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Microstructural white matter changes in Alzheimer's disease: A diffusion tensor imaging study.

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy

in

Clinical Psychology

by

Nikki Renee Horne

Committee in charge:

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2008

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Chair

University of California, San Diego

San Diego State University

2008

DEDICATION

To Margaret Horne, my inspiration

and

Larry Horne, for making it possible.

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LIST OF ABBREVIATIONS

1.5T	1.5 Tesla
3T	3 Tesla
AD	Alzheimer's disease
ADC	apparent diffusion coefficient
ADRC	Alzheimer's Disease Research Center
AFNI	Analysis of Functional NeuroImages
ANOVA	analysis of variance
ANCOVA	analysis of covariance
APOE ϵ4	apolipoprotein ε4 allele
B0	no diffusion weighting
BNT	Boston Naming Test
CP	cerebral peduncles
CSF	cerebrospinal fluid
CVLT	California Verbal Learning Test
DA	axial diffusivity
DKEFS	Delis Kaplan Executive Function System
DR	radial diffusivity
DRS	Mattis Dementia Rating Scale
DTI	diffusion-tensor imaging
DWI	diffusion-weighted imaging
EEG	electroencephalography

EPI	echo-planar imaging
FA	fractional anisotropy
FA_D	FA skeleton voxels that were significantly different across groups
FLAIR	fluid-attenuated inversion recovery
FMRI	functional magnetic resonance imaging
FOV	field of view
FSRP	Framingham Stroke Risk Profile
GM	gray matter
ICp	posterior limb of the internal capsule
ILF	inferior longitudinal fasciculus
MCI	mild cognitive impairment
MD	mean diffusivity
MEG	magnetoencephalography
MMSE	Mini-Mental State Examination
MNI	Montreal Neurological Institute
MPRAGE	magnetized prepared rapid gradient echo
MRI	magnetic resonance imaging
MTL	medial temporal lobe
NEX	number of excitations
NFT	neurofibrillary tangles
PCA	principle components analysis
PET	positron emission tomography

R_2	transverse relaxation rate
RA	relative anisotropy
ROI	region of interest
SLF	superior longitudinal fasciculus
TBSS	tract-based spatial statistics
TE	echo time
TR	repetition time
UF	uncinate fasciculus
VBM	voxel-based morphometry
WAIS-III	Wechsler Adult Intelligence Scale – Third Edition
WAIS-R	Wechsler Adult Intelligence Scale – Revised
WMS-R	Wechsler Memory Scale – Revised
WM	white matter
WMH	white matter hyperintensities

ACKNOWLEDGEMENTS

I would like to thank my research mentor and committee chair, Mark Bondi. This work would not have been possible without your guidance and support; thank you for giving me the opportunity to pursue my own ideas. Also, I would like to thank Brian Schweinsburg for his many hours of hands-on technical guidance and teaching.

Thank you to all the members of the Bondi Lab who were extremely helpful with data collection and processing: Lisa Delano-Wood, Christina Wierenga, Katie Bangen, Amy Jak, and Hera Patail.

Thank you to the research volunteers at the Alzheimer's Disease Research Center for participating in this study and to David Salmon, Sue Johnson, and Cecily Jenkins for helping with subject recruitment.

Thanks also to the Directors of the SDSU/UCSD Joint Doctoral Clinical Program: Robert Heaton and Elizabeth Klonoff, for running a wonderful program.

Finally, I would like to give special thanks to John Stricker for his patience and willingness to help me through all stages of this project.

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ABSTRACT OF THE DISSERTATION

Microstructural white matter changes in Alzheimer's disease:
A diffusion tensor imaging study.

by

Nikki Renee Horne

Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2008
San Diego State University, 2008

Professor Mark W. Bondi, Chair

The retrogenesis model of Alzheimer's disease (AD) posits that changes in white matter (WM) follow an inverse pattern of myelogenesis. Diffusion tensor imaging (DTI) was used to test the retrogenesis model. Specifically, greater loss of WM microstructural integrity (e.g., lower values of fractional anisotropy; FA) was predicted in late-myelinating WM fiber pathways (e.g., association pathways) in AD patients relative to healthy older adults, whereas early-myelinating fiber pathways (e.g., projection pathways) were not expected to show group differences. Furthermore, it has been proposed that AD includes a disconnection syndrome. Thus, higher cognitive functions dependent upon the synchronization of distributed neural networks (e.g., executive functions) were predicted to correlate with WM integrity.

This study included 16 AD patients (mean age = 77.4, 64% female) and 14 demographically-matched healthy older adults (mean age = 77.3, 50% female). Image processing via tract-based spatial statistics (TBSS) was used to perform voxelwise statistics across subjects on FA skeleton maps. Additionally, region of interest (ROI) group comparisons were performed on early-myelinating (posterior limb of internal capsule, cerebral peduncles), late-myelinating (inferior longitudinal fasciculus, superior longitudinal fasciculus), and commissural (genu, splenium) fiber pathways. Permutation-based voxelwise analysis corrected for multiple comparisons revealed significantly lower FA values in AD patients compared to healthy older adults in late-myelinating association fiber pathways (superior longitudinal fasciculus, inferior longitudinal fasciculus, and uncinate fasciculus) and other fiber pathways that connect brain regions afflicted early by AD neuropathology (cingulum, fornix, splenium; $p < .05$). No significant differences were seen in early-myelinating pathways. These group differences remained significant after controlling for grey matter, WM, and white matter hyperintensity volumes. ROI analyses showed significantly lower FA in the inferior longitudinal fasciculus ($p < .05$). Pearson correlations revealed that dementia severity and neuropsychological composite scores in the domains of executive functions, processing speed, and memory were significantly related to WM integrity ($p < .05$). In conclusion, we found that patients with AD show demonstrable changes in vulnerable WM fiber pathways that likely reflect both retrogenesis and Wallerian degeneration (WM degeneration secondary to neuronal loss). WM integrity was associated with changes in higher-order cognition, supporting the view of AD as a

disconnection syndrome. Knowledge of the pattern of WM microstructural changes in AD and its underlying mechanisms may contribute to earlier detection and intervention in at-risk groups.

Chapter 1. Introduction

1.1 Introduction

Alzheimer's disease (AD) is a late-life neurodegenerative disorder that results in the insidious onset and gradual progression of cognitive impairment (Katzman, 1986). As the leading cause of dementia, AD is responsible for more than half of all dementia cases. As atrophy, neuron loss, and the formation of senile plaques and neurofibrillary tangles progress, patients with AD present with a gradual decline of memory and other cognitive abilities, eventually leading to severe functional impairment and the need for total care. Although there is no clinically effective treatment for AD, a variety of neuroprotective agents designed to decelerate disease progression are either currently available or on the horizon (e.g., cholinesterase inhibitors, NMDA receptor antagonists, amyloid vaccine, non-steroidal anti-inflammatory drugs, estrogen replacements, anti-oxidants).

Researchers have recently begun to focus on the importance of white matter (WM) changes in the pathogenesis of AD. It has been hypothesized that changes in WM may precede the accumulation of neurofibrillary tangles and plaques, following an inverse pattern of myelogenesis (Bartzokis, 2004). In other words, areas with large diameter fibers that myelinate first in development, such as primary sensory areas, are the last to be affected by AD pathology, and those areas with small diameter fibers that myelinate last in normal development, such as neocortical association areas and the allocortex, are the first to be affected by the AD degenerative process (termed "retrogenesis"; see section 2.3).

Diffusion-tensor imaging (DTI) has high sensitivity for detecting microscopic structural changes in WM and provides a means of assessing these changes *in vivo*. Researchers have begun to advocate that this imaging technique holds great promise for the early detection of AD and for tracking the efficacy of neuroprotective drugs in clinical trials (Sullivan & Pfefferbaum, 2003). For example, researchers have shown that assessing microstructural changes in WM with DTI may be more sensitive to the detection of early AD than macrostructural measures of brain volume alone (Kantarci et al., 2005; Muller et al., 2006; Persson et al., 2006; Rose et al., 2006). However, relatively few studies have used DTI to characterize the microstructural WM changes that occur in patients with AD and fewer have correlated diffusion parameters with neuropsychological performance. In addition, results have been inconsistent across studies, with some researchers finding greater loss of WM integrity in posterior than anterior regions (Head et al., 2004; Medina et al., 2006; Rose et al., 2000; Takahashi et al., 2002), and others reporting an anterior-posterior gradient of degeneration (Bozzali et al., 2002; Choi, Lim, Monteiro, & Reisberg, 2005; Duan et al., 2006; see section 5.9.c).

1.2 Overview of Literature Review

To address the extant literature relevant to the study, neuropathologic changes that occur in normal aging and in AD will be summarized. Next, the cognitive changes that occur in normal healthy elderly and in individuals with AD will be reviewed. This will be followed by an overview of the structural changes in gray matter and WM in these two populations, and of how these changes relate to cognition. Then, the

principles and methods of DTI will be presented, followed by a summary of the reported changes in diffusion parameters observed during normal aging and during the AD process, along with a discussion of how diffusion parameters relate to cognition in these populations. Finally, the aims and hypotheses of the study will be presented.

