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THE ROLE OF FRONTAL LOBE WHITE MATTER INTEGRITY AND EXECUTIVE FUNCTIONING IN PREDICTING ADAPTIVE FUNCTIONING IN ALZHEIMER'S DISEASE

by

MATTHEW ARON MUMAW

Under the Direction of Dr.Tricia Z. King

ABSTRACT

Alzheimer's disease (AD) is the most common form of dementia and is characterized by a gradual deterioration of the patients' ability to independently perform day to day activities. Researchers have discovered significant changes in neuroanatomy, cognition and behavior that are related to the disease process of AD and researchers continue to uncover new variables, such as the presence of vascular risk factors, which may further increase our ability to understand and characterize the disease. The purpose of this study is to identify the neuroanatomical, cognitive and behavioral variables that best predict impairment of instrumental activities of daily living in individuals with probable AD.

Reduced white matter integrity in the dorsolateral prefrontal cortex as well as the presence of vascular risk factors significantly predicted impairments in activities of daily living (ADLs). Executive functioning skills, typically described as frontal lobe system behaviors, were positively associated with ADLs. Further, executive functions fully mediated the relationship between frontal lobe white matter integrity and ADLs. A better understanding of the variables responsible for diminished ADLs in AD will allow researchers and clinicians to better target prevention and intervention strategies and ultimately help individuals with AD to maintain their independence for a longer duration.

INDEX WORDS: Executive functions, Neuroanatomy, Neuroimaging, Adaptive functioning, Vascular risk factors

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A Dissertation Submitted in Partial Fulfillment of Requirements for the Degree of

Doctor of Philosophy

in the College of Arts and Sciences

Georgia State University

2012

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Matthew Aron Mumaw
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CHAPTER 1: INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative condition that ultimately leads to dementia and deterioration in the ability to function independently in day to day activities. These deficits in the ability to function independently constitute a challenge not only for the patient, but also for caregivers and society. Minimizing the impact of functional deficits, whether through treatment or prevention, necessitates a clear understanding of the variables that are responsible for the deficits. Given the profound impact of AD upon individuals and society, research into the disease has investigated a wide range of variables including neuroanatomy, cognitive deficits and behavioral changes. Despite the efforts of researchers, much remains to be learned about the factors that contribute to the onset and progression of the disease as well as how these different variables relate to functional outcome. The purpose of the proposed research is to identify neuroanatomical and cognitive changes that predict deficits in the ability to perform instrumental activities of daily living (IADLs) in individuals with AD.

Individuals with AD have been found to differ from healthy controls on several important variables within the domains of neuropathology and cognition. However, the ultimate impact of the disease may be best represented by the changes in the ability of those affected to function successfully and independently. The criteria for a diagnosis of dementia published within the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association [DSM-IV-TR], 2003) requires the presence of impairment in social or occupational functioning and this impairment must represent a decrease from previous levels of functioning. In both research and clinical work, this is often assessed through questionnaires and interviews that try to establish the patient's

ability to function independently and perform activities which most individuals perform on a day to day basis. These activities of daily living (ADLs) are frequently subdivided into easier tasks and more difficult tasks. Basic activities of daily living (BADLs) are activities that are generally concerned with self-care tasks such as bathing, toileting, and eating. Instrumental activities of daily living (IADLs) are more complex tasks required to function effectively and independently within the context of a community and involves activities such as using the telephone, managing money, and housework.

1.1 Neuropathology

Changes in cognition and behavior may be the direct result of disease related changes in the structure and function of the brain. Until recently, studies have traditionally relied on MRI, fMRI, and histopathology to identify potential brain changes in AD that are distinct from changes that occur in Mild Cognitive Impairment (MCI) and normal aging.

Research using conventional imaging techniques has consistently found changes in the gross structural anatomy of the brains of normally aging individuals. Increased age is associated with increased volume of cerebrospinal fluid filled spaces, such as the ventricles, reflecting a reduction in the size of the brain itself (Guttman et al., 1998; Jernigan et al., 2001). Researchers have typically not found similar reductions of white matter or very small changes in white matter within the aging brain (Raz et al., 1997). Despite the inability of conventional MRI to detect significant changes in white matter, postmortem studies have found that the white matter in older individuals is subject to microstructural degradation in the precentral gyrus and the anterior corpus callosum

that could lead to interruption of the frontal-subcortical circuits and cause age-related declines in cognitive functioning (Aboitiz et al., 1996). Likewise, imaging studies have discovered changes in the gross anatomy of those with MCI (De Leon et al., 1997) and AD (Townsend et al., 2002), including atrophy of gray matter in medial temporal lobe structures such as the entorhinal cortex and hippocampus. Although traditional MRI and histopathology have identified potential anatomical correlates of the disease process, until recently researchers were unable to explore microstructural changes of the brain in vivo.

1.2 Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) is a recent development in neuroimaging technology that provides additional and unique information about the microstructure of both gray and white matter. DTI differs from other techniques in that it provides information about the diffusion of water in multiple directions within tissues of the brain. Theoretically, the nature and direction of water diffusion should differ within the brain according to the degree and type of organization of the structures within a given region (Horsfield et al., 2002). Water should diffuse freely (isotropic motion) in areas with little structure such as within the ventricles. In contrast, white matter consists of well organized collections of fibers with a predominant direction of alignment and diffusion within the white matter of the brain should be characterized by highly directional (anisotropic) diffusion. This methodology represents a significant improvement over normal MRI and other imaging techniques in that it allows researchers to make inferences about the structure of the tissues on a much smaller scale than with the

traditional techniques (Basser, 1995). This is beneficial in that it is difficult to differentiate between specific white matter tracts using MRI or even during visual inspection, post mortem (Mori, 2007). In addition to allowing researchers to identify particular tracts within bundles of white matter tissue, DTI also allows researchers to detect small microstructural changes within both gray and white matter by examining the proportion and magnitude of diffusion within the tissues. Researchers investigating white matter use many different DTI indices including mean diffusivity (MD) and fractional anisotropy (FA). MD is an overall measure of the diffusion within brain structures and provides a general assessment of the structural integrity of the tissue. FA also indicates the magnitude of water diffusion within a tissue but also indicates the direction of diffusion.

1.3 DTI in Normal Aging

Research conducted with conventional MRI has revealed small reductions in white matter volume (Courchesne et al., 2000) and greater numbers of white matter hyperintensities (DeCarli et al., 2001) in normal aging when compared to the brains of younger controls. Although, these findings suggest possible white matter deterioration as a part of normal aging, conventional MRI does not have the ability to allow researchers to identify more subtle regional changes or microstructural changes. Using DTI, however, researchers have been able to detect more subtle changes in white matter structure related to normal aging. Researchers have found significant declines in FA values in the genu of the corpus callosum, and bilateral frontal and parietal pericallosal white matter (Sullivan 2003). Salat et al. (2005) performed a study

comparing DTI measurements in younger and older adults which found that FA in the prefrontal regions of the older adults was significantly reduced compared to the younger adults. These researchers also found that, despite the assumption that frontal white matter was well-preserved until later life, significant reductions in FA could be seen in middle age participants. Although reductions in FA were common across the frontal lobe areas, the white matter of the ventromedial and deep prefrontal regions appeared to be more significantly affected. These reductions in FA indicate reductions in white matter integrity and less alignment of cells with white matter pathways and tend to follow an anterior to posterior pattern of deterioration.

