman, M., Koenig, P., DeVita, C., Glosser, G., Moore, P., Gee, J., . . . Alsop, D. (2003). Neural Basis for Verb Processing in Alzheimer's Disease: An fMRI Study. *Neuropsychology, 17*, 658-674. doi: 10.1037/0894-4105.17.4.658

Gunning-Dixon, F. M., Brickman, A. M., Cheng, J. C., & Alexopoulos, G. S. (2009). Aging of cerebral white matter: a review of MRI findings. *International Journal of Geriatric Psychiatry, 24*, 109-117. doi: 10.1002/gps.2087

Guralnik, J. M., Simonsick, E. M., Ferrucci, L., Glynn, R. J., Berkman, L. F., Blazer, D. G., & Wallace, R. B. (1994). *Journal of Gerontology, 49,* M85-M94.

Hämäläinen, A., Pihlajamaki, M., Tanila, H., Hanninen, T., Niskanen, E., Tervo, S., … Soininen, H. (2007). Increased fMRI responses during encoding in mild cognitive impairment. *Neurobiology of Aging, 28*, 1889–1903.

Han, S. D., Bangen, K. J., & Bondi, M. W. (2009). Functional Magnetic Resonance Imaging of Compensatory Neural Recruitment in Aging and Risk for Alzheimer's Disease: review and recommendations. *Dementia and Geriatric Cognitive Disorders, 27*, 1-10. doi: 10.1159/000182420

Hardy, J. A., & Higgins, G. A. (1992). Alzheimer's disease: the amyloid cascade hypothesis. *Science, 256*, 184-185. doi: 10.1126/science.1566067

Harman, D. (1981). The aging process. *Proceedings of the National Academy of Sciences of the United States of America, 78*, 7124-7128.

Hodges, J. R., & Patterson, K. (1995). Is semantic memory consistently impaired early in the course of Alzheimer's disease? Neuroanatomical and diagnostic implications. *Neuropsychologia, 33*, 441–459

Huettel, S. A., Song, A. W., & McCarthy, G. (2008). *Functional Magnetic Resonance Imaging* (2nd ed.). Sunderland, MA: Sinauer Associates, Inc.

Hughes, C. P, Berg, L, Danziger, W. L, Coben, L. A, & Martin, R. L. (1982). A new clinical scale for the staging of dementia. *The British Journal of Psychiatry, 140*, 566-572. doi: 10.1192/bjp.140.6.566

Ichikawa, H., Koyama, S., Ohno, H., Ishihara, K., Nagumo, K., & Kawamura, M. (2008). Writing errors and anosognosia in amyotrophic lateral sclerosis with dementia. *Behavioural Neurology, 19*, 107-116.

Jackson, G., & Owsley, C. (2003). Visual dysfunction, neurodegenerative diseases, and aging. *Neurologic Clinics, 21*, 709-728. doi: 10.1016/s0733-8619(02)00107-x

Jacobs, B., Driscoll, L., & Schall, M. (1997). Life-span dendritic and spine changes in areas 10 and 18 of human cortex: A quantitative golgi study. *The Journal of Comparative Neurology, 386*, 661-680. doi: 10.1002/(sici)1096-9861

Jankovic, J. (2008). Parkinson's diesease: clinical features and diagnosis. *The Journal of Neurology, Neurosurgery, & Psychiatry, 79,* 368-376. doi: :10.1136/jnnp.2007.13104

Jefferson, A., Paul, R., Ozonoff, A., & Cohen, R. (2006). Evaluating elements of executive functioning as predictors of instrumental activities of daily living (IADLs). *Archives of Clinical Neuropsychology, 21*, 311-320. doi: 10.1016/j.acn.2006.03.007

Jernigan, T. L., Archibald, S. L., Fennema-Notestine, C., Gamst, A. C., Stout, J. C., Bonner, J., & Hesselink, J. R. (2001). Effects of age on tissues and regions of the cerebrum and cerebellum. *Neurobiology of Aging, 22*, 581-594. doi: 10.1016/s0197-4580(01)00217-2

Kao, M., Mandal, A., Lazar, N., & Stufken, J. (2009). Multi-objective optimal experimental designs for event-related fMRI studies. *NeuroImage, 44*, 849-856.