Chapter 2. Neuropathology of Alzheimer's disease

2.1 Neuropathologic Changes in Normal Aging and AD

Among normal individuals, advancing age increases the probability of losing neurons, synapses and neurotransmitters. Studies have produced conflicting results regarding whether various neuropathologic changes, such as loss of neocortical neurons and decreases in synaptic density, receptor binding, transmitter turnover, cortical blood flow, and the functional coherence of neural networks, inevitably occur with increasing age or whether there is a proportion of elderly individuals in whom such changes do not occur (Mesulam, 2000). In the AD disease process, the formation of an abnormal tau protein in certain susceptible types of neurons destabilizes microtubules responsible for transporting substances between cellular compartments, obstructing axonal transport and altering the cytoskeleton. These processes eventually lead to the formation of neuropil threads and neurofibrillary tangles (NFTs). A second process, which usually begins later than and is independent of the intraneural alterations just described, is the deposition of beta-amyloid. This occurs extracellularly and may lead to the development of senile plaques (Braak et al., 1999). These two types of pathological lesions (NFTs and senile plaques) are necessary in a certain density and distribution for a post-mortem diagnosis of AD (Braak & Braak, 1996b). In addition, NFT and amyloid plaques will occur in the majority of elderly individuals over the age of 60, whether or not they will eventually develop AD (Mesulam, 2000). Some argue that the development of NFT and amyloid plaques in otherwise normal healthy elderly is part of the normal aging process (Delacourte et al., 1999), whereas

others assert that such changes cannot be considered a normal consequence of aging and instead indicate the beginning of AD (Braak, Braak, Bohl, & Reintjes, 1996).

The accumulation of NFT occurs in consistent temporal and spatial patterns and increases with age, whereas amyloid plaque deposits do not display a consistent pattern and do not necessarily increase with age or correlate with clinical symptoms (Braak et al., 1999). The cognitive and behavioral changes seen throughout the course of AD correspond to the known procession of NFT accumulation in the brain. Braak and Braak (1996b) outlined this progression, describing that NFT first accrue in the entorhinal cortex. The destructive process then increases in density and spreads into the hippocampal formation and other limbic and paralimbic cortices, eventually encroaching upon the neocortical association areas and the striatum.

2.2 Neuropathologic Changes of WM in Normal Aging and AD

In contrast to a relative preservation of nerve fibers within the gray matter of the cerebral cortex, there is a reduction in the number and length of WM nerve fibers with age (Peters, 2002; Tang, Nyengaard, Pakkenberg, & Gundersen, 1997). In addition, degeneration of myelin has been shown to occur during normal aging. Peters (2002) described that two common age-related myelin defects are the formation of splits with an accompanying encasement of dense cytoplasm and the formation of balloons within the myelin sheaths. In addition, myelin production continues with age but may be less well-controlled and thus more vulnerable to insult. This continued production leads to redundant myelin and to splits in the circumference of sheaths (i.e., the average thickness of myelin sheaths is greater in older adults, but they show

more circumferential splitting), which may be indicative of changes in oligodendrocytes during normal aging (Bartzokis, 2004; Peters, 2002). For example, the characteristics of oligodendrocytes differ according to when in the process of brain development they began to produce myelin. Myelination of axons within association areas (e.g., prefrontal, inferior temporal, and temporoparietal regions) has been reported to continue into the fifth or even sixth decades of life (Bartzokis, 2004). These late-differentiating oligodendrocytes myelinate numerous small diameter axons. In contrast, motor and primary sensory areas that are the first to myelinate in the developing brain can have oligodendrocytes that myelinate only one segment of a large diameter axon (Bartzokis, 2004).

Neuropathologic studies have demonstrated that WM changes are present in roughly 60% of AD patients (Brun & Englund, 1986). Brun and Englund (1986) described that a WM disorder resembling incomplete infarction exists in a majority of AD patients and often is accompanied by an abnormality of the small-vessels of deep WM. They enumerated a number of microscopic changes in the WM that appear only as pale areas on gross, macroscopic brain sections. These changes include a partial loss of axons, myelin sheaths, and oligodendroglia cells that possibly precedes the macroscopic attenuation of WM tissue, along with a mild glial reaction and the presence of a few macrophages. Changes in myelin have been reported in AD, even at the earliest stages of the disease, among individuals free of infarction or WM amyloid angiopathy (Bartzokis, 2004; Bronge, Bogdanovic, & Wahlund, 2002; Brun & Englund, 1986; Roher et al., 2002). As discussed below, some investigators have

proposed that myelin degeneration may be a primary disease process (Bartzokis, 2004; Bronge et al., 2002; Kobayashi et al., 2002). Alternatively, others argue that factors such as oligomeric beta-amyloid may accelerate the observed myelin breakdown (Roher et al., 2002). Further, many researchers have indicated that Wallerian degeneration (WM damage secondary to neuronal loss) might contribute to the changes seen in the WM of AD patients (Roher et al., 2002).

2.3 Retrogenesis Model

Recently, researchers have begun to focus on the importance of WM neuropathologic changes in the pathogenesis of AD. It has been proposed that changes in WM, specifically in oligodendrocytes, may even precede the accumulation of NFTs and plaques (Bartzokis, 2004; Braak & Braak, 1996a; Reisberg et al., 1999). It is hypothesized that the known pattern of progression of AD pathology throughout the brain follows the reverse pattern of myelogenesis. In other words, areas with large diameter fibers that myelinate first in development, such as primary sensory areas, are the last to be affected by AD pathology, whereas those areas with small diameter fibers that myelinate last in normal development, such as neocortical association areas and the allocortex, are the first to be affected by the AD degenerative process (termed "retrogenesis" by Reisberg et al., 1999).

Bartzokis (2004) highlighted that by modeling AD as a "disconnection" syndrome, it necessarily follows that higher cognitive functions that are dependent upon the synchronization of distributed neural networks (e.g., multi-modal functions) are the most vulnerable to the effects of aging or the AD process. Other researchers

have also proposed that AD includes a disconnection syndrome (Delbeuck, Van der Linden, & Collette, 2003) and experimental studies of cognition (Festa et al., 2005; Lakmache, Lassonde, Gauthier, Frigon, & Lepore, 1998; Mohr, Cox, Williams, Chase, & Fedio, 1990), as well as electrophysiological studies using EEG and MEG in AD (Berendse, Verbunt, Scheltens, van Dijk, & Jonkman, 2000; Leuchter et al., 1992), have provided support for this assertion. Bartzokis (2004) also emphasized that portraying AD as a "development-to-degeneration" model with myelin as the central construct underscores the importance of utilizing *in vivo* methods that reflect WM microstructure, such as DTI, as it will be a critical component in testing this model (Bartzokis, 2004).

Chapter 3. Cognitive changes

3.1 Normal Aging

Researchers have shown that cognitive decline is a nearly universal finding in studies of cognition and aging. Declines in information processing speed, executive functions, and efficiency of learning and recall have frequently been reported (Corey-Bloom et al., 1996; Desgranges, Baron, & Eustache, 1998; Gunning-Dixon & Raz, 2000; Hulette et al., 1998; Mittenberg, Seidenberg, O'Leary, & DiGiulio, 1989; Schacter, Savage, Alpert, Rauch, & Albert, 1996; Ylikoski et al., 1993). A recent review (Park, O'Connell, & Thomson, 2003) reported that some degree of cognitive decline was evident in all 19 studies reviewed, although the magnitude of decline varied. A number of factors may contribute to cognitive decline in the elderly, including sensory deficits, motor changes, health conditions, poor nutrition, suboptimal motivation, and undetected early dementing processes. Other factors, such as education, occupation, expertise, and fitness, may protect against such decline. Certain cognitive abilities are more vulnerable to decline with age than are others. Crystallized or knowledge-based abilities, such as vocabulary and comprehension, do not decline (and often improve) with age. Conversely, fluid or process-based abilities, such as processing speed, working memory, reasoning, and other abilities that are largely independent of experience, do evidence declines with age.

Though common, cognitive decline is not inevitable in all individuals, as some studies have shown that there is a subgroup of individuals that perform as well as younger adults on cognitive tests, representing “successful aging” (Rowe & Kahn,

1987; Ylikoski et al., 1999). Longitudinal studies of elderly individuals also indicate pronounced and increasing heterogeneity of individual differences in memory performance over time (Christensen et al., 1999; Wilson et al., 2002). Thus, it is important to keep in mind that the aging process is associated with increasing variability in cognitive abilities and in the degree of change across individuals.

3.2 Theories of Cognitive Decline in Normal Aging

Several common factor theories have been put forth in an effort to parsimoniously explain age-related cognitive declines. These models have suggested that a single factor, such as processing speed, working memory, inhibition, sensory function or motor function (Kramer, Bherer, Colcombe, Dong, & Greenough, 2004; Park et al., 2003; Salthouse, 1996), can account for a substantial proportion of age-related variance across a number of cognitive domains. The processing speed theory put forth by Salthouse (1996) is a popular example of a common factor model of cognitive aging. This theory asserts that declines in cognitive abilities can largely be explained by a slowing of processing speed. Thus, because certain abilities, such as encoding, rehearsal, retrieval, and integration and organization of information are facilitated by efficient processing speed, the slowing of this process that occurs during aging will result in declines in these abilities, and to the extent that information has not been encoded and is not as accessible, will also result in declines in higher order cognitive functions such as reasoning and memory.