1.4 DTI in Mild Cognitive Impairment

Mild cognitive impairment has frequently been viewed as a prodrome of AD and has generated much attention from researchers hoping to understand the earliest stages of AD as a means to developing methods for preventing the complete conversion to AD. Using DTI, studies have demonstrated the ability of DTI to detect microstructural changes in the hippocampus of individuals with MCI (Muller et al. 2005; Muller et al, 2007). Muller et al. (2007) explored the ability of FA and mean diffusivity (MD) measurements of DTI in comparison with hippocampal volume measurements of standard MRI in MCI to correctly distinguish between a group of healthy controls and individuals previously diagnosed with MCI. When researchers set the specificity to 80%, left hippocampal volumes demonstrated significantly lower sensitivity (50%) when compared to left hippocampal mean diffusivity (89%) and FA (78%) measurements. Overall, the DTI measures were more sensitive to smaller changes to the structure of

hippocampal tissue when compared to hippocampal volume. Increased mean diffusivity has also been found in other brain regions including the left and right entorhinal cortices, posterior occipital-parietal cortex, right parietal supramarginal gyrus, and right frontal precentral gyri in patients with MCI (Rose et al, 2006). The same group found reduced FA in the MCI group in the limbic parahippocampal subgyral white matter, right thalamus and left posterior cingulate. Furthermore, these regional differences in FA and MD were correlated with performance on neuropsychological measures. Mean diffusivity in the left hippocampus has also been found to be superior to left hippocampal volume in predicting the conversion of MCI to AD (Fellgiebel, 2006).

1.5 DTI in Alzheimer's disease

As with MCI, studies using DTI have consistently demonstrated reduced white matter integrity in individuals with AD when compared to healthy controls; however, there is not a consensus on the nature of these differences. The involvement of the frontal lobe in the disease process has been a primary area of contention, with some researchers finding that WM integrity does not differ between AD and healthy age-matched controls (Head et al., 2004; Fellgiebel et al., 2004) and others finding significant reductions in frontal white matter integrity (Naggara et al., 2006; Duan et al., 2006; Choi et al., 2005). Head et al. (2004) found that healthy aging was associated with changes in white matter roughly following an anterior to posterior gradient. Individuals with AD did not demonstrate additional deterioration in frontal or temporal white matter integrity when compared with the normally aging group, showing instead increased deterioration in the posterior lobar regions. Given the differences in the

pattern of white matter deterioration between the AD group and the normal controls, the authors argued that different mechanisms were responsible for white matter deterioration in AD when compared to normal aging. In contrast, Choi et al. (2005) found increased MD and reduced FA within superior frontal white matter thereby calling into question the hypothesis that AD involves a process of deterioration separate from normal aging. The authors alternatively suggest that the results support the retrogenesis theory that states that the process of degeneration reverses the order of human development. Other researchers have found significant differences in both gray matter and white matter between individuals with AD and normal, age-matched controls (Rose et al., 2008; Naggara et al., 2006). Rose et al. (2008) found evidence of increased diffusivity within the hippocampus and amygdala as well as the medial temporal, parietal, and frontal lobe gray matter in the AD group. Reductions in FA were localized in the thalamus, parietal white matter, and posterior limbs of the internal capsule reflecting disturbance to the thalamocortical loop. White matter changes also have been discovered in preclinical and presymptomatic carriers of the genes responsible for familial AD. Ringman et al. (2007) found that carriers of the mutated genes had decreased white matter integrity reflected by decreases in FA within the columns of the fornix, the bilateral perforant pathway, and the left orbitofrontal lobe.

1.6 Vascular Risk Factors and ADLs

The neuropathology and brain changes described in the sections above are representative of the disease process in AD that ultimately leads to impairment in the ability to perform IADLs. Even as researchers make progress in understanding the

neuroanatomical changes that occur in AD using new technologies such as DTI, new variables are being discovered that contribute to the onset, progression, and severity of the disease. The presence of vascular risk factors such as hypertension and diabetes mellitus has recently emerged as a potentially significant variable in the disease process of AD. The presence of vascular risk factors has not only been associated with changes in white matter, but has also been associated with significant cognitive and behavioral changes in elderly populations.

The presence of vascular risk factors has been associated with declines in adaptive functioning. In a longitudinal study, Kuo et al. (2005) found that both hypertension and Diabetes Mellitus (DM) were associated with reduced physical functioning as assessed on the SF-36. Furthermore, individuals with DM exhibited a faster rate of decline in IADLs after a two year follow-up. Similarly, Kamper et al. (2005) found that the presence of DM at baseline was an independent risk factor for the reduction of IADLs when reassessed at a 3 year follow-up. Connelly et al. (2005) investigated the roles of white matter lesions and hypertension in the development of dysfunction in activities of daily living and found that while neither white matter lesions nor hypertension independently influenced functional outcome, there was an interaction between these variables. Patients with both white matter lesions and hypertension exhibited significant reductions in IADLs. A similar interaction between large white matter lesions and the presence of stroke on activities of daily living was found by (Berger et al. 2005). While large white matter lesions and stroke both independently resulted in significant reductions of ADLs and IADLs, the presence of both brain changes greatly increased this dysfunction.

1.7 Executive Functions

Many different factors have been proposed and investigated to explain the deficits in adaptive functioning that are exhibited in cases of dementia. The association between cognitive deficits and impairments in IADLs has been a primary area of focus while impairments due to physical impairments are not considered to be characteristic of dementia. A key area of investigation has involved the presence of executive functioning deficits in AD and their impact upon the ability to function adaptively.

The construct of executive functions refers to the ability to plan and conduct complex, goal oriented behaviors such as abstraction, sequencing, planning, inhibition, and regulation of ongoing activity (Miller, 2007). The emphasis on the control function of frontally-mediated activities in the neuropsychological context came from the observation that many people would score within the normal range on cognitive tests and yet were unable to successfully and independently behave in an independent and adaptive manner (Duke & Kaszniak, 2000). Given the origin of the concept of executive functions, assessing these abilities appears to be particularly important in understanding deficits in the ability to perform IADLs in AD. Lezak (2004) has broadly categorized executive functions into four components including: 1) volition; 2) planning; 3) purposive action; and 4) effective performance. While each of these areas represent specific and unique sets of skills and abilities, it is rare to have deficits in just one of the four components of executive functioning. Instead, a person may have deficits with multiple components of executive functioning with more serious deficits with respect to a particular component (Lezak, 2004). The presence of a particular type of executive functioning deficit rarely happens in isolation from other executive functioning deficits.

1.8 Executive Functioning and ADLs

Deficits in executive functions have recently been found to influence the presence and severity of impairments in IADLs. Executive dysfunction has a particularly strong affect on the IADLs, as opposed to BADLs due to their complex nature (Schindler, 2005). Boyle et al. (2003) investigated the roles of executive dysfunction and apathy as predictors of impairments in adaptive functioning in patients with mild to moderate AD. With respect to the more complex IADLs executive functions explained 17% of the variance in IADLs while apathy predicted an additional 27% of the variance. Executive functioning explained 28% of the variance in BADLs while apathy accounted for additional unique variance in BADLs. Executive functioning deficits have also been linked to impairments in IADLs in VaD patients (Jefferson, 2006; Boyle, 2004). Boyle et al. (2004) investigated the influence of subcortical neuropathology and executive functions on the development of IADLs in individuals with VaD and found that baseline levels of executive functions predicted IADL levels at the time of a 1-year follow-up. Subcortical neuropathology did not predict IADLs.