Kaufmann, L., Ischebeck, A., Weiss, E., Koppelstaetter, F., Siedentopf, C., Vogel, S. E., . . . Wood, G. (2008). An fMRI study of the numerical Stroop task in individuals with and without minimal cognitive impairment. *Cortex, 44*, 1248-1255. doi: 10.1016/j.cortex.2007.11.009

Kawas, C., Resnick, S., Morrison, A., Brookmeyer, R., Corrada, M., Zonderman, A., . . . Metter, E. (1997). A Prospective Study of Estrogen Replacement Therapy and the Risk of Developing Alzheimer's Disease: The Baltimore Longitudinal Study of Aging. *Obstetrical & Gynecological Survey, 52*, 694-695.

Khan, M. T. (2009). *The Effects of Ageing on Driving Related Performance.* Ph.D Dissertation, University of Southampton, Southhampton. Retrieved from http://eprints.soton.ac.uk/73700/1/Thesis_tariq_final.pdf

Kinsella, K. & Wan, H. (2009). *U.S. Census bureau: international population reports An Aging World: 2008.* Washington, DC: U.S. Government Printing Office.

Kirby, E., Bandelow, S., & Hogervorst, E. (2010). Visual Impairment in Alzheimer's Disease: A Critical Review. *Journal of Alzheimer's Disease, 2*, 15-34. doi: 10.3233/JAD-2010-080785

Kolb, B., & Wishaw, I. Q. (2009). *Fundamentals of Human Neuropsychology*. New York, NY: Worth Publishers.

Lafleche, G., & Albert, M. S. (1995). Executive Function Deficits in Mild Alzheimer's Disease. *Neuropsychology, 9*, 313-320.

Laine, M., Tuokkola, T., Hiltunen, J., Vorobyez, V., Bliss, l., Baddeley, A., & Rinne, J. O. (2009). Central executive function in mild cognitve impairment: A PET activation study: Cognition and Neurosciences. *Scandinavian Journal of Psychology, 50*, 33-40.

Larsen, P. (2009). A Review of Cardiovascular Changes in the Older Adult: Access Research Network.

Launer, L. J., Andersen, K., Dewey, M. E., Letenneur, L., Ott, A., Amaducci, L. A., . . . Hofman, A. (1999). Rates and risk factors for dementia and Alzheimer's disease: Results from EURODEM pooled analyses. *Neurology, 52*, 78-84.

Letenneur, L., Gilleron, V., Commenges, D., Helmer, C., Orgogozo, J. M., & Dartigues, J. F. (1999). Are sex and educational level independent predictors of dementia and Alzheimer's disease? Incidence data from the PAQUID project. *Journal of Neurology, Neurosurgery & Psychiatry, 66*, 177-183. doi: 10.1136/jnnp.66.2.177

Lewis, M., & Miller, L. S. (2007). Executive Control Functioning and Functional Ability in Older Adults. *The Clinical Neuropsychologist, 21*, 274-285. doi: 10.1080/13854040500519752

Lezak, M., Howieson, D. B., & Loring, D. W. (2004). *Neuropsychological Assessment* (4th ed.). New York, NY: Oxford University Press.

Li, C., Zheng, J., Wang, J., Gui, L., & Li, C. (2009). An fMRI Stroop Task Study of Prefrontal Cortical Function in Normal Aging, Mild Cognitive Impairment, and Alzheimer's Disease. *Current Alzheimer Research, 6*, 525-530. doi: 10.2174/156720509790147142

Lindh, W. Q., Pooler, M. S., Tamparo, C. D., & Dahl, B. M. (2009). *Delmar's Clinical Medical Assisting* (4th ed.). Clifton Park, NY: Cengage Learning.

Liu, T., Wen, W., Zhu, W., Trollor, J., Reppermund, S., Crawford, J., . . . Sachdev, P. (2010). The effects of age and sex on cortical sulci in the elderly. *NeuroImage, 51*, 19-27. doi: 10.1016/j.neuroimage.2010.02.016

Llewellyn, D. J., Lang, I. A., Matthews, F. E., Plassman, B. L., Rogers, M. A., Morgenstern, L. B., . . . Langa, K. M. (2010). Vascular health, diabetes, APOE and dementia: the Aging, Demographics, and Memory Study (2010). *Alzheimer's Research & Therapy, 2*, 1-8. doi: 10.1186/alzrt44

Lloyd, S., Cormack, C. N., Blais, K., Messeri, G., McCallum, M. A., Spicer, K., & Morgan, S. (2001). Driving and dementia: a review of the literature. *Canadian Journal of Occupational Therapy, 68*, 149-156.