More recently, much enthusiasm has been generated for a common factor model with a biological basis, the frontal lobe hypothesis of neurocognitive aging

(Greenwood, 2000; West, 1996). As will be delineated shortly, there appears to be an anterior-posterior gradient in the degree of atrophy and WM changes seen in normal aging, with increased atrophy and decreased WM structural integrity in the frontal lobe (and particularly in the prefrontal area) than in temporal, parietal and occipital areas. Due to this differential decline, cognitive abilities thought to be dependent upon these areas (or on their functional connections), such as working memory, task-switching, speeded verbal fluency, directing attention away from irrelevant stimuli, setting response criteria, and monitoring performance, are hypothesized to be more susceptible to age-related declines (Grady & Craik, 2000; Raz, 2005; West, 1996). Researchers have expanded their focus on gray matter changes to include WM fiber pathways supporting the integration of networks of brain regions. A "disconnection" syndrome can ensue if WM connectivity is interrupted, leading some to view the process of cognitive aging as a disconnection model, with integrity of WM pathways being the common factor, as opposed to the frontal lobes exclusively (Bartzokis, 2004; O'Sullivan et al., 2001; Pfefferbaum, Adalsteinsson, & Sullivan, 2005; Raz, 2005). Some researchers, however, caution that a common factor model is insufficient to explain the increasing heterogeneity of cognitive abilities seen in normal aging, and instead purport that multiple processes with different life span trajectories likely underlie these changes and thus a multifactor model is needed (Band, Ridderinkhof, & Segalowitz, 2002; Buckner, 2004; Kramer et al., 2004).

3.3 Preclinical Alzheimer's Disease

Numerous studies have shown that measures of the ability to learn new information and retain it over time are quite sensitive in differentiating early AD from normal aging, with early AD being characterized by rapid forgetting (Delis, Massman, Butters, Salmon, Cermak, Kramer, 1991; Eslinger, Damasio, Benton, & Van Allen, 1985; Storandt, Botwinick, Danziger, Berg, & Hughes, 1984). As a failure of anterograde memory is usually the most prominent neuropsychological feature during the early stages of AD, researchers have investigated whether such changes are evident before a clinical diagnosis can be obtained. As anticipated, measures of memory and learning have revealed cognitive declines that precede clinical diagnosis by several years or more (Albert, Moss, Tanzi, & Jones, 2001; Bondi, Salmon, Galasko, Thomas, & Thal, 1999; Bondi et al., 1995; Grober & Kawas, 1997; Snowdon, 1997). In addition, nondemented older adults who possess the apolipoprotein ε4 allele (APOE ϵ4) have demonstrated mild episodic memory decrements (Bondi et al., 1999; Bondi et al., 1995; Hyman et al., 1996).

3.4 Cognitive Discrepancies in Preclinical AD

Although the episodic memory decline described above appears to be one of the most salient markers of preclinical AD, recent studies suggest that mild asymmetric cognitive decline may also detect preclinical AD (Jacobson, Delis, Bondi, & Salmon, 2002, 2005a; Jacobson et al., 2005b). Jacobson, Delis, Bondi, and Salmon (2002) demonstrated that the initial presentation of cognitive deficits in AD may have asymmetrical involvement as a common feature (i.e., language decrements

significantly greater than visuospatial decrements, or vice versa). Measures of asymmetric cognitive profiles were derived using difference scores on tests of verbal and visuospatial ability. Although both groups performed similarly on the individual cognitive tests (i.e., mean score analyses between groups), the use of difference scores measuring asymmetric cognitive performance yielded consistent evidence of subtle differences in cognition in a subgroup of preclinical AD patients. The preclinical AD group showed significantly larger discrepancies between naming and visuoconstructive skills relative to matched control participants, and a higher frequency of asymmetric cognitive profiles compared to a larger normative group. Cognitive discrepancies have also been demonstrated on tests of auditory and spatial attention (Jacobson et al., 2005a), verbal and design fluency (Houston et al., 2005), global versus local item processing (Jacobson et al., 2005b), as well as response inhibition and cognitive flexibility (Wetter et al., 2005). This paradigm has also been extended to another at-risk group, the Very-Old, which revealed a similar increase in prevalence of asymmetric cognitive profiles compared to younger elderly groups (Horne, Bondi, & Delis, 2006). Although the neuropsychological mechanism underlying cognitive asymmetry in preclinical AD remains unknown, the findings are consistent with a number of reports of lateralized onset with asymmetric neuroanatomic changes (Thompson et al., 1998) or metabolic asymmetry in the early presentation of AD in a subset of patients (Grady et al., 1990; Reiman et al., 1996).

3.5 Alzheimer's Disease

As noted above, a deficit in episodic memory is often the initial symptom in AD, and it is characterized by rapid forgetting, a tendency to display a recency effect and a deficient primacy effect on list-learning tasks, intrusion errors, and a positive response bias upon recognition testing (Bayley et al., 2000; Delis, Massman, Butters, Salmon, Cermak, Kramer, 1991). Episodic memory impairment may be exacerbated by working memory or attention deficits (Baddeley, Della Sala, & Spinnler, 1991). After the development of episodic memory impairment, there is increasing impairment across a number of cognitive domains. Executive dysfunction may also occur early in the clinical presentation of the disease, leading to poor performance on tasks requiring novel problem solving, concept formation, abstract reasoning, manipulation of information, set-shifting and sequencing, as well as impaired judgment and insight. Affective and personality changes may also occur. In addition to anterograde amnesia, retrograde amnesia is also present and typically follows a temporal gradient: older memories are better preserved than more recent events. Deficits in semantic memory are evidenced by a reduced ability to recall overlearned facts (Norton, Bondi, Salmon, & Goodglass, 1997), and by impairment on tests of confrontation naming (Bowles, Obler, & Albert, 1987; Martin & Fedio, 1983), verbal fluency (Butters, Granholm, Salmon, Grant, & Wolfe, 1987; Martin & Fedio, 1983; Monsch et al., 1992) and semantic priming (Salmon, Shimamura, Butters, & Smith, 1988). As deficits in semantic memory become more severe, language functions become increasingly impaired. Initially, naming and word finding difficulties are exhibited, which later

expands to disrupted verbal and written comprehension and expression. Constructional tasks such as clock drawing and Block Design often elicit deficits in visuospatial abilities, which may be evidenced in every day life by becoming lost even in familiar places. As the disease progresses further, AD patients may exhibit agnosia and apraxia, and ultimately a loss of self-hygiene, eating, ambulatory abilities, incontinence and motor dysfunction.

3.6 Diagnostic Criteria for AD

In order to establish a clinical diagnosis of probable AD, according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, a clinical exam and mental status testing must establish the presence of dementia (a syndrome of acquired intellectual impairment of sufficient severity to interfere with social or occupational functioning), deficits in two or more areas of cognition, progressive worsening of memory and other cognitive functions, no disturbance of consciousness, and the absence of systemic or other brain disease capable of producing a dementia.

Chapter 4. Structural changes

4.1 Normal Aging

4.1.a Volumetric changes of gray matter and WM in normal aging.

Magnetic Resonance Imaging (MRI) cross-sectional studies that have included a large age span covering young adults to the elderly have shown that changes in brain volume follow an inverted U trajectory, with an increase in volume during young adulthood, a plateau in middle age, and then a decline throughout old age (Courchesne et al., 2000; Jernigan et al., 2001; Raz et al., 2005). Researchers have investigated whether gray and WM volumes show differential patterns and rates of change throughout the life span. Cortical gray matter volumes begin to decline in adolescence, whereas WM volumes continue to increase in adulthood. Subsequently, gray matter shows a linear decline with advancing age, whereas WM volume loss and other WM changes seem to be delayed until middle adult life and then may accelerate after age 70 (Courchesne et al., 2000; Ge et al., 2002; Jernigan et al., 2001). Jernigan et al. (2001) reported that, despite the longer period of decline in gray matter volumes, WM volume loss exceeds gray matter volume loss in individuals past age 70, and they estimated a loss of 26.5% of WM volume from age 30 to age 90.

As mentioned previously in section 2.3, WM volume loss is thought to begin in late-myelinating areas, such as the prefrontal cortex, that contain more thin myelinated fibers that are more vulnerable to age-related declines (Bartzokis, 2004; Raz, 2005). This pattern has been most commonly demonstrated in studies of the corpus callosum. The genu, in particular, is reported to be differentially susceptible to

age-related changes (Head et al., 2004; Sullivan, Pfefferbaum, Adalsteinsson, Swan, & Carmelli, 2002). For example, Head et al. (2005) analyzed volumes of the anterior and posterior callosal regions in 50 young adults aged 18 to 30 years and 50 nondemented older adults aged 65 to 93 years. Significant volumetric declines were found in older adults compared to young adults for all callosal regions measured, and these age differences were greater in anterior regions than posterior regions.

This pattern of age-related anterior-posterior regional differences in the corpus callosum is consistent with previous findings that anterior regions of the cortex (i.e., prefrontal cortex volume) tend to show greater age-related volumetric declines than more posterior regions (Raz, 2005; Van Petten et al., 2004). This pattern of decline supports the general finding that changes in cognition with age are most evident among measures of executive function and memory, processes thought to be supported largely by the prefrontal and temporal regions, respectively (Kramer et al., 2004).

Given its prominence in the AD literature, the hippocampus has been extensively studied in normal aging. Results from some studies have suggested that hippocampal decline accelerates with increasing age (Head, Snyder, Girton, Morris, & Buckner, 2005; Jernigan et al., 2001; Raz, Rodrigue, Head, Kennedy, & Acker, 2004). Although studies investigating the relationship between memory performance and hippocampal volume have consistently shown significant quantitative relationships among individuals with AD or other pathology affecting the MTL, similar studies among normal healthy elderly have produced inconsistent results, with some studies

reporting such a relationship and others failing to find a significant association (Van Petten, 2004).