It appears that decreases in abstract verbal reasoning are particularly relevant when trying to characterize cognitive deficits related to AD. These features of EF are some of the earliest cognitive deficits to appear in the progression of AD (Giovannetti et al., 2001) and are more frequently present during MCI in individuals who ultimately progress to develop AD.

1.9 Neuroanatomy of Executive Functioning

The frontal lobes are the last areas of the brain to mature during the course of development and have traditionally been seen as the source of the highest cognitive functions. Specifically, the frontal lobes have been regarded as the origin of processes responsible for the control of behavior and cognition. Although significant evidence implicates the involvement of the frontal lobes in executive functioning deficits, the strict localization of executive functioning skills within the frontal lobes has not held up to research (Duke, 2000; Miller, 2007). Lesions in the frontal lobes do not always lead to executive functioning deficits and lesions in other areas of the brain can also lead to the same executive functioning deficits. Recently, neuroanatomical models of executive functioning have developed in which various cortical and subcortical structures connect to form networks or circuits which are collectively responsible for producing executive functions. Damage to any part of this circuit may be responsible for executive dysfunction. Variability of symptom expression within a given syndrome may be the result of differences in the particular part of the network that is disrupted and whether multiple networks are disrupted by an insult or disease process.

Executive functioning deficits have been found in AD that represent each of the four areas of executive functioning conceptualized by Lezak (2004). In attempts to better understand the neuropathology of AD and how it relates to cognitive decline, researchers have focused on circuits which have been associated with particular executive functions. Alexander (1986) described five circuits in which specific cortical regions of the frontal lobes operate with subcortical regions in order to perform complex actions. In each of these circuits, the cortical areas both send output to and receive

input from the subcortical structures. Of the five circuits that Alexander (1986) originally identified, three have been associated with various aspects of executive functioning: 1) the dorsolateral prefrontal cortex (DLPFC); 2) the orbitofrontal cortex; and 3) the medial frontal cortex (Lichter, 2001).

The first of the frontal-subcortical circuits is the medial-frontal circuit originating in the anterior cingulate. Following the anterior cingulate, the pathway includes the ventromedial striatum, globus pallidus and substantia nigra, and the mediodorsal thalamus which projects back to the anterior cingulate. In addition to its connections with subcortical structures, the anterior cingulate has connections with the DLPFC. The medial-frontal cortex appears to be involved in the executive functions which Lezak (2004) categorized as functions of volition. Damage to the medial frontal circuit has been demonstrated to lead to apathy, lack of psychic and motor initiative, spontaneous movements, and response to commands (Tekin & Cummings, 2002). The orbitofrontal circuit involves the connection of the frontal monitoring systems with limbic structures. The pathway of this circuit originates in the orbitofrontal cortex and continues with the ventromedial caudate nucleus, the medial and dorsomedial globus pallidus, and the ventral and medial dorsal thalamic nuclei. The orbitofrontal cortex also has interconnections with the DLPFC, the temporal pole, and amygdala. The orbitofrontal subcortical circuit has been associated with social behavior and damage to this system could disrupt mood and lead to a reduction of self-directed action (Tekin & Cummings, 2002; Marin, 1997) as well as the increase in impulsivity and disinhibition (Cummings, 1995). The last circuit is the dorsolateral prefrontal circuit and projects from the DLPFC to the dorsolateral caudate nucleus, the lateral and dorsomedial globus pallidus and the

ventral and mediodorsal thalamic nuclei. The dorsolateral prefrontal circuit is crucially involved with executive functions and its dysfunction has been linked to decreased fluency, perseveration, difficulty shifting set, reduced mental control, limited abstraction ability and poor response inhibition (Cummings, 1995; Tekin & Cummings, 2002; Marin 1997).

While these three frontal subcortical circuits are most frequently linked to executive functions, other regions have been found to contribute. Damage to the right parietotemporal circuits may impact upon awareness of the emotional significance of events and information, resulting in failure to integrate emotional consequences into the planning or initiation of activities. Increases in prevalence of executive dysfunction throughout the course of the disease also have been predicted to have particular neuropathological explanations.

The structure of the frontal-subcortical circuits and their interconnections with each other have important implications for the impact of brain damage on executive functions. Small lesions can influence multiple circuits. On both the cortical and subcortical levels, the circuits are segregated anatomically but have functional connections to other cortical and subcortical regions outside of the circuit (Cummings, 2001). Despite being anatomically segregated, a small subcortical lesion can span multiple circuits due to their close proximity. A small lesion in cortical areas of the circuits might likewise have far reaching effects due to the interconnectedness of the frontal subcortical circuits. The DLPFC, for example, has connections with both the medial frontal cortex and the orbitofrontal cortex as well as functionally related subcortical structures. It is in the DLPFC that information about the external world is

integrated with information about the individual's emotional and cognitive state in order to produce complex behaviors such as executive functioning (Duke et al., 2000). Evidence for the involvement of the frontal-subcortical structures in the presence of executive functioning deficits (e.g. concept formation, abstract verbal reasoning) in AD has come from both neuroanatomical and functional studies.

1.10 Effects of Vascular Risk Factors on Executive Functioning

Studies examining the role of vascular risk factors in normal aging and vascular dementia have repeatedly found an association with impairments in abilities that are regarded to be frontally mediated. Deficits in executive functions have been associated with the presence and severity of white matter hyperintensities (WMH) in a community sample (O'Brien et al., 2002) and in individuals with vascular dementia (Cohen et al., 2002). Verdelho et al. (2007) found deficits in executive functioning and attention related to both diabetes and hypertension. Systolic blood pressure lower than 120 mmHg has been associated with better performance on tests of fluency and flexibility (Oosterman et al., 2007).

Although AD and vascular dementia have traditionally been viewed as distinct diseases, more recent research has investigated the role of vascular risk factors in the onset and progression of AD. Scherder et al. (2007) has proposed a model in which gray and white matter degeneration resulting from ischaemic hypopefusion (i.e., deficient blood supply) and cerebrovascular disease leads to the disconnection of fronto-cortical and fronto-subcortical circuits and ultimately to impairments in executive functioning. The link between vascular risk factors and the degeneration of white and

gray matter is supported by research (Roman et al., 2004) and researchers have begun to examine the link between vascular risk factors and executive functioning in AD. Goldstein et al. (2005) found that African American AD patients with Stage 3 hypertension performed worse than patients without hypertension on the conceptualization and Initiation/Perseveration subtests of the Mattis-Dementia Ratings Scale. In another study, Goldstein et al. (2008) found that having a greater number of vascular risk factors was associated with poorer performance on tasks of verbal reasoning and set shifting. Interestingly, the severity of the vascular risk factors was not associated with poorer performance.