Lord, S. R., & George, R. S. (2003). Neurophysiological, sensory and motor changes with ageing. In P. Sachdev (Ed.), *The Ageing Brain*. Lisse, NL: Lisse Swets & Zeitlinger.

Lowenstein, D.A., Amigo, E., Duara, R., Guterman, A., Hurwitz, D., Berkowitz, N., . . . Eisdorfer, C. (1989). A New Scale for the Assessment of Functional Status in Alzheimer's Disease and Related Disorders. *Journal of Gerontology, 44*, 114-121. doi: 10.1093/geronj/44.4.P114

Luggen, A. S. (2010). Physiologic Changes with Aging. In M. Bernstein & A. S. Luggen (Eds.), *Nutrition for the Older Adult*. Sudbury, MA: Jones and Bartlett Publishers.

Lustig, C. , Hasher, L. , & Zacks, R. T. (2007). Inhibitory deficit theory: Recent developments in a "new view". In D. S. Gorfein & C. M. MaCLeod (Eds.), *The place of inhibition in cognition* (pp. 145-162). Washington, DC: American Psychological Association.

Mandzia, J. L., McAndrews, M. P. P., Grady, C. L., Graham, S. J., & Black, S. E. (2009). Neural correlates of incidental memory in mild cognitive impairment: An fMRI study. *Neurobiology of Aging, 30,* 717 - 730.

Marcotte, T. D., Scott, J. C., Kamat, R., & Heaton, R. (2010). Neuropsychology and the Prediction of Everyday Functioning. In T. D. Marcotte & I.Grant (Ed.), *Neuropsychology of Everyday Functioning* (pp. 5-39). New York, NY: Guilford Press.

Marin, D. B., Flynn, S., Mare, M., Lantz, M., Hsu, M. A., Laurans, M., … Mohs, R. C. (2001) Reliability and validity of a chronic care facility adaptation of the Clinical Dementia Rating scale. *International Jounral of Geriatric Psychiatry, 16*, 745-750.

MATLAB (Version 6.1.0. 4863a) (2003). Natwick, MA: The Mathworks, Inc.

McKeith, I. G. (2002). Dementia with Lewy bodies. *The British Journal of Psychiatry, 180*, 144-147. doi: 10.1192/bjp.180.2.144

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D. & Stadlan, E.M. (1984). Clinical diagnosis of Alzheimer's disease. Report of the NINCDS—ADRDA work group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, *34,* 939 -944.

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Jr., Kawas, C. H., . . . Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia, 7*, 263-269. doi: 10.1016/j.jalz.2011.03.005

Meguro, K., Constans, J. M., Shimada, M., Yamaguchi, S., Ishizaki, J., Ishii, H., . . . Sekita, Y. (2003). Corpus Callosum Atrophy, White Matter Lesions, and Frontal Executive

Dysfunction in Normal Aging and Alzheimer's Disease. A Community-Based Study: The Tajiri Project. *International Psychogeriatrics, 15*, 9-25. doi: 10.1017/S104161020300872X

Meguro, K., Ishii, H., Yamaguchi, S., Ishizaki, J., Sato, M., Hashimoto, R., . . . Sekita, Y. (2004). Prevalence and Cognitive Performances of Clinical Dementia Rating 0.5 and Mild Cognitive Impairment in Japan: The Tajiri Project. *Alzheimer Disease & Associated Disorders, 18*, 3-10.

Miezin, F. M., Maccotta, L., Ollinger, J. M., Petersen, S. E., & Buckner, R. L. (2000). Characterising the hemodynamic response: effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing. *Neuroimage, 11,* 735-759.

Milham, M. P., Erickson, K. I., Banich, M. T., Kramer, A. F., Webb, A., Wszalek, T., & Cohen, N. J. (2002). Attentional Control in the Aging Brain: Insights from an fMRI Study of the Stroop Task. *Brain and Cognition, 49*, 277-296. doi:10.1006/brcg.2001.1501

Mitchell, M., & Miller, L. S. (2008). Executive Functioning and Observed Versus Self-Reported Measures of Functional Ability. *The Clinical Neuropsychologist, 22*, 471 - 479.

Morris, J. C. (1993). The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology, 43*, 2412-2414. doi: citeulike-article-id:7846480

Morris, J. C. (1997). Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. *International Psychogeriatrics, 9*, 173-176.