4.1.b Prevalence of WMH in normal aging. In addition to declines in WM volume, other WM changes, such as white matter hyperintensities (WMH; also referred to as WM abnormalities, WM lesions, or leukoaraiosis) and decreases in WM tract integrity (discussed in chapter 5), can also occur during the aging process and may have important clinical implications. WMH are areas of increased signal intensity on T_2-weighted MRI scans. Volumes of WMH are often calculated separately for different regions, such as periventricular hyperintensities, deep white matter hyperintensities, and WMH within lobes of the neocortex. The proportion of individuals with WMH has been reported to increase sharply with age (Allen, Bruss, Brown, & Damasio, 2005; de Leeuw, de Groot, & van Gijn, 2001; Jernigan et al., 2001). The reported prevalence of WMH among the elderly has ranged from 5% to 90% (de Leeuw et al., 2001), possibly due to variability in sample age ranges, whether individuals with vascular risk factors were excluded from the study, and whether rating scales or volumetric calculations were used. Because WMH have multiple causes and are often asymptomatic, they are considered nonspecific indicators of WM pathology (Erkinjuntti et al., 1996). In addition to age, a quantitative review reported that the number and extent of WMH correlated with vascular risk factors, such as a history of transient ischemia attack-cerebrovascular accident (TIA-CVA) and, to a lesser extent, hypertension (Gunning-Dixon & Raz, 2000). Accordingly, post-mortem studies have promoted three hypotheses for the pathogenesis of WMH. The first and

most strongly supported hypothesis is that WMH have an ischemic origin (Pantoni & Garcia, 1997). The observation that lesions in watershed zones surrounding tissue destroyed by an acute ischemic event resemble WMH provides evidence for this hypothesis and suggests that WMH may represent less severe or incomplete infarction (Brun & Englund, 1986). Two other possible mechanisms include disturbed CSF circulation (which would result in alterations in the ependymal lining of the ventricles) and increased permeability of the blood brain barrier (Pantoni et al., 1993).

4.1.c Cognitive correlates of WMH in normal aging. WMH have frequently been a focus of study in normal healthy elderly and in persons with dementia, but their relationship to cognition has yet to be firmly established and characterized. Although some studies have failed to find a relationship between WMH and cognition in nondemented older adults (Almkvist, Wahlund, Andersson-Lundman, Basun, & Backman, 1992; Schmidt, Fazekas, Kapeller, Schmidt, & Hartung, 1999; Wahlund, Almkvist, Basun, & Julin, 1996), several studies have shown significant correlations (Dufouil, Alperovitch, & Tzourio, 2003; Garde, Lykke Mortensen, Rostrup, & Paulson, 2005; Petkov et al., 2004; Skoog, Berg, Johansson, Palmertz, & Andreasson, 1996; Van Petten et al., 2004). For example, an increased number of subcortical WMH was shown to be related to declines in both memory performance and executive functions in a study of 48 healthy elderly aged 65 to 86 years (Van Petten et al., 2004). In a recent meta-analysis of 23 studies of adults without dementia (total $N = 4,476$, mean age = 69.2, range of 38.6 – 79.1), Gunning-Dixon and Raz (2000) found a small to medium effect (Pearson's $r = .22$, SD = .19, $p<.001$) of WMH burden on global

cognitive functioning. They found that an increase in WMH burden attenuated performance in several cognitive domains, including speed of processing (r = .22, SD = .13, p<.001), executive functions (r = .30, SD =.26, p<.01), delayed memory (r = .20, SD = .10, p<.01), and immediate/recent memory (r = .12, SD = .16, p<.05). WMH burden was not significantly correlated with crystallized intelligence, fluid intelligence (represented by mostly non-speeded tasks), or motor functioning (p's>.05), but the correlations were in the positive direction. The authors propose that this pattern of cognitive deficits, like those of normal aging, resemble the pattern observed in demyelinating diseases. These results are congruent with Salthouse's (1996) processing speed theory of cognitive aging and the "disconnection" hypothesis of age-related cognitive decline (discussed in section 3.2, Bartzokis, 2004).

4.2 Alzheimer's Disease

4.2.a Volumetric changes of gray matter and WM in AD. Structural MRI studies of patients with AD have shown results consistent with neuropathologic data. Hippocampal atrophy, as revealed by MRI, is one of the most characteristic features of AD. Researchers have consistently found significant differences in volumetric MRI measures of the medial temporal lobe (MTL), particularly the hippocampus and entorhinal cortex, between patients with AD and nondemented older adults (Chetelat & Baron, 2003; Zakzanis, Graham, & Campbell, 2003). Chetelat and Baron (2003) suggest that hippocampal atrophy does have a significant predictive value for conversion to AD according to the studies they reviewed, but that this predictive value is attenuated by the possible moderation of hippocampal atrophy by episodic memory

impairment (as part of normal aging or preclinical AD). When memory impairment already exists, as in subjects with mild cognitive impairment (MCI), the volume of MTL structures are poor predictors of conversion, because significant atrophy is already present in the MTL of such subjects. Therefore, continued investigation of the diagnostic utility of areas beyond the hippocampus and of parameters from non-volumetric imaging modalities is necessary, and consideration should be given to age and to dementia severity.

For example, Schott et al. (2003) compared presymptomatic, mild, and moderately affected AD patients with age and sex-matched controls, demonstrating increasing global atrophy with disease progression. The authors concluded that although the rate of hippocampal atrophy may be useful at early disease stages, the precuneus and posterior cingulate, which show significant, consistent and increasing rates of atrophy with increasing disease severity, may be more useful markers of progression throughout the disease course (Schott et al., 2003). A quantitative review (Zakzanis et al., 2003) found consistent results, with hippocampal deterioration offering the best discriminability between normal aging and the early stages of AD (i.e., duration of illness less than four years), and the MTL and anterior cingulate gyrus showing the most diagnostic sensitivity in later stages of AD.

The extent of hippocampal atrophy has also been compared to the extent of atrophy in the corpus callosum (Teipel et al., 2003). Based on receiver operator characteristic (ROC) derived indices, Teipel et al. (2003) found a lesser degree of atrophy for the total area of the corpus callosum relative to the hippocampus-amygdala

formation (HAF), but an equal extent of atrophy to HAF when only examining the splenium. They proposed that, contrary to expectations from neuropathologic studies of AD, their results suggest that degeneration of the allocortex (as represented by the HAF) and degeneration of the neocortex (or more specifically, parietotemporal neocortical areas whose fibers run through the splenium) are both present early in the AD process. Other studies have also found atrophy of the splenium in early AD (Lyoo, Satlin, Lee, & Renshaw, 1997). Rates of decline in the splenium have also been shown to correlate with increasing severity of AD (Teipel et al., 2002), although another study found that the middle sections of the corpus callosum (rostral body and midbody) were significantly correlated with dementia severity, whereas the splenium did not (Pantel et al., 1999). A longitudinal study reported that the splenium, rostrum, and total callosal volume demonstrated greater initial atrophy and greater declines over time relative to controls (Teipel et al., 2002). Although inconsistencies in the reported results are evident, in general there is some degree of atrophy in the corpus callosum, which may be magnified in the splenium, among individuals with AD.

4.2.b Prevalence of WMH in AD. Although the role of WMH in AD is unclear (see below for discussion), their presence in a large percentage of individuals with AD is evident. WMH have been reported to be more extensive in AD patients than in normal healthy elderly (Barber et al., 2000; Capizzano et al., 2004; Scheltens et al., 1992), even in early stages of the disease (Burns et al., 2005). Regional differences in the prevalence of WMH across lobes in individuals with AD have been reported, with the frontal lobes showing the highest prevalence (70%), followed by the

parietal lobes (22%; Capizzano et al., 2004), and this pattern has been corroborated (Gootjes et al., 2004).

4.2.c Neuropathology of WMH in AD. As previously mentioned, WMH are nonspecific indicators of white matter pathology (Erkinjuntti et al., 1996). In AD, WMH are thought to reflect selective incomplete WM infarction that results in partial loss of axons, myelin, and oligodendroglial cells and mild reactive gliosis (Brun & Englund, 1986; Sjobeck, Haglund, & Englund, 2006). Some have argued that WMH represent small vessel cerebrovascular disease (de Leeuw et al., 2004), whereas others suggest that WMH are not merely age-related phenomena, but might be related to the neuropathology of AD (Bronge et al., 2002; Leys et al., 1991).

4.2.d Cognitive correlates of WMH in AD. The relationship between WMH and cognition has yet to be firmly established and characterized. Although some studies have failed to find a relationship between WMH and cognition in AD patients (Hirono, Kitagaki, Kazui, Hashimoto, & Mori, 2000; Mungas et al., 2001; Mungas et al., 2002), several studies have shown significant correlations (Almkvist et al., 1992; Capizzano et al., 2004; Gootjes et al., 2004; Skoog et al., 1996; Stout, Jernigan, Archibald, & Salmon, 1996; Wolf, Ecke, Bettin, Dietrich, & Gertz, 2000). Possible contributing factors to the inconsistent findings across studies include the variety of rating scales used, the differing age ranges of the samples, methods of quantifying WMH, and differences in imaging protocols (Capizzano et al., 2004). Further, given that WM changes represent a shift in signal values that approaches or surpasses the range of signal values characteristic of gray matter, automated segmentation

algorithms may fail to accurately capture all WMH and, instead, may misclassify deteriorating WM as gray matter (Jernigan et al., 2001). This represents a common methodological problem that could contribute to cross-study variability. In addition to cognition, some studies have argued that WMH are associated with neuropsychiatric symptoms such as depression (Barber et al., 2000) or aberrant motor behaviors (Hirono et al., 2000).