1.11 Present Study

Alzheimer's disease is a progressive neurodegenerative condition that gradually impairs a patient's ability to perform day to day activities and to function independently. Neuropathological and cognitive changes and vascular risk factors associated with AD have been linked with functional impairment of patients with AD, but relationships among the variables have not been fully explored. The proposed study sought to quantify the effects of these variables on daily functioning and to identify the likely pathways through which they exert their influence. A better understanding of these variables and their interactions will assist in identifying those patients at increased risk for worse disease progression as well as suggesting means of targeting intervention to optimize functioning in AD patients.

1.12 Specific Aims

Aim 1: Investigate differences in white matter integrity and executive functioning between AD participants and healthy control participants

Hypothesis 1: Fractional anisotropy (FA) in the DLPFC will be lower in the AD group compared to controls.

Hypothesis 2: The AD group will score significantly lower on executive functioning (Similarities) compared to the control group.

Aim 2: Investigate the contribution of executive functioning ability in the prediction of IADLs and its potential as a mediator of the relationship between white matter integrity and IADLs.

Hypothesis 1: Worse white matter integrity as represented by lower fractional anisotropy within the DLPFC will be associated with worse IADLs.

Hypothesis 2: Worse executive functioning (Similarities) is expected to be associated with worse IADLs (Functional Activities Questionnaire).

Hypothesis 3: Executive Functioning (Similarities) is expected to mediate the relationship between White Matter integrity and activities of daily living.

Aim 3: Investigate the contribution of executive functioning ability in the prediction of adaptive function and its potential as a mediator of the relationship between vascular risk factors and adaptive functioning.

Hypothesis 1: The presence of greater numbers of vascular risk factors will be associated with increased impairment in IADLs.

Hypothesis 2: Worse executive functioning (Similarities) is expected to be associated with worse IADLs (Functional Activities Questionnaire).

Hypothesis 3: Executive Functioning (Similarities) is expected to mediate the relationship between the number of vascular risk factors and IADLs.

CHAPTER 2: METHOD

2.1 Participants

Data from 21 adults with Alzheimer's disease (AD) and 10 healthy aging adults were obtained for this study. Medical records for each potential participant were reviewed to identify details of their medical history in order to determine whether they meet inclusion or exclusionary criteria for participation in the proposed study. Patients and controls with metabolic diseases that can affect cognition, a history of seizures, current addiction or the presence of a pacemaker were excluded from the study. Vision and hearing were screened and participants with deficits that remained after remediation (corrective lenses, hearing aides) were omitted from the study. Participants were included in the AD group if they met the criteria set forth by the National Institute of Neurologic and Communicative Disorders (McKhann et al., 1984). Specifically, inclusion in the AD group required that 1) dementia had been established based upon neuropsychological testing and clinical evaluation, 2) cognitive deficits occurred in at least two or more areas of functioning and were progressive in nature, 3) the onset of the symptoms occurred between the ages of 40 and 90 and the participant did not have any additional medical conditions or diseases which could account for the impairments in cognitive functioning. Participants were included in the healthy control group based

upon the absence of neurological diseases including stroke, neurodegenerative disease, head injury or addiction. Controls did not meet the criteria for the AD group.

Initially, 24 AD and 14 control participants were recruited tested and received diffusion tensor imaging as part of their participation in the study. Of these participants, all 24 of the AD participants met the criteria of the National Institute of Neurologic and Communicative Disorders and all other requirements. The 14 control participants likewise met all inclusion criteria. During data cleaning and analyses of the DTI data, the data from five participants (2AD; 3 control) were excluded due to artifact on the images. An additional 2 participants (1 AD; 1 control) were missing data needed in the current study and were omitted from analysis. Following exclusions due to DTI artifact and missing data, the data for 21 AD participants and 10 control participants were included in the study.

2.2 Measures

The neuropsychological data for the proposed research were obtained from data collected for a larger research program conducted through Wesley Woods Geriatric Hospital. As part of that study, participants completed a large battery of tests including the Dementia Screening Battery from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Morris et al., 1989). The CERAD includes the Mini-Mental State Examination (MMSE; Folstein et al., 1975); a test of semantic fluency; a 15-item version of the Boston Naming Test (Kaplan et al., 1983); Constructional Praxis requiring the drawing of four distinct geometric figures; a three trial, 10 word list learning task; a delayed recall memory task for the ten item word list; and a word list recognition

task. Participants were also given Digit Span (Wechsler, 1997), Similarities, the Wisconsin Card Sorting Test (Heaton, 1981), verbal fluency-animals, Trail Making Test and the Neuropsychiatric Inventory (Cummings et al., 1994).

2.2.1 Activities of Daily Living

The Functional Activities Questionnaire (FAQ; Pfeffer et al., 1982, Pfeffer et al., 1984) was created to assess the ability to independently perform activities of daily living in normal aging and dementia. The scale was designed to include a range of activities that are universal to all older adults in order to limit the possible confounding influence of intelligence, level of education, and socioeconomic status. The FAQ (Pfeffer et al., 1982) consists of ten items that assess instrumental activities of daily living (IADLs) such as the ability to manage finances, prepare meals, perform household tasks, and travel independently. For each of the items on the FAQ, a family member or caregiver assesses the patient's ability to perform the activity independently. Ratings are based on a four point scale with three indicating significant dependence on others and zero indicating independence. Summary scores can range from 0 to 30.

Prior to the introduction of the FAQ, the established questionnaire for assessing the ability to function independently was the Instrumental Activities of Daily Living Scale (Lawton et al., 1969). The FAQ correlated .72 with the Lawton IADL Scale and was more strongly correlated with mental status than the IADL scale. The difference in correlations with mental status may reflect a greater reliance on physical capacity when determining functional ability in the IADL scale (McDowell et al., 1996). Item-total

correlations were greater than 0.80 for each of the items for the scale. Test-retest reliability was 0.97.

The assessment of activities of daily living was limited to instrumental activities of daily living requiring the ability to perform more complex, social activities. The present study investigated the impact of executive functioning on activities of daily living in individuals with mild to moderate AD. The decision to limit the investigation to IADLs reflects the more complex nature of IADLs when compared to the more basic self-care skills required to perform ADLs. Furthermore, the sample of AD participants were limited to individuals with mild to moderate stages of the disease in which deficits in ADLs may not be as severely affected. Lastly, the form of the FAQ that was administered as part of the project was limited to IADLs. Additional information on ADLs is available from the Lawton Activities of Daily Living Scale, however, this scale is affected by a greater dependence of physical capacity as indicated above (McDowell et al., 1996).

2.2.2 Attention

The Digit Span-forward subtest of the of the Wechsler Memory Scale-III (WMS-III) was administered as a test of attention span. In this test, the test administrator reads a sequence of numbers at a rate of one per second that the participant must repeat back to the administrator after the sequence has been completed. The number sequences begin at two numbers and increase to nine numbers if the participant successfully repeats letter sequences of increasing length. Raw scores were used for analysis and range from 0 to 16.

Attention span has been found to be resistant to performance declines in AD (Wilson et al., 1996) particularly in the early milder stage (Storandt et al., 1984). Test-retest reliability for the digit span subtest decreases with increasing age and was .89 for individuals aged 55-74 and .83 for individuals aged 75 to 89.