Morris, J. C., McKeel, D. W., Fulling, K., Torack, R. M., & Berg, L. (1988). Validation of clinical diagnostic criteria for Alzheimer's diesase. *Annals of Neurology, 24,* 17-22. doi: 10.1002/ana.410240105

Morris, J. C., Storandt, M., Miller, J. P., McKeel, D. W., Price, J. L., Rubin, E. H., & Berg, L. (2001). Mild Cognitive Impairment Represents Early-Stage Alzheimer Disease. *Archives of Neurology, 58*, 397-405. doi: 10.1001/archneur.58.3.397

Naarding, P., Kremer, H. P. H., & Zitman, F. G. (2001). Huntington's disease: a review of the literature on prevalence and treatment of neuropsychiatric phenomena. *European Psychiatry, 16*, 439-445. doi: 10.1016/s0924-9338(01)00604-6

Newman, L. M., Trivedi, M. A., Bendlin, B. B., Ries, M. L., & Johnson, S. C. (2007). The Relationship Between Gray Matter Morphometry and Neuropsychological Performance in a Large Sample of Cognitively Healthy Adults. *Brain Imaging and Behavior, 1*, 3-10. doi: 10.1007/s11682-007-9000-5

Nourhashemi, F., Ousset, P. J., Gillette-Guyonnet, S., Cantet, C., Andrieu, S. & Vellas, B. (2008). A 2-year follow-up of 233 very mild (CDR 0.5) Alzheimer's disease patients. *International Journal of Geriatric Psychiatry, 23*, 460-465.

O'Brien, J. T. (2007). Role of imaging techniques in the diagnosis of dementia. *British Journal of Radiology, 80*(Special Issue), 71-77. doi: 10.1259/bjr/33117326

Peach, J., Koob, J. J., & Kraus, M. J. (2001). Psychometric evaluation of the Geriatric Depression Scale (GDS): Supporting its use in health care settings. *Clinical Gerontologist, 23*, 57–68.

Peavy, G. M., Jacobson, M. W., Goldstein, J. L., Hamilton, J. M., Kane, A., Gamst, A. C., . . . Corey-Bloom, J. (2010). Cognitive and functional decline in Huntington's disease: Dementia criteria revisited. *Movement Disorders, 25*, 1163-1169. doi: 10.1002/mds.22953

Perry, R. J., & Hodges, J. R. (1999). Attention and executive deficits in Alzheimer's disease. *Brain, 122*, 383-404. doi: 10.1093/brain/122.3.383

Persson, J., Nyberg, L., Lind, J., Larsson, A., Nilsson, L., Ingvar, M., & Buckner, R. L. (2006). Structure–Function Correlates of Cognitive Decline in Aging. *Cerebral Cortex, 16*, 907-915. doi: 10.1093/cercor/bhj036

Petersen, R. C. (2003). Conceptual overview. In R. C. Petersen (Ed.), *Mild Cognitive Impairment: aging to Alzheimer's Disease* (pp. 1-14). Oxford, UK: Oxford University Press.

Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine, 256*, 183-194. doi: 10.1111/j.1365-2796.2004.01388.x

Petersen, R. C., Doody, R., Kurz, A., Mohs, R. C., Morris, J. C., Rabins, P. V., . . . Winblad, B. (2001). Current Concepts in Mild Cognitive Impairment. *Archives of Neurology, 58*, 1985-1992. doi: 10.1001/archneur.58.12.1985

Petersen, R. C., Roberts, R. O., Knopman, D. S., Boeve, B. F., Geda, Y. E., Ivnik, R. J., . . . Jack, C. R. (2009). Mild Cognitive Impairment: Ten Years Later. *Archives of Neurology, 66*, 1447-1455. doi: 10.1001/archneurol.2009.266

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild Cognitive Impairment Clinical Characterization and Outcome. *Archives of Neurology, 56,* 303-308.

Plassman, B. L., Langa, K. M., Fisher, G. G., Heeringa, S. G., Weir, D. R., Ofstedal, M. B., . . . Wallace, R. B. (2007). Prevalence of Dementia in the United States: The Aging, Demographics, and Memory Study. *Neuroepidemiology, 29*, 125-132. doi: 10.1159/000109998

Potter, L. M., Grealy, M. A., & O'Connor, R. C. (2009). Healthy ageing, perceived motor-efficacy, and performance on cognitively demanding action tasks. *British Journal of Psychology, 100*, 49-70. doi: 10.1348/000712608x304478

Predictive Analytics Software, 2002. Predictive Analytics Software (version 18.0). Chicago, IL: SPSS Inc.