Results from a recent study (Burns et al., 2005) suggest that WMH in individuals with early AD are more highly correlated with cognition than WMH in nondemented older adults, leading the authors to conclude that individuals with early AD may be more vulnerable to the deleterious effects of WMH. Studies investigating the influence of WMH on brain function in AD via functional magnetic resonance imaging (FMRI) or positron emission tomography (PET) have shown that increased WMH are associated with decreased activation in the prefrontal cortex (Tullberg et al., 2004) or other brain regions (DeCarli et al., 1996). The combination of both medial temporal lobe atrophy and WMH has been reported to increase both one's risk of having AD and the frequency and severity of cognitive deficits (van der Flier et al., 2005). Others have proposed that a certain threshold of WMH may be necessary before their effect on cognition is expressed (Boone et al., 1992; van der Flier et al., 2005; van der Flier et al., 2004). Neuropathologic studies have also demonstrated that the presence of WMH, in addition to plaques and neurofibrillary tangles, increases the risk of developing AD (Petrovitch et al., 2005; Snowdon et al., 1997). This effect has also been qualified, with some researchers suggesting that WMH increase the risk of

developing AD more in senile onset than presenile onset AD (de Leeuw et al., 2004; Scheltens et al., 1992).

4.2.e Role of WMH in AD. There is considerable debate about the role of WMH in normal aging and AD, and conflicting findings have been reported regarding whether WMH represent an additional neurodegenerative process in AD. Specifically, results from other studies have implied that these two processes may be independent (Fazekas et al., 1996; Hirono et al., 2000), whereas others suggest that WMH and atrophy may be additive or may exert a synergistic effect in AD (van der Flier et al., 2005; van der Flier et al., 2004). Moreover, some studies (Burns et al., 2005; Esiri, Nagy, Smith, Barnetson, & Smith, 1999) suggest that WMH may have a greater effect on cognition in early, mild AD compared to moderate or severe AD. Given the nonspecific nature of WMH, it is also possible that the etiology of WMH may vary with increasing age, which could further affect the relationship between WMH and cognition. Additionally, WM changes may have a different etiology in AD patients with an APOE ε4 allele (Bronge et al., 1999) or the etiology of WMH may vary by location (e.g., deep WMH versus periventricular WMH, Barber et al., 2000; Fazekas et al., 1993; O'Brien et al., 1996). Still other investigators suggest that vascular processes precede AD neuropathology, and that AD is primarily a vascular disorder with neurodegenerative consequences (de la Torre, 2002).

4.2.f Detection of mild WM changes with MRI. Mild WM changes may go undetected by conventional structural MRI. For example, an autopsy study (Bronge et al., 2002) revealed that less pronounced WM pathology was not seen on conventional

Fast-Spin Echo (FSE) MRI and that the changes consisted mainly of areas with reduced myelin density with a concomitant increase in tissue water content. More severe changes that included cell loss were required for visibility on MRI. It is also important to note that WMH reflect a number of pathological processes and structural MR methods cannot discriminate between various underlying cellular mechanisms. Emerging diffusion tensor imaging (DTI) techniques have high sensitivity for microscopic structural changes in the white matter and allow for the assessment of the directionality of white matter damage, which may provide more information regarding the etiology of white matter pathology in AD (Le Bihan et al., 2001).

Chapter 5. Diffusion-Tensor Imaging

5.1 Overview of Chapter

As summarized above, neuropathologic studies have demonstrated that changes in the macrostructure of WM are evident in AD. However, such studies are limited by their inherent post-mortem design where the cause of mortality can create confounds in inference and the possibility of predicting outcomes is obviously nonexistent. Volumetric MR studies have also identified macroscopic changes in WM in AD, in the form of atrophy or WMH. However, neither provides strong diagnostic information and their relationship to cognition is relatively weak. In contrast to both neuropathologic and morphometric studies, DTI provides a means of assessing, *in vivo*, microstructural changes in AD. Compared to other MR imaging modalities, relatively few studies have applied DTI to the study of AD, although the popularity of this technique is rapidly increasing with the advent of new, more promising approaches of image acquisition and post-processing. These DTI studies will be reviewed after briefly discussing the basic principles of diffusion-weighted imaging, the strengths and weaknesses of different approaches of acquiring and processing diffusion-weighted images, and the reported changes in diffusion parameters in normal aging.

5.2 Basic Principles of Diffusion

Diffusion MR imaging measures the diffusion of water. Diffusion can be described as random molecular motion (i.e., Brownian motion) caused by thermal energy (Le Bihan et al., 2001). A group of molecules that start at one location, such as

a drop of ink in water, will spread out over time. The likelihood of finding the location of a particular ink molecule after a span of time follows a Gaussian distribution (Mori, 2002). Diffusion is unrestricted in pure water mediums, such as CSF, and can be characterized as isotropic. This implies that diffusion expands spherically (i.e., it is orientation-independent) and therefore can be represented by a single parameter. In contrast to isotropic diffusion, diffusion in the presence of physical barriers, such as axonal fibers, facilitates the movement of water parallel to the fibers and restricts perpendicular movement, producing anisotropic diffusion. In this case, diffusion is no longer spherical. It cannot be characterized by a single scalar parameter because the extent of water diffusion may differ depending on the measurement orientation, and instead it must be described by a diffusion tensor, which defines the shape of an ellipsoid. A tensor is a mathematical construct that characterizes a multi-dimensional vector system (Moseley, Bammer, & Illes, 2002).

5.3 Principles of Diffusion-Weighted Imaging

When measuring pure diffusion, which is not constrained by any physical barriers, a single scalar parameter, namely the diffusion coefficient (*D*), can adequately summarize the diffusion of water molecules (Le Bihan et al., 2001; Mori, 2002). In a biological system where diffusion is influenced by multiple factors and therefore is not pure, another term is used to reflect the uncertainty of this single scalar parameter, the "apparent" diffusion coefficient (ADC, Beaulieu, 2002). For example, the ADC can vary depending upon the diffusion-sensitizing gradient factor (i.e., the "*b* value") employed (Beaulieu, 2002) and the interactions of the diffusing water

molecules with cellular structures that can create multiple subcompartments within a voxel (e.g., intra- and extracellular compartments, see Le Bihan et al., 2001). Early diffusion-weighted imaging (DWI) studies calculated an ADC value for each voxel. Therefore, DWI is a one-dimensional technique and only one diffusion gradient needs to be applied at a time to derive a single ADC (Basser & Jones, 2002). The value of such indices (that are not derived from the full diffusion tensor) can be highly dependent on the choice of gradient directions applied and on the relative orientation of the subject to the gradient hardware, making these indices extremely sensitive to head movement (Le Bihan et al., 2001).

5.4 Principles of Diffusion-Tensor Imaging

Unlike one-dimensional DWI, diffusion-tensor imaging (DTI) is three-dimensional, requiring a minimum application of six noncollinear directions to garner enough information to estimate the six independent elements of the 3x3 symmetric matrix **D** that comprises the diffusion tensor (Basser & Jones, 2002). The first three elements (the diagonal of the matrix) represent the longest (λ_1), middle (λ_2), and shortest (λ_3) eigenvalues (also referred to as principle axes or eigen diffusivities) that define the shape of the diffusion ellipsoid and denote the maximum to the minimum amount (or eigenvalue) of diffusion, respectively. The second three off-diagonal elements are vectors (*v*1-3) or angles that define the orientations of the principle axes relative to the measurement axis (Mori, 2002). Without the information contained within the off-diagonal elements of the diffusion tensor, fiber orientation cannot be determined (Basser, Mattiello, & LeBihan, 1994). In contrast to a single scalar ADC,

one advantage of scalar parameters derived from the 6 independent elements of the diffusion tensor is that such parameters are rotationally invariant. This is a desired quality of an MR variable because it implies that the parameter is not affected by the orientation of the subject's head relative to the direction of the applied gradients (Basser & Jones, 2002). As an alternative to measuring the diffusion tensor, several researchers have recently proposed methods to measure the ellipsoid directly, without estimating the tensor (e.g., high angular resolution diffusion; Frank, 2002). While this is a promising technique because it potentially allows for error parcellation and has the potential to identify crossing fibers within a voxel, this has not yet been applied to clinical studies due to extensive scanning times.

5.5 DTI Parameters

Although the diffusion tensor provides valuable three-dimensional information, such data is not as directly amenable to statistical analysis or visualization as is more traditional two-dimensional maps of image pixels (Kanaan et al., 2005). Therefore, researchers typically employ a variety of indices to summarize the three-dimensional data contained within the diffusion tensor. The average diffusion of a voxel can be represented by the mean diffusivity (MD), which is derived from the three eigenvalues ($\lambda_1 + \lambda_2 + \lambda_3 / 3$, Le Bihan et al., 2001). The shape of the ellipsoid, or the degree of intravoxel diffusion anisotropy, is most commonly represented as fractional anisotropy (FA, see Le Bihan et al., 2001 for formula). Studies have found that FA is one of the most robust measures of anisotropy (Pierpaoli & Basser, 1996). For example, Hasan et al. (2004) applied Monte Carlo simulations

and bootstrap analysis to both phantom and human DTI data and concluded that FA has higher signal-to-noise ratio than another common measure, relative anisotropy (RA). FA is derived from the three eigenvalues and the value of FA varies between 0 (isotropic diffusion) and 1 (complete anisotropy) depending on the brain tissue (e.g., cerebrospinal fluid has FA values near 0) and the specific brain structure that is measured. Researchers have reported that the corpus callosum, which is comprised of highly ordered, parallel white matter fibers has FA values approaching 1, whereas less ordered WM tracts that contain fibers of varying orientations within the same voxel will have lower FA values (Moseley, 2002; Sullivan & Pfefferbaum, 2003). For instance, in a study of 64 normal individuals aged 23-85, FA values were shown to vary roughly 43% across different WM regions, ranging from 0.70 to 0.40 in the splenium and the centrum semiovale, respectively (Pfefferbaum & Sullivan, 2003). Orientation of the diffusion can be represented by the largest eigen diffusivity (λ_1). This is also known as the principal diffusion direction or as axial diffusivity (DA, Basser, 1995). DA is thought to run parallel to WM fibers. Radial diffusivity (DR) represents diffusion perpendicular to WM fibers and is the average of the two smaller eigen diffusivities ($\lambda_2 + \lambda_3 / 2$).