2.2.3 Executive Functioning

The Similarities test was included as a measure of abstract verbal reasoning. The test has been found to be independent of memory abilities making it ideal for working with AD in which memory is one of the primary areas of deficit. Many tests of executive functioning involve timed tasks with a motor skills component. This can be problematic for an AD population and healthy controls, as processing speed and motor skills may both be diminished in these populations. As an untimed task that does not require significant motor skills, the Similarities test is a better fit for the aging and AD populations. Furthermore, the Similarities subtest has been associated with increased activity in the frontal areas of the brain (Duke, 2000). Performance on Similarities has been associated with dementia such that lower scores are predictive of the onset of AD. Others researchers have failed to find reductions in Similarities scores in early AD or found very small reductions. Test-retest reliability of Similarities ranged from .70 to .80 in a group of adults 75 years or older when testing delays occurred in one month intervals.

2.2.4 Vascular Risk Factors

In order to examine relationships between vascular risk factors, EF and IADLs, the presence of four vascular risk factors (hypertension, hypercholesterolemia, cardiac disease, and diabetes mellitus) were assessed and included in analyses. Selection of vascular risk factors was informed by previous research suggesting that they are prevalent in the aging population, risk factors for white matter disease, and associated with impairments in EF. A binary score for the presence (1) or absence (0) of each of the vascular risk factors was assessed and summed to create a summary variable of vascular risk factors (0-4).

Hypertension- Participants interacted with the nurse for a minimum of 30 minutes prior to blood pressure measurement to limit elevations due to anxiety. Average blood pressure was determined from two separate readings separated by two minutes. If the values of the two readings differed by 5 mm Hg of higher, additional measurements were obtained. A participant was determined to have hypertension if their systolic blood pressure was 140 mm Hg or higher, diastolic blood pressure was 90 mm Hg or higher, or if they were taking antihypertensive medication.

Hypercholesterolemia- Participants were required to fast for a minimum of 8 hours prior to having their cholesterol profile assessed. Participants were determined to have hypercholesterolemia if their total cholesterol level was 240 mg/dl or greater, or if they were taking medication to lower cholesterol.

Cardiac Disease- A board certified cardiologist examined the results of a 12-lead electrocardiogram to diagnose cardiac disease. Participants with abnormal EEG (e.g.

atrial fibrillation) or those who were taking cardiac medication were defined as having cardiac disease.

Diabetes Mellitus- Blood samples were taken from participants following an 8 hour fasting period to assess blood glucose levels. Participants with a fasting glucose of 126 mg/dl or higher or who were taking insulin or hypoglycemic treatments were defined as having Diabetes Mellitus.

2.2.5 Diffusion Tensor Imaging

Diffusion Tensor Imaging was used to assess potential microstructural changes in frontal white matter that may contribute to the disease processes in AD, in general, and explore potential neuropathological changes associated specifically with executive functioning in AD. As described above, executive functions are linked to the dorsolateral prefrontal circuit, orbitofrontal circuit, and the medial frontal circuit and each of these circuits has interconnections with other brain regions. The dorsolateral prefrontal circuit, however, appears to be in a unique neuroanatomical position in that it has interconnections with each of the other two circuits and plays a role in integrating information from these circuits in order to produce executive functions. White matter integrity of the DLPFC was examined given the association between activity in this region and executive functioning. Furthermore, according to the retrogenesis hypothesis of AD, the DLPFC should be among the first brain regions to degenerate because it was the last to undergo myelination during development. Given the retrogenesis hypothesis indicating anterior to posterior white matter degradation in cortical structures, white matter within the primary visual cortex was assessed as a control region.

The data obtained in a diffusion weighted scan can be represented in several different indices of diffusion. Two of the indices most commonly used are mean diffusivity (MD) and fractional anisotropy (FA). MD is a measure that calculates the overall diffusion within a structure and provides important information about the structural integrity of a given region. As with MD, FA values provide information about the magnitude of water diffusion, but also convey information about the direction of water diffusion. The choice of which coefficient to use depends upon the research question and which areas of the brain will be examined (Mori, 2007). For instance, although gray matter and white matter are both highly structured tissue types, white matter is also organized in such a way that the fibers that make up the track are organized consistently such that water diffusion is restricted in particular directions. Within white matter tracts, researchers may wish to know about more than the overall level of diffusion and rely upon the added directional information that comes from FA measurements. White matter within the brain represents important pathways for the transmission of information and communication between regions of a network and FA values can be seen as an index of the health of these pathways. When the white matter of a particular region is affected by an insult, the coherences of the fiber organization can be reduced, theoretically resulting in the impaired efficiency of the transmission of information through these fibers.

Region of interest (ROI) analyses were used to calculate fractional anisotropy (FA) within a prescribed anatomical region within each participant. The degree of accuracy attained in ROI analyses depends upon both the size of ROI drawn and the choice of image upon which the ROIs are drawn. Large ROIs reduce the noise of a

measurement, while small ROIs reduce the risk of error by minimizing the inclusion of multiple tissue values (partial volume effects). Given that controlling partial volume effects is particularly important for measurements of anisotropy and the direction of diffusivity is of particular interest in the present study, a small region of interest measuring 48 pixels was employed for analysis. Because drawing ROIs on maps of interest (such as an FA map) can introduce bias into the process of ROI placement, raters drew ROIs on standardized structural T1 images. T1 weighted images provide the clearest image of structures while diffusion maps are typically distorted and it is not possible to completely align them with conventional scans. T1 weighted images and diffusion weighted images were both transformed into Talairach space to allow for direction comparison of participant data and to assist in guiding the placement of ROIs to correspond to the DLPFC. Raters hand drew ROIs using Talairach coordinates (Y: 39-42; Z:31-33) to verify correct placement of 16 voxel ROIs place on 3 consecutive ROIs. ROI placement corresponded with the Superior Frontal Gyrus within Brodman area 9.

Table 1. Scanning Parameters

Parameter	Diffusion weighted	T1 high contrast
Scanning Seq.	Echo Planar	Gradient Recalled/Inversion Rec
FoV	2048*2048	240*256
Slice Thickness	2 mm	1.2 mm
Repetition time	8700 ms	2300 ms
Echo time	93 ms	2.91 ms
Inversion time	N/A	900 ms
Diffusion directions	20	NA

CHAPTER 3: RESULTS

3.1 Participants

Demographic variables were analyzed with t-tests to determine possible confounding variables. Analyses revealed significantly older age in the AD participants, $t(29)=3.23$, $p=.03$, and significantly higher level of education in the control group, $t(29)=-3.54$, $p=.01$. Furthermore, age and education were significantly related to IADLs and Similarities performance scores. Age and education were included as covariates in further analyses. See Table 2.

3.2 Aim 1: Group Comparisons

3.2.1 Group differences in white matter integrity.

To identify hypothesized group differences in prefrontal white matter integrity, mean FA values were obtained from the left and right DLPFC. Mean FA values from the left and right primary visual cortex served as a control region. The mean FA values of each region between the AD and control group were compared using univariate analysis of variance (ANCOVA) with age and education entered as covariates. As predicted, the AD group demonstrated significantly lower FA in the left DLPFC, $F(3, 26) = 3.46$, $p = .03$. Lower FA in the AD group approached significance in the right DLPFC, $F(3, 26) = 2.65$, $p = .07$. Despite lower WMI in the AD group in the DLPFC, there were no significant differences in the FA values between the groups in the left, $F(3, 26) = 1.52$, $p = .37$, or right, $F(3, 26) = 1.63$, $p = .32$, primary visual cortex.