Price, J. L., & Morris, J. C. (1999). Tangles and plaques in nondemented aging and “preclinical” Alzheimer's disease. *Annals of Neurology, 45*, 358-368. doi: 10.1002/1531-8249(199903)45:3<358::aid-ana12>3.0.co;2-x

Prvulovic, D., Hubl, D., Sack, A., Melillo, L., Maurer, K., Frolich, L., . . . Linden, D. (2002). Functional Imaging of Visuospatial Processing in Alzheimer's Disease. *NeuroImage, 17*, 1403-1414. doi: 10.1006/nimg.2002.1271

Psychology Software Tools. 2006. E-Prime (Version 2.0). Pittsburgh, PA: Psychology Software Tools.

Putcha, D., Brickhouse, M., O'Keefe, K., Sullivan, C., Rentz, D., Marshall, G., . . . Sperling, R. (2011). Hippocampal Hyperactivation Associated with Cortical Thinning in Alzheimer's Disease Signature Regions in Non-Demented Elderly Adults. *The Journal of Neuroscience, 31*, 17680-17688. doi: 10.1523/JNEUROSCI.4740-11.2011

Qiu, C, Winblad, B., & Fratiglioni, L. (2005). The age-dependent relation of blood pressure to cognitive function and dementia. *The Lancet Neurology, 4,* 487-499. doi:10.1016/S1474-4422(05)70141-1

Randolph, C. (1998). Repeatable battery for the assessment of neuropsychological status. San Antonio, TX: The Psychological Corporation.

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., . . . Acker, J. D. (2005). Regional Brain Changes in Aging Healthy Adults: General Trends, Individual Differences and Modifiers. *Cerebral Cortex, 15*, 1676-1689. doi: 10.1093/cercor/bhi044

Resnick, S. M., Pham, D. L., Kraut, M. A., Zonderman, A. B., & Davatzikos, C. (2003). Longitudinal Magnetic Resonance Imaging Studies of Older Adults: A Shrinking Brain. *Journal of Neuroscience, 23*, 3295-3301.

Rocca, W. A., Amaducci, L. A., & Schoenberg, B. S. (1986). Epidemiology of clinically diagnosed Alzheimer's disease. *Annals of Neurology, 19*, 415-424. doi: 10.1002/ana.410190502

Rockwood, K., Strang, D., MacKnight, C., Downer, R., & Morris, J. C. (2000). Interrater reliability of the Clinical Dementia Rating in a multicenter trial. *Journal of the American Geriatrics Society, 48*, 558-559.

Rodgers, A. B. (2009). Alzheimer's Disease: Unraveling the mystery. Retrieved from http://www.nia.nih.gov/Alzheimers/Publications/Unraveling/

Rorden, C. (2007). Dcm2nii to NIFTI convertor.

Rosano, C., Aizenstein, H. J., Cochran, J. L., Saxton, J. A., De Kosky, S. T., Newman, A. B., …Carter, C. S. (2005). Event-related functional magnetic resonance imaging investigation of executive control in very old individuals with mild cognitive impairment. *Biological Psychiatry, 57*, 761-767. doi: 10.1016/j.biopsych.2004.12.031

Rosenthal, R. (1991). *Meta-analytic procedures for social research (rev. ed.).* Newbury Park, CA: Sage.

Roubenoff, R., & Hughes, V. A. (2000). Sarcopenia: Current Concepts. *Journal of Gerontology, 12,* M716-M724. doi: 10.1093/gerona/55.12.M716

Rowland, L. P., & Shneider, N. A. (2001). Amyotrophic Lateral Sclerosis. *New England Journal of Medicine, 344*, 1688-1700. doi: 10.1056/NEJM200105313442207

Royall, D. R., Palmer, R., Chiodo, L. K., & Polk, M. J. (2004). Declining Executive Control in Normal Aging Predicts Change in Functional Status: The Freedom House Study. *Journal of the American Geriatrics Society, 52*, 346-352. doi: 10.1111/j.1532-5415.2004.52104.x

Rueter-Lorenz, P. A., & Cappell, K. A. (2008). Neurocognitive Aging and Compensation Hypothesis. *Current Directions in Psychological Science, 17,* 177-182. doi: 10.1111/j.1467-8721.2008.00570.x

Saxon, S. V., Etten, M. J., & Perkins, E. A. (2010). *Physical change and aging: a guide for helping professions*. New York, NY: Springer Publishing Company.