As will be discussed below, the possible inferential implication of these various diffusion parameters to underlying neuropathologic changes remains an active area of research. In general, greater anisotropy is thought to signify a higher degree of WM microstructural integrity. Thus, if one were to compare the same WM tract across groups, lower FA and higher MD values in the patient group relative to the control

group would signify less anisotropy and thus less WM integrity in the patient group. Other, non-biological factors can also influence the value of diffusion parameters. Partial voluming, which is the infiltration of cerebrospinal fluid or gray matter into presumably WM voxels due to large voxel size or motion artifacts, can artificially lower FA values. Also, choice of *b* value can affect the sensitivity of DTI to detect microstructural changes. Yoshiura et al. (2003) examined the influence of different *b* values on sensitivity of DTI to detect differences between AD patients and controls. MD was found to significantly decrease with higher *b* values (1000, 2000, and 4000 s/mm^2). Although significant group differences in the integrity of subcortical WM of the parietal lobe were found for all three *b* values employed, the percentage elevation of MD in AD relative to controls grew larger with increasing *b* value. Specifically, parietal WM MD values were found to be 13.2% higher in AD relative to controls when $b = 1000$, 21.8% higher when $b = 2000$, and 30.1% higher when $b = 4000$. Contrast-to-noise ratio also increased with increasing *b* value in AD patients (but not in normal controls), indicating that the use of a higher *b* value is more sensitive to changes in the microstructure of WM in AD patients. The authors point out that a limitation of using a higher *b* value is that it lowers the signal-to-noise ratio. They suggest that use of a higher magnetic field (3T) can significantly increase the signal-to-noise ratio and permit the use of higher *b* values (Yoshiura et al., 2003).

In addition to FA and MD values, another recent development in DTI has been the advent of fiber tracking techniques. Fiber tracking is currently the only *in vivo* method that permits delineation of white matter anatomy and connectivity. Through

the use of a selected algorithm applied to the principle axis of the diffusion tensor (representing the predominant "direction" within a voxel; discussed earlier in this section), adjacent pixels or voxels sharing the same orientation as the principle diffusivity are assumed to be "connected." In this way, fiber tracts are reconstructed. Fiber tracking can be used to delineate regions of interest (for an example, see Sullivan, Adalsteinsson, & Pfefferbaum, 2006), and several parameters can be derived within an ROI, including number of fibers, the average diffusion, and the degree of anisotropy. However, fiber tracking techniques are based on the assumption that the principle axis of a diffusion tensor of a voxel does indeed represent the presence of uniform underlying fibers. Unfortunately, the accuracy of this method is highly dependent upon the sound estimation of the principal diffusion direction (Le Bihan, Poupon, Amadon, Lethimonnier, 2006). In addition, many voxels contain crossing fibers that, when averaged, obscure the principle direction of any individual WM tract. New methods of acquisition and increasingly sophisticated algorithms are being developed to help overcome the problem of crossing fibers and the inhomogeneous nature of WM for increasingly accurate fiber tracking results, but a detailed discussion of such methods are beyond the scope of this proposal (Le Bihan, Poupon, Amadon, Lethimonnier, 2006; Mori & van Zijl, 2002).

5.6 Possible Pathological Inferences

Most early DTI studies attributed findings of decreased anisotropy in diseased groups to demyelination, although other hypotheses of underlying neuropathologic change included damage to membranes, inflammation, and axonal loss due to

Wallerian degeneration secondary to cortical neurodegeneration (Englund, 1998). The assumption that anisotropy is due to the myelin sheath restricting perpendicular water diffusion was challenged by Beaulieu and Allen (1994) when they found anisotropic water diffusion in the non-myelinated olfactory nerve of the garfish that was similar to that of the garfish optic nerve, which is myelinated. Corroborative results have been shown in neonates. For example, anisotropic diffusion in nonmyelinated fibers of the corpus callosum in neonates has been demonstrated (Huppi et al., 1998). These results show that myelin is not required for anisotropic diffusion. Myelin may play a role in anisotropy, but the other structural aspects of the axons alone (e.g., axonal membranes) are enough to yield anisotropic diffusion (Beaulieu, 2002). There is some evidence that examining directional diffusivities (i.e., DA and DR) may yield important information about the underlying neuropathology driving differences in FA, with DR signifying loss of myelin, and DA implicating axonal damage (Song et al., 2003; Song et al., 2002; Sun et al., 2005).

5.7 Post-Processing Approaches

Most studies that have examined microscopic WM changes have used a region of interest (ROI) approach. While this approach has the advantage of reducing partial volume effects by selectively choosing voxels within WM regions that do not contain gray matter or cerebrospinal fluid, systematic bias can be introduced if the raters are not blind to diagnosis or if diagnostic status is evident due to enlargement of ventricles and generalized atrophy. In addition, there is substantial variability across different studies in ROI placement despite similar anatomical labels. Further, regions that are

targeted in more than one study frequently have incongruent operational definitions for how to define their boundaries. Some investigators have employed color-coded DTI to increase the precision and accuracy of the ROI tracing process and to allow for visualization of different fiber orientations (see Rose et al., 2000 for an example). It is conventional for the orientation of the principle diffusion direction to be represented as green for anterior-posterior fibers, red for left-right fibers, and blue for vertical fibers. Such a color scheme facilitates differentiation of adjacent, but differently oriented, WM tracts (such as differentiating the cingulum from the corpus callosum, see Fellgiebel et al., 2005).

As an alternative to ROI, some researchers have applied whole brain voxel-based morphometry (VBM) techniques to DTI analysis. Such an approach greatly broadens the regions studied because a priori selection of ROIs is not needed. This also increases the likelihood for type I error, but this problem can be ameliorated through the application of conservative corrections for multiple comparisons. In addition, some of the VBM processing steps routinely used for morphometric analysis are problematic for use with DTI data. For example, both the process of alignment and registration to standard space and the process of smoothing can exacerbate partial volume effects and lead to questionable correspondence of brain regions across subjects (Smith et al., 2006). These problems are particularly relevant in studies that compare groups that present with differing degrees of generalized atrophy, as is the case in AD. Although ROI approaches obviate the need for alignment, they restrict the investigation to the few areas defined a priori and they are highly time-consuming.

The current study used tract-based spatial statistics (TBSS, Smith et al., 2006). This is a new approach that contains the strengths of traditional VBM analysis in that it avoids user bias and the necessity of limiting the investigation to a small number of regions because, like VBM, it is an automated whole-brain approach. At the same time, many of the weaknesses of traditional VBM, namely alignment and smoothing, are greatly attenuated in TBSS. Briefly, this is accomplished by the creation of a group mean FA skeleton (see Figure 1 below). The FA skeleton represents the mean FA values of the central portion of all the WM pathways throughout the brain that are common to the group. Next, each individual's FA map is probabilistically projected onto the skeleton, such that the individual's FA skeleton should contain the center of their unique WM tracts, adjusted to the alignment of the group. Finally, voxelwise statistics can be applied across subjects on the skeleton-space FA data (Smith et al., 2006).

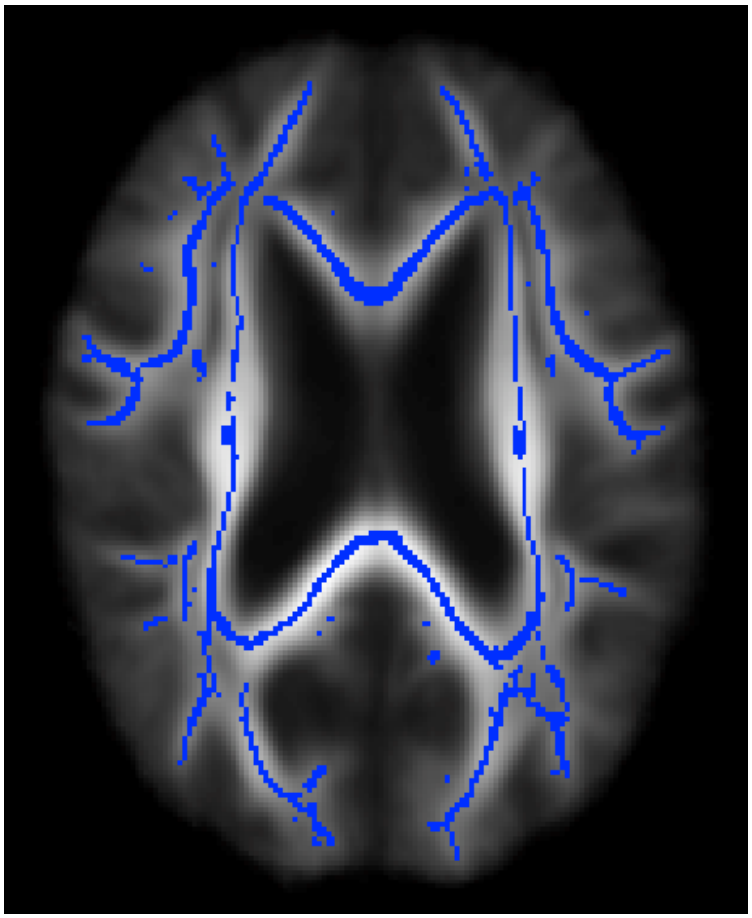

Figure 1. Group mean FA skeleton (in blue) overlaid on the group mean FA image.