3.2.2 Group differences in executive functioning.

In order to verify group differences between the AD and control groups, mean scores for Similarities were computed for each group. Given previous research indicating relatively intact attention in AD, mean digit span forward scores were computed to serve as a control variable. Mean scores of executive functioning and attention were compared using ANCOVA with age and education entered as covariates. The t-tests indicated significantly lower Similarities scores in the AD group when compared to the control group, $F(3, 26) = 4.85$, $p < .001$, providing support for the hypothesis. Although Digit Span forward scores were not expected to differ between

groups, a comparison of these scores approached significance, t(3, 26)=2.314, *p*=.09, with AD showing a trend toward lower performance.

3.3 Aim 2: Relationship between WMI, EF, and IADLs

3.3.1 Relationship between EF and IADLs.

In order to test the hypothesis that executive functioning abilities are positively associated with the ability to perform IADLs, IADLs were regressed upon Similarities scores. Members of the AD and control groups were combined to assure adequate sample size and variability in scores. Executive functioning ability was a significant predictor of IADLs, B= -1.10, *p<.001,* as expected. A regression was also performed with IADLs regressed on digit span forward (attention) to serve as a comparison task. Attention has previously been found to be relatively stable in AD, and digit span did not significantly predict IADLs, B=-.65, *p=.10.*

Table 2. Relationship between EF and IADLs

Measure	Mean	SD	B	p (one-tailed)	R2
Age (years)			.14	.367	.30
AD	75.7	6.10			
Control	67.8	6.76			
Education (years)			-.40	.015	.33
AD	12.9	3.23			
Control	17.0	2.54			
Similarities			-1.10	.000	.58
AD	11.1	6.47			
Control	24.5	3.33			

3.3.2 Relationship between WMI and EF.

In order to test the hypothesis that WMI within the DLPFC is positively associated with EF, Similarities scores were regressed upon mean FA of the DLPFC. Fractional Anisotropy within the right DLPFC was found to be a significant predictor of executive functioning ability, B= 82.9, *p=.003.* The ability of FA within the left DLPFC to predict EF approached significance, B=40.9, p=.065. In order to assess the specificity of FA differences between the AD and control group, EF was also regressed upon FA within the left and right primary visual cortex. The relationship between the FA in the primary visual cortex and EF was nonsignificant for both the left, B= 20.4, *p=.47,* and right, B= 27.8, *p=.30* hemispheres.

3.3.3 EF as a mediator of the relationship between WMI and IADLs

Mediational analyses employing bootstrapping (Preacher and Hayes, 2004) were conducted to test our hypotheses that executive functioning would mediate the relationship between white matter integrity (FA) and IADLs (Figure 1). The indirect pathway indicating a mediational role for executive functioning was significant (B=-51.3, CI: -133.6- -5.7) for the right DLPFC, but not the left DLPFC (B=-23.7, CI: -67.5- -8.3). In the right DLPFC, after accounting for the indirect pathway, the direct pathway from FA to IADLs was no longer significant indicating full mediation. Mediational analyses were not performed for the right and left PVC as the PVC was not found to be a significant predictor of EF in the previous step.

Table 3. Relationship between WMI and IADLs

Measure	B	p (one-tailed)	R2
Age (years)	.14	.367	.30
Education (years)	- .40	.015	.33
Right DLPFC	- .43	.005	.47
Left DLPFC	- .32	.041	.45

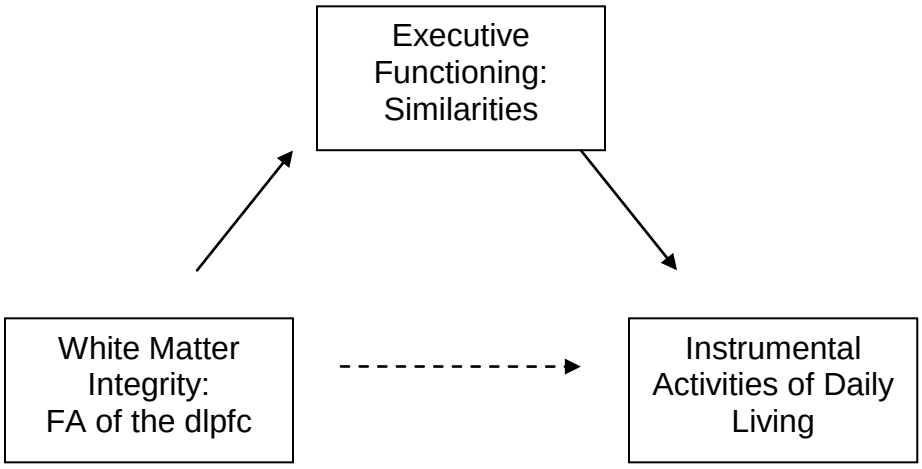

Figure 1. Mediational model examining executive functioning as a mediator of the relationship between white matter integrity in the DLPFC and IADLs.

Table 4. EF as a mediator of the relationship between WMI and IADLs

Functional Asessment Questionnaire (FAQ) (DV)	Effect of IV on *M* (*a*)	Effect of *M* on DV (*b*)	Total effects (*c*)	Direct effects (*c'*)	B	BCa 95% CI	
						Lower	Upper
Right Hemisphere DLPFC	61.26**	-.84**	-103.02**	-51.72	.761	-133.65	-5.74
Left Hemisphere DLPFC	24.70	-.96**	-58.03*	-34.32	.761	-67.53	8.26

3.4 Aim 3: Relationship between vascular risk factors, EF, and IADLs

3.4.1 Relationship between EF and IADLs.

In order to test the hypothesis that executive functioning abilities are positively associated with the ability to perform IADLs, IADLS were regressed upon Similarities scores. Members of the AD and control groups were combined to assure adequate sample size and variability in scores. Executive functioning ability was a significant predictor of IADLs, B= -.84, *p=.011,* as expected.

Relationship between vascular risk factors and IADLs.

In order to test the hypothesis that vascular risk factors are positively associated with IADLs, IADLs total scores were regressed upon number of vascular risk factors. Vascular risk factor count was not found to be a significant predictor of ability to perform IADLs, B= -5.7, *p=.784.*

3.4.2 EF as a mediator of the relationship between vascular risk factors and IADLs.

As the previous analyses established no relationship between vascular risk factors and IADLs, further mediational analyses were not warranted. A regression analyses found that vascular risk factor count did not predict EF, B=-1.19, p=.277.