Schofield, P. (1999). Alzheimer's Disease and Brain Reserve. *Australasian Journal on Ageing, 18*, 10-14. doi: 10.1111/j.1741-6612.1999.tb00081.x

Schönheit, B., Zarksi, R. & Ohm, T. (2004). Spatial and temporal relationships between plaques and tangles in Alzheimer's-pathology. *Neurobiology of Aging, 25*, 697-711

Schulz, R. , & Beach, S. R. (1999). Caregiving as a risk factor for mortality: the Caregiver Health Effects Study. *Journal of the American Medical Association, 282*, 2215-2219.

Schulz, R., O'Brien, A. T., Bookwala, J., & Fleissner, K. (1995). Psychiatric and Physical Morbidity Effects of Dementia Caregiving: Prevalence, Correlates, and Causes. *The Gerontologist, 35*, 771-791. doi: 10.1093/geront/35.6.771

Sifrit, K. J. (2005). *The effects of aging and cognitive decrements on simulated driving performance.* Ph.D Dissertation Wichita State University Wichita ProQuest Dissertations and Theses database. (AAT 3219428)

Skoog, I., & Gustafson, D. (2006). Update on hypertension and Alzheimer's disease. *Neurological Research, 28*, 605-611. doi: 10.1179/016164106x130506

Smith, G. E., & Ivnick, R. J. (2003). Normative neuropsychology. In R. C. Petersen (Ed.), *Mild Cognitive Impairment: Aging to Alzheimer's disease* (pp. 63-88). New York, NY: Oxford University Press.

Snowden, J. S., Neary, D., & Mann, D. M. A. (2002). Frontotemporal dementia. *The British Journal of Psychiatry, 180*, 140-143. doi: 10.1192/bjp.180.2.140

Sperling, R. A., Dickerson, B. C., Pihlajamaki, M., Vannini, P, Laviolette, P. A., Vitolo, O.V., . . . Johnson, K. A. (2010). Functional alterations in memory networks in early Alzheimer's disease, *Neuromolecular Medicine, 12*, 27-43.

Staffen, W., Ladurner, G., Holler, Y, Bergmann, J., Alchhorn, M., Golaszewski, S., & Kronbichler, M. (in press). Brain activation disturbance for target detection in patients with mild cognitive impairment: an fMRI study. *Neurobiology of Aging.*

Stern, Y. (2003). The concept of cognitive reserve: A catalyst for research. *Journal of Clinical and Experimental Neuropsychology, 25,* 589-593.

Stern, Y. (2006). Cognitive Reserve and Alzheimer Disease. *Alzheimer Disease & Associated Disorders, 20,* 112-117.

Storey, E., Slavin, M. J., & Kinsella, G. J. (2002). Patterns of cognitive impairment in Alzheimer's disease: assessment and differential diagnosis. *Frontiers in Bioscience, 7*, 155-184.

Stroop, J. R. (1938). Factors affecting speed in serial verbal reactions. *Psychological Monographs, 50*, 38-48.

Tierney, M. C., Fisher, R. H., Lewis, A. J., Zorzitto, M. L., Snow, W. G., Reid, D. W., & Nieuwstraten, P. (1988). The NINCDS-ADRDA Work Group criteria for the clinical diagnosis of probable Alzheimer's disease: a clinicopathologic study of 57 cases. *Neurology, 38,* 359-364.

The Canadian Study of Health and Aging: risk factors for Alzheimer's disease in Canada. (1994). *Neurology, 44*, 2073-2080.

Thompson, P. M., Hayashi, K. M., de Zubicaray, G., Janke, A. L. Rose, S. E., Sempe, … Tonga, A.W. (2003). Dynamics of gray matter loss in Alzheimer's disease. *Journal of Neuroscience, 23*, 994-1005.

Trivedi, M.A., Stoub, T. R., Murphy, C. M., George, S., deToledo-Morrell, L., Shah, R. C., . . . Stebbins, G. T. (2011). Entorhinal cortex volume is associated with episodic memory related brain activation in normal again and amnesic mild cognitive impairment. *Brain imaging and behavior, 5*, 126-136.

Tulving, E. (1972). Episodic and semantic memory. In E. Tulving & W. Donaldson (Eds.), *Organization of memory* (pp. 381-403.). New York, NY: Academic Press.