5.8 Microstructural WM Changes in Normal Aging

Several studies have investigated changes in the integrity of WM tracts during normal aging, as measured by DTI or by calculating transverse relaxation rates (R_2; an indirect measure of the structural integrity of WM). In general, results have shown that FA values decrease and MD values increase with advancing age (Charlton et al., 2006; Moseley, 2002; O'Sullivan et al., 2001; Pfefferbaum et al., 2005; Salat et al., 2005a). Additionally, most researchers have concluded that there is an anterior-posterior gradient in age-related changes in diffusion parameters. This conclusion is congruent

with results from volumetric studies (reviewed in section 4.1.a) that have also suggested that age-related decline of gray matter and WM volume follows an anterior-posterior gradient in the cortex and the corpus callosum (Head et al., 2004; Raz, 2005; Van Petten et al., 2004).

Bartzokis et al. (2003) calculated R_2 in the splenium and genu in 252 healthy adults aged 19 to 82 years. They found that the rate of decline in R_2 with age was significantly faster in the genu than in the splenium. A quadratic, inverted U function best represented the changes in the genu over time, with the rate of decline beginning to accelerate at age 38, whereas changes in the splenium over time were best characterized by a linear function. Mean group differences were significant in both regions when younger subjects (under age 50) and older subjects (age 50 and older) were compared, but these differences were three times greater in the genu than in the splenium.

Similar results were found in a DTI study by O'Sullivan et al. (2001) that examined diffusion anisotropy in 20 normal elderly (56 to 85 years) and 10 younger adults (23 to 37 years). Overall diffusivity was higher and overall FA was lower in the normal elderly compared to the younger adults. In older subjects, FA was significantly reduced by 9.9% in anterior WM and 6.0% in middle WM, and did not show a significant reduction in posterior WM. MD was increased by 13.5%, 12.1%, and 8.7% in the anterior, middle, and posterior WM of older subjects compared with younger adults. Correlations with age were also calculated separately for the normal elderly group (no correlations were significant in the younger adults) and they showed the

expected anterior-posterior gradient. There were significant negative and positive correlations between age and FA and MD, respectively, in anterior and middle, but not posterior, WM.

Pfefferbaum et al. (2005) found evidence for a strong frontal distribution of low FA and high MD in healthy elderly relative to younger adults, both through a whole-brain voxel-based profile approach and a focal regional approach to analysis of high-field strength 3 Tesla (3T) DTI data. They proposed that this selective degradation of frontal circuitry likely underlies the age-related decline in cognitive domains thought to rely on these circuits, thus supporting the "disconnection" model of cognitive aging (O'Sullivan et al., 2001; Raz, 2005). A separate study on this same set of data also found support for this model by using fiber tracking to investigate regional age-related WM changes across the corpus callosum (Sullivan et al., 2006). As predicted, older individuals showed lower FA, higher ADC and fewer fibers than younger individuals, with differences being greater in anterior relative to posterior fiber bundles (significant group x bundle interaction). Number of fibers did not show differences across age groups or across regions.

Some researchers disagree with the view that changes in the microstructural integrity of WM during the normal aging process follow a strictly anterior-posterior gradient pattern (Madden et al., 2004; Salat et al., 2005b). Comparing younger and older adults, Madden et al. (2004) failed to find evidence for more selective age-related decline in FA in anterior regions. Instead, they proposed that a decrease in WM microstructural integrity is a widely distributed phenomenon, occurring throughout the

brain rather than in specific regional locations. To explain their set of results, the authors indicated that it may be those regions with a relatively lower FA value that show a magnified decline in FA in some studies. Similarly, Salat et al. (2005) argue that WM changes are regionally selective, not according to the anterior-posterior gradient but instead to the vulnerability of particular fiber bundles. They point out that although changes in the corpus callosum do indeed suggest an anterior-posterior gradient, other findings are incongruent with that pattern. For example, they compared FA maps of 15 young (21-39), 9 middle-aged (40-59), and 14 older (60 and above) adults by whole-brain VBM analysis and ROIs and found converging findings with both approaches. Specifically, they found statistically significant declines in FA with increasing age bilaterally in the WM of deep frontal, posterior limb of the internal capsule (but not anterior), medial orbitofrontal, and posterior periventrical (but not anterior) regions, as well as in the genu. Consistent with their argument for regionally selective WM changes, they proposed that the forceps minor are the most affected of the frontal lobe fibers, along with anterior callosal fibers and the corticospinal tracts (although the latter was reportedly an unexpected finding).

5.9 Microstructural WM Changes in AD

5.9.a Diffusion-weighted imaging studies of AD. The use of DWI (as opposed to DTI) represents a major limitation of earlier studies (and more recent longitudinal studies that began before the development of new acquisition techniques). As reviewed above, DWI yields summary diffusion parameters that are extremely sensitive to head movement (i.e., that are not rotationally invariant like parameters

drawn from the diffusion tensor), which may help explain discrepant findings across studies. For example, of four studies investigating the ADC value of the hippocampus in AD patients versus normal healthy elderly, two studies found a significant increase in ADC in AD patients compared to controls (Kantarci et al., 2001; Sandson, Felician, Edelman, & Warach, 1999) and two failed to find a difference (Bozzao, Floris, Baviera, Apruzzese, & Simonetti, 2001; Hanyu et al., 1998). In addition, Hanyu et al. (1999) reported higher ADC values in the anterior and posterior portions of the corpus callosum in AD patients relative to normal controls, whereas Bozzao et al. (2001) failed to find a significant difference between AD patients and normal controls in either region of the corpus callosum. Discrepant placement of ROIs, especially given the complex structure and small size of the hippocampus and the various methods used to divide regions of the corpus callosum, may have also contributed to these inconsistent results. Some results, however, have been consistent across studies. For example, both Kantarci et al. (2001) and Hanyu et al. (1998) found that AD patients had significantly higher ADC values in the temporal stem than normal healthy elderly.

5.9.b Diffusion-tensor studies of AD. Essentially all DTI studies that have included groups of AD patients and healthy controls have found diffusion changes in at least one of the regions studied, and no one has reported a significant difference in an unexpected direction (i.e., group differences consistently reveal a loss of WM microstructural integrity in AD patients relative to normal elderly). The most consistent findings across studies are of reduced structural integrity in AD patients compared to normal elderly in the posterior corpus callosum, posterior cingulate

bundles, and WM of the frontal, temporal and parietal lobes. Of six investigations that have examined the splenium (i.e., the posterior corpus callosum), four studies have found significantly decreased anisotropy or higher MD in AD patients when compared to normal elderly (Duan et al., 2006; Naggara et al., 2006; Rose et al., 2000; Takahashi et al., 2002) and two failed to find any differences (Choi et al., 2005; Head et al., 2004). It has been proposed that having a group of mild AD patients, as opposed to moderate or severe AD patients, may explain some null results (Choi et al., 2005). In contrast to the splenium, less support has been generated for group differences in the genu (i.e., the anterior corpus callosum) because most studies have failed to find any significant difference between AD patients and controls in this region (Choi et al., 2005; Duan et al., 2006; Head et al., 2004; Naggara et al., 2006; Takahashi et al., 2002), and only one found significant differences (Teipel et al., 2007). The splenium may be disproportionately affected by the AD disease process because a large proportion of its fibers are of the more vulnerable, small diameter type (but see discussion below regarding this feature in the genu as well, Bartzokis, 2004; Tang et al., 1997) and, in addition, it contains fibers from the medial temporal and parietal regions that are affected early (Naggara et al., 2006; Seltzer & Pandya, 1986).

In accordance with the evidence for greater loss of WM integrity in posterior than anterior regions of the corpus callosum, similar findings have been reported for the whole brain. Medina et al. (2006) applied whole-brain VBM analysis to their DTI data. Results from this study offer support for the general trend reported in the literature for greater posterior than anterior involvement in AD. They reported that

roughly 87% of the voxels showing a significant group difference were in posterior regions, with only the remaining 13% in anterior regions (defined as anterior to the anterior commissure).

Evidence supporting a group difference in the posterior cingulate bundle is strong. Takahashi and colleagues (2002) reported that the posterior cingulate bundle exhibited the most dramatic reduction of FA values (approximately 33% less than normal controls) out of 9 ROIs. The FA of the anterior cingulate bundle was also significantly reduced in AD patients relative to controls, but to a lesser extent. Another study also noted that the FA of the posterior cingulate bundle and the superior longitudinal fasciculus, both of which lie within the deep posterior WM, were affected to a greater extent than other regions in MCI and AD patients compared to normal elderly (Medina et al., 2006). Further, they reported that the only region showing a significant reduction in FA when comparing MCI to AD patients was the posterior cingulate bundle. A study by Fellgiebel et al. (2005) focused solely on the posterior cingulate bundle, using color-coded DTI to derive more reliable ROI tracings of this structure. In agreement with the aforementioned studies, Fellgiebel et al. reported significant differences in WM microstructural integrity of the posterior cingulate bundle bilaterally (lower FA, higher MD) in AD patients versus normal elderly. There was evidence for greater left than right-sided involvement in MCI patients, with a significant difference in both FA and MD values reported in the left, but not the right, posterior cingulate bundle in MCI patients relative to normal controls. Similarly, Rose and colleagues (2000), who also employed color-coded DTI to assist in accurate ROI

placement, reported a significant reduction of the structural integrity of the anterior-to-posterior fibers of the left cingulum and the superior longitudinal fasciculus in AD patients compared with normal elderly. These results are consistent with studies that have championed reduced glucose metabolism in the posterior cingulate as both a sensitive and specific early marker of AD (Minoshima et al., 1997; Reiman et al., 1996) that also may contribute to learning and memory deficits (Fellgiebel et al., 2005).