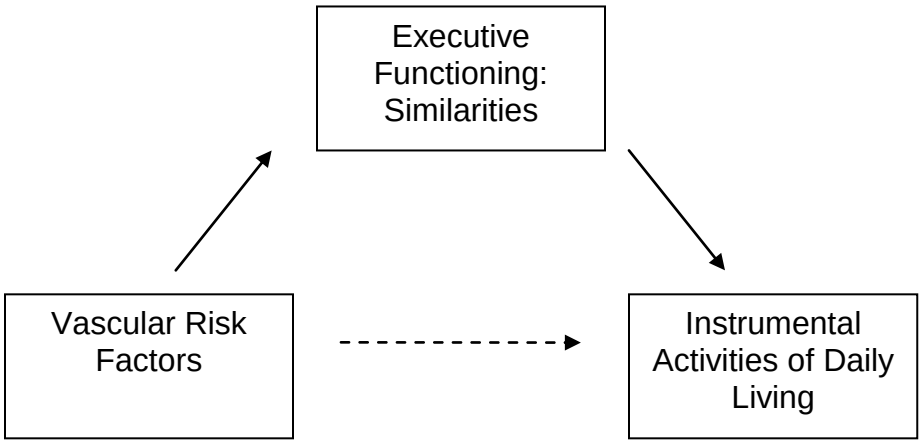

Figure 2. Mediational model examining executive functioning as a mediator of the relationship between vascular risk factors and IADLs.

CHAPTER 4: DISCUSSION

4.1 Group Comparisons

Prior to investigating relationships among WMI, executive functioning and adaptive functioning in individuals with AD and healthy controls, initial analyses focused on differences in these variables between these groups. The cognitive differences between AD and normally aging adults have been more extensively studied and there is a broader consensus on the types of impairments that are to be expected in the AD group. There is less consensus, however, on differences in brain structure and function

related to the disease process. This lack of consensus may be due, in part, to the limitations of the technologies used to probe these questions. Newer technologies, such as DTI, may provide a more sensitive tool for exploring these questions and researchers have recently begun to use DTI to examine differences in the microstructure between individuals with AD and healthy controls. Between group comparisons were made to confirm established differences in cognitive abilities, and to better understand potential differences in brain microstructure.

4.1.1 Covariates

Examination of the demographic variables revealed that, despite efforts to match participants on key variables, age and education were significantly different between the AD group and healthy controls. Given previous research and theoretical considerations, it was expected that WMI, cognitive abilities, and IADLs would be influenced by different levels of these variables. There is evidence, for instance, that WMI of the prefrontal cortex and cognitive abilities decline with advancing age even in normally aging individuals. The retrogenesis hypothesis describes anterior to posterior demyelination as part of the normal aging process that merely advances more rapidly in AD. Additionally, higher levels of education have been associated with better cognitive abilities and ability to perform IADLs. Analyses revealed that older age and lower education level were both associated with worse EF and IADLs. For this reason, age and education were entered as covariates in further analyses in order to identify additional group differences not related to these variables.

4.1.2 Group Differences in Executive Functioning

The results of this study provide additional support for the presence of executive functioning deficits as a component of the disease process of AD. Individuals with AD obtained significantly lower scores on the Similarities subtest when compared to healthy controls indicating diminished abstract verbal reasoning skills.

As discussed above, the nature of executive functioning deficits in individuals with AD remains somewhat unclear. Executive functions refers to a broad range of higher ordered skills falling broadly within the categories of volition, planning, purposive action, and effective performance (Lezak, 1995). Furthermore, different executive functions may be more strongly associated with particular cortical areas. Given differences in skills defined as executive functions and differences in associated brain regions, a theoretical foundation for the selection of variables for investigation is crucial. The retrogenesis hypothesis of brain degeneration in AD provided the theoretical framework that informed the selection of abstract verbal reasoning as the executive function of interest. Based upon the assumptions of the retrogenesis hypothesis, cognitive abilities in those areas myelinated last during development would be most likely to be susceptible to impairment. The DLPFC is the last to be myelinated and is associated with several executive functions associated with planning and abstraction. The Similarities test taps into the process of abstract verbal reasoning that has been previously tied to the DLPFC. Furthermore, while the DLPFC is associated with other important executive functioning tasks, Similarities (abstract verbal reasoning) is not confounded by processing speed which is common in other EF tasks. Differences in Similarities suggests deficits in abstract verbal reasoning in individuals with AD.

4.1.3 Group differences in WMI

In order to better understand potential differences in brain structure between individuals with AD and healthy controls, DTI was used to obtain a measurement of WMI within the left and right DLPFC and the left and right pvc. Significantly lower WMI was found in the left and right DLPFC of the AD group when compared to the healthy controls. No significant differences were found in the WMI of the pvc between these groups. These findings are consistent with the initial hypothesis of lower WMI in the prefrontal cortex in AD. As described above, the nature of structural differences remains an area of debate among researchers with some finding significantly lower WMI in the frontal lobe in AD (Naggara, et al., 2006; Duan et al., 2006; Choi et al., 2005) and others finding no significant differences (Head et al., 2004; Fellgiebel et al, 2004). While the present study cannot resolve this debate, the findings provide additional, compelling evidence for differences in frontal white matter in individuals with AD.

The rationale for the hypothesis of lower WMI in AD was built upon theory and previous empirical evidence. The retrogenesis hypothesis provides a theory of the pathological process of white matter in AD such that the process of human brain development is reversed. Specifically, this theory predicts that the disease process of AD reverses the process of myelinization, such that the areas that were myelinated last in development are the first to lose white matter in AD. In trying to identify differences between AD and healthy controls, therefore, it would be most appropriate to target the areas that were last to be myelinated in childhood because, according to this theory, differences would be most likely to be found in these areas. The previous studies investigating potential differences in white matter in AD did not, however, consistently

investigate regions of interest in line with this consideration. Additionally, the specificity with which the ROIs were drawn varied considerable between studies. It is noteworthy that the studies that previously found significant differences in frontal white matter in AD tended to have more anterior ROIs (Choi et al., 2005; Naggara et. al, 2006) while the studies that found no significant differences were more posterior (Head et al., 2004). The ROI within the present study, however, was selected based upon the retrogenesis hypothesis such that it would provide the most sensitive indicator of differences in WMI. ROIs were drawn in the DLPFC as this area is the last to become myelinated and the first to be affected according to the retrogenesis hypothesis. That the current study found differences in WMI where other studies failed to do so suggests that future studies investigating WMI in AD should more carefully choose ROIs based upon theoretical considerations.

4.2 Relationship between WMI, EF, and IADLs

The group comparisons provide a description of two groups characterized by significant differences in EF abilities and the white matter integrity of the DLPFC associated with those abilities. Previous research has linked both EF and white matter changes to the ability to perform IADLs, but the current study extends research by providing an explanation of the relationships among anatomy, cognition and functioning.

4.2.1 Relationship between EF and IADLs

The ability to perform more difficult day to day tasks (IADLS: e.g., playing a game of skill, working on a hobby; paying attention to, understanding, discussing television, or

books) diminishes in both normal aging and AD, although individuals with AD experience such declines more severely and more rapidly. Significant diminishment or loss of function in these day to day tasks can cause significant life disruptions and may eventually necessitate significant homecare or placement in a nursing home. Given the impact of impaired daily functioning on people's lives, many researchers have investigated the role of various cognitive functions on IADLs. IADLs were selected for the current study due to the more complex nature of the activities which necessitate the use of planning, organizing, and initiating skills categorized as EF. As predicted, the results of the current study demonstrate that EF (abstract verbal reasoning) significantly predicts the ability to perform IADLs.