Uhlhaas, P. J., Pantel, J., Lanfermann, H., Prvulovic, D., Haenschel, C., Maurer, K., & Linden, D. (2008). Visual Perceptual Organization Deficits in Alzheimer's Dementia. *Dementia and Geriatric Cognitive Disorders, 25*, 465-475. doi: 10.1159/000125671

Van der Linden, M., Bredart, & Beerten, A. (1994). Age related differences in updating working memory. *British Journal of Psychology, 85,* 145-152. doi: 10.1111/j.2044-8295.1994.tb02514.x

van Doorn, C., Gruber-Baldini, A. L., Zimmerman, S., Richard Hebel, J., Port, C. L., Baumgarten, M., . . . Magaziner, J. (2003). Dementia as a Risk Factor for Falls and Fall Injuries Among Nursing Home Residents. *Journal of the American Geriatrics Society, 51*, 1213-1218. doi: 10.1046/j.1532-5415.2003.51404.x

Visser, P. J., & Verhey, F. R. J. (2007). Mild cognitive impairment as predictor for Alzheimer's disease in clinical practice: effect of age and diagnostic criteria. *Psychological Medicine, 38*, 113-122. doi: 10.1017/s0033291707000554

Wechsler. (2001). Wechsler Test of Adult Reading Manual. San Antonio, TX: The Psychological Corporation.

Weinert, B. T., & Timiras, P. S. (2003). Invited Review: Theories of aging. *Journal of Applied Physiology 95*, 1706-1716. doi: 10.1152/japplphysiol.00288.2003

West, R., & Alain, C. (2000). Age-related decline in inhibitory control contributes to the increased Stroop effect observed in older adults. *Psychophysiology, 37*, 179-189. doi: 10.1111/1469-8986.3720179

Wimo, A., Winblad, B., & Jönsson, L. (2010). The worldwide societal costs of dementia: Estimates for 2009. *Alzheimer's and Dementia, 6*, 98-103. doi: 10.1016/j.jalz.2010.01.010

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L. O., . . . Petersen, R. C. (2004). Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *Journal of Internal Medicine, 256*, 240-246.

Wolf-Klein, G. P., & Silverstone, F. A. (1994). Weight Loss in Alzheimer's Disease: An International Review of the Literature. *International Psychogeriatrics, 6*, 135-142. doi: doi:10.1017/S1041610294001705

Woodruff-Pak, D. S. (1997). *The Neuropsychology of Aging*. Oxford, UK: Blackwell Publishers Inc.

World Health Organization. (1992). *The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines*. World Health Organization

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., & Leirer, V. O. (1983). Development and validation of a geriatric depression screening scale: A preliminary report. *Journal of Psychiatric Research*, *17*, 37–49. doi: 10.1016/0022-3956(82)90033-4

Zacks, R. T., Hasher, L., & Li, K. Z. K. (2000). Human Memory. In F. I. M Craik & T. A. Salthouse (Eds.), *The handbook of aging and cognition,* 2nd ed (pp. 293-357). New York, NY: Lawrence Erlbaum Associates Publishers.

Zakzanis, K. K., Graham, S. J., & Campbell, Z. (2003). A meta-analysis of structural and functional brain imaging in dementia of the Alzheimer's type: a neuroimaging profile. *Neuropsychology Review, 13*, 1-18.

APPENDIX

Jittering Design

1. Settings:

   - ISI = 3s; TR = 2s; two types of 3s stimuli
   - 64 trials for each stimulus type; the length of design is set to 192
   - objectives are detection and counterbalancing
   - contrasts:

     1 0

     0 1

     1 −1

2. model assumptions:

   - AR (1) noise with $\rho = 0.3$
   - second-order polynomial drift
   - the HRF is the convolution of a 3s epoch and the canonical HRF of SPM2 (doublegamma function normalized to have a maximal of 1)

3. Design:

```
00011111221220001111
2222000012222220000 1
11122222000111122222
00000111112000011111
22220000112222200000
11111122000011112222
00001121122000000122
22222000001111112212
20001111222220001111
```

2222000011211

4. The design and the attained efficiency vs. GA generations: blue = 0; green = 1; brown = 2

5. This design attains 93% of the best design for detection under this setting (the best design yields Fd = 77.8335); it also has an F* c -value of 93.6% when 3rd-order counterbalancing is considered (The maximal F*c is 100%, indicating a counterbalanced design)