In general, studies investigating WM within the four lobar regions of the brain have found evidence of significantly lower WM integrity in AD patients compared to normal elderly in ROIs placed within the WM of the frontal, temporal, and parietal lobes, however there is some inconsistency across studies. Bozzali et al. (2002) placed bilateral ROIs in the WM of the four lobes and found that FA values were lower and MD values were higher in AD patients compared to controls in the frontal, temporal, and parietal lobes (all p's < .004), but not in the occipital lobe or the internal capsule. They therefore concluded that loss of microstructural WM integrity occurs in WM regions connected with the association cortices, likely due to Wallerian degeneration secondary to neuronal loss, while those WM regions connected to motor or visual areas are spared. Finding similar results, Duan et al. (2006) also argued that Wallerian degeneration likely drives changes in WM microstructural integrity of cortico-cortical and cortical-subcortical WM fiber tracts in AD. They found significantly reduced FA in the splenium, and the WM of the temporal, parietal and frontal lobes and

significantly increased MD in the splenium and parietal WM in AD patients compared to normal elderly.

Naggara et al. (2006) placed ROIs in the superior frontal, superior temporal, parietal, and occipital WM, as well as in the genu, splenium, cingulum, and internal capsule. Similar to the results of Duan et al. (2006), they reported reduced FA in the splenium, superior frontal WM, and superior temporal WM and increased MD in the splenium, superior frontal WM, and parietal WM in AD patients compared to normal elderly. Despite the presence of both posterior and anterior decreases in the integrity of WM microstructure in their AD sample, the authors focused their interpretation on the significant difference in frontal WM. Accordingly, they deemed their results consistent with the retrogenesis theory, and they explained that because their sample consisted of individuals with early-stage AD, posterior changes may not have been evident. Choi et al. (2005) performed a more direct test of the retrogenesis theory by comparing later-myelinating superior frontal WM to earlier-myelinating inferior frontal WM. Consistent with the retrogenesis theory, they found decreased FA and increased MD and DR in the superior frontal WM in patients with early AD compared to controls, whereas there were no significant group differences in the inferior frontal WM. It should be noted, however, that unlike several other studies, these investigators did not exclude individuals with more severe periventricular WMH and did not avoid these WMH when drawing their ROIs (although they also argue that the inclusion of WMH could not account for the differences found).

Head et al. (2004) also placed bilateral ROIs in the WM of the four lobes, although they specified that their frontal ROIs represented prefrontal WM. They found a somewhat different pattern of results, reporting a lack of difference between AD patients and normal elderly in the diffusivity of the prefrontal WM and significantly higher diffusivity in the temporal, parietal, and occipital lobes. Comparison of FA values across groups revealed no significant lobar differences. In addition, no diffusivity or anisotropy differences were found in either the genu or splenium of the corpus callosum when comparing normal elderly and AD. The authors argue that their results indicate that anterior WM changes are not accelerated in AD. Another group also failed to find a significant difference between normal elderly and AD patients in frontal WM (Takahashi et al., 2002). In the only published study to date employing a higher magnetic field (3.0 T) to compare AD patients to normal elderly, Takahashi et al. (2002) placed ROIs within the subcortical WM of the middle frontal gyrus (frontal lobe), angular gyrus (parietal lobe), temporal lobe, and occipital lobe, as well as in the internal capsule, anterior and posterior cingulate bundle, and anterior and posterior corpus callosum. FA values were significantly lower in AD patients compared to normal controls in the temporal lobe WM, anterior and posterior cingulate bundles, and the posterior corpus callosum, but no significant differences were found in the WM of the frontal, parietal or occipital lobes, the anterior corpus callosum, or the internal capsule.

Teipel et al. (2007) used a multivariate approach to determine the profile of changes in AD patients relative to normal subjects on FA maps. Thus, any difference

between AD patients and normal subjects is relative to the whole brain and not a localized effect. Results revealed relatively lower FA values in AD subjects compared to normal elderly in intracortical projecting WM tracts (e.g., the anterior corpus callosum, WM of the parahippocampal gyrus, and fornix) and in frontal, temporal, and occipital WM. In contrast, FA values within extracortical projecting WM tracts (e.g., extra-pyramidal and pyramidal systems, somatosensory system) were relatively higher in AD subjects compared to normal elderly.

Most DTI studies have focused on WM, but Bozzali et al. (2001) found that the MD of temporal lobe cortical gray matter and total cortical gray matter was significantly higher in AD patients relative to normal healthy elderly. In addition, Kalus et al. (2006) found significantly lower diffusion anisotropy in two gray matter structures, the hippocampus and entorhinal cortex, in addition to the white matter tract that connects these two structures (perforant pathway) in AD patients compared to normal healthy elderly.

5.9.c Theoretical implications of DTI studies of AD. In accordance with the model put forth by Bartzokis (2004), researchers finding differences in the diffusion properties of WM in AD patients relative to normal elderly in frontal WM regions have argued for an anterior-posterior gradient of degeneration in aging and AD. Though this may appear contradictory to the results summarized above, when WM degeneration in aging and AD is conceptualized as reverse myelination (Bartzokis, 2004; H. Braak & Braak, 1996a; Reisberg et al., 1999), these two seemingly discrepant patterns of greater posterior than anterior involvement versus a proposed

anterior-posterior gradient of degeneration can coexist. This is because the anterior-posterior gradient theory of degeneration is often presented simultaneously with retrogenesis. That is, if one assumes that the degeneration of WM follows an inverse pattern of myelogenesis, then it can be further specified that it is those regions that continue to develop myelin into the fourth and fifth decades of life (that are characterized by small-diameter myelinated fibers and multiple myelinated axons being supported by a single oligodendrocyte) that will first show loss of WM integrity with age or with disease processes such as AD (Bartzokis, 2004; Reisberg et al., 1999). This is also consistent with Salat et al.'s (2005) argument that WM changes are regionally selective depending on the vulnerability of particular fiber bundles as opposed to being exclusively restricted to a regional location (as discussed in section 5.8).

Although these vulnerable fibers are more highly concentrated in anterior regions (i.e., the genu), they are also present, though to a lesser extent, in posterior regions (i.e., the splenium, Hofer & Frahm, 2006). Therefore, AD patients may present with reduced anisotropy in anterior regions following the anterior-posterior gradient hypothesis, along with superimposed AD pathology that accelerates the process of retrogenesis, thus affecting structures beyond the anterior regions. In addition, inconsistencies across studies of AD patients may be explained by degree of dementia severity of each AD group. It may be that studies including only mild AD patients may result primarily in an age-related pattern of decline in WM microstructural integrity and those with higher disease severity will additionally show the posterior

involvement associated with the more advanced disease process. One additional explanation for the seemingly discrepant conclusions of greater anterior versus greater posterior involvement is the heavy use of the ROI approach in these studies. As Pfefferbaum, Adalsteinsson, and Sullivan (2005) point out, "to make claims about the selective vulnerability of frontal brain regions to aging, frontal sites must be examined within the context of the rest of the brain" (p. 892). If studies are placing ROIs in arbitrarily selected regions within each lobe to represent anterior and posterior change, especially without investigation of both inferior and superior regions within each lobe, then conclusions drawn may be an artifact of ROI placement.

A similar problem may occur for studies employing a crude division of the corpus callosum into thirds, or even for those employing the widely accepted Witelson criteria (Witelson, 1989), which were derived primarily from data from nonhuman primates. Such divisions may be less applicable to human connectivity anatomy than previously believed. Hofer and Frahm (2006) used DTI tractography (discussed in section 5.5) to obtain cortical connectivity information and created a new classification scheme for vertical partitioning of the corpus callosum based on *in vivo* human anatomy. Their results demonstrate that, in comparison with the Witelson criteria, their proposed scheme more accurately delineates the prefrontal fiber bundles (Region I) as a region separate from that containing the premotor and supplementary motor fibers (Region II), whereas Witelson's scheme groups fibers from these three regions together in the anterior third (Region I) of the corpus callosum (see Hofer & Frahm, 2006). A well-delineated microscopic structure of the corpus callosum defined

by light microscopic examinations has revealed a higher density of small diameter fibers in the genu and the splenium, with larger diameter fibers predominating in the posterior midbody (Aboitiz, Scheibel, Fisher, & Zaidel, 1992). A similar pattern of regional differences is observed in FA values, with the highest values in the most anterior and the most posterior regions of the corpus callosum, and the smallest values in the middle region (Hofer & Frahm, 2006). Drawing an ROI in the anterior corpus callosum that includes not only prefrontal fibers, but also premotor and supplementary motor fibers, as would be the case if one were to follow Witelson's criteria or if one divided the corpus callosum into thirds, may obscure any existing FA differences existing selectively in the prefrontal fibers