4.2.2 Relationship between WMI and EF

In addition to establishing that EF can predict an individual's ability to perform IADLS, the present study provides evidence that WMI within the DLPFC are associated with EF, such that lower WMI predicts worse IADLs. Based upon the retrogenesis theory, these findings suggest that a progressive, degenerative process of demyelination occurs in individuals with AD and the deterioration of these brain areas results in diminished cognitive abilities associated with that region. The white matter of the DLPFC begins to lose its structure and fiber organization through the disease process and diminished EF (abstract verbal reasoning) skills result.

4.2.3 EF as a mediator of the relationship between WMI and IADLs

The mediation model (Figure 1) was proposed to explain the apparent close relationships among WMI, EF, and IADLs found previously in the literature. Because the retrogenesis theory proposes that a natural disease process occurs that follows a specific pattern, WMI was selected as the independent variable in the relationship. As IADLs are our dependent variable, EF was hypothesized to mediate the relationship between WMI and IADLs. The findings of the current study provide compelling evidence that the ability to complete IADLs is associated with the degree of WMI as mediated through EF. More specifically, EF fully mediated the relationship between WMI and IADLs, indicating that all of the predictive power of WMI is accounted for by EF.

As discussed previously, the careful selection of variables based upon prior research and theory likely played an important role in the ability to identify major group differences in cognition and brain microstructure and a mediational model resulting in full mediation. Nevertheless, some caution should be exercised in interpreting these results. These results suggest that all of the variability in IADLs within the DLPFC are accounted for by performance on the Similarities subtest (abstract verbal reasoning) but does not necessarily mean that other cognitive variables or brain regions are unimportant in the ability to perform IADLs. It may be that other brain regions are crucial for other cognitive abilities and could account for additional variability in IADLs.

4.3 Relationship between vascular risk factors, EF, and IADLs

Underlying the current research is the hypothesis that differences in WMI of the prefrontal cortex are reflected in EF ability and the ability to perform IADLs. As previous research has suggested that white matter changes frequently accompany vascular disease (Roman et al., 2004) and have been associated with activities of daily living (Kamper et al., 2005; Connelly et al 2005), the number of vascular risk factors (hypercholesterolemia, diabetes, high blood pressure, cardiac disease) present was compiled and used to investigate the possible relationship of vascular risk factors with EF and IADLs. In contrast to the hypotheses, vascular risk factor count was not significantly associated with either IADLs or EF.

These results were unexpected, particularly as they relate to the inability to establish a relationship between abstract verbal reasoning and vascular risk factors. Vascular risk factors have been associated with reduced abstract verbal reasoning in healthy individuals (Elias et al., 2005). The presence of vascular risk factors also appears to be associated with greater EF deficits in individuals with AD compared to AD patients without vascular risk factors (Goldstein et al., 2005). Furthermore, the presence of vascular risk factors have been associated with more likely conversion to AD and more rapid disease progression suggesting that the current research would have likely found a relationship between the presence of vascular risk factors and IADLs. Although the selection and measurement of vascular risk factors was informed by previous studies, it should be noted that there is some variability with respect to how this variable was selected and measured in other studies. Many studies selected individual vascular risk factors (Robbins et al., 2005) or measured them on a continuous

scale (Elias et al., 2005). Although our data included participants at each level of vascular risk (0-4 risk factors: AD 0-4; Control 0-3), this variable has a limited range compared to other continuous indices of vascular risk (e.g. blood pressure). Using variables on a continuous scale allows for more variability that may be obscured when vascular risk factors are compiled as a count of different risks. Perhaps this added variability might allow for the detection of an association between vascular risk factors and EF or IADLs although some researchers have found the opposite to be the case (Goldstein et al., 2008). For example, it may warrant weighting of different risk factors (e.g. hypertension, diabetes) over other risk factors. Although there is significant evidence linking vascular risk factors to increased EF impairment in both AD and healthy controls, not all researchers have found this to be the case (Hayden et al., 2006).

4.4 Limitations of the Study

The current study adds to the literature by using powerful neuroimaging and statistical methods together to identify relationships between the microstructure of the brain, cognitive abilities and adaptive functioning. DTI, in particular, allows researchers to obtain information about the structure of the brain that would otherwise be inaccessible. Neverthess, due to the expense and difficulty of obtaining data, studies using neuroimaging frequently involve fewer participants. Additionally, mediational models require larger numbers of participants to obtain the power necessary to detect real relationships between variables. Although 30 participants represents a sizable sample when compared to most neuroimaging studies, it is a smaller sample with

respect to mediational studies and additional participants could increase confidence in the current findings. Additionally, a larger number of participants could allow for moderated mediation that could test for differences between groups in the relationships among WMI, EF, and IADLs. That said, there appears to be sufficient power to detect relationships among EF, IADLs, and WMI. Given the limitations associated with collecting neuroimaging data, however, it seems unlikely that such research will be feasible in the foreseeable future.

Although the retrogenesis hypothesis informed the current research and the results appear consist with the theory, the current study was not designed in such a way that allowed for a true test of the theory or any other theory of degeneration. The current study was cross sectional and did not take into account differing severities of dementia, therefore it is not reasonable to draw conclusions regarding anterior to posterior progress of degeneration in AD or normal aging according to the theory. Additionally, ROIs were limited to the DLPFC and the pvc in the current study and a better understanding of the degenerative process would require ROIs in additional regions for a more comprehensive understanding of the process. Nevertheless, the results of the current study were able to identify key differences in the microstructure of the DLPFC between AD and healthy controls using the retrogenesis hypothesis to guide ROI selection.

4.5 Future Directions

Some of the limitations mentioned above could potentially be addressed by future research. While challenging, research employing a longitudinal design and a

mediational model such as the one described in the current paper could provide a wealth of information regarding the process of neurodegeneration and how that relates specifically to cognition and functional outcome. The current study demonstrates that it is possible to delineate a specific relationship leading from neuroanatomy to cognition and finally to functional abilities. Adding an understanding of how these processes evolve over time could have important implications for treatments that might allow individuals to optimize their level of functioning. Despite the obvious benefit of such a research project, clear obstacles to such research would include the difficulty of obtaining sufficient neuroimaging data and limiting loss of subjects over time. For that reason, cross sectional designs that include degree of dementia as a variable could also provide important clues regarding the process of neurodegeneration and how it relates to cognition and IADLs.

While the current study examined WMI within a small area of the DLPFC and treated it as an isolated structure, future studies could look at white matter pathways connecting significant brain areas in an effort to better understand the process of degeneration. In other words, the research could focus more on networks and connections that might be susceptible to degeneration and attempt to understand how they are related to cognition and adaptive functioning. Given the relationship established between WMI in the DLPFC and executive functioning/ IADLs in the current study, future research could use tractography originating with the DLPFC as a starting point.

In general, the current study has important implications for future research. Specifically, it demonstrates that it is possible to detect small differences in brain

microstructure and to outline a specific relationship leading from neuroanatomy to cognition and ultimately, ability to perform day to day functioning. As such, other researchers can be encouraged to employ mediational models in their own research. Clinically, it is hoped that this research and future research using the same methodology, may provide important clues for targeted treatment interventions. A better understanding of the neurodegenerative process and related cognitive decline may assist in earlier identification of the disease and implementation of treatment with the ultimate goal of limiting the impact of the disease on the patient’s functioning.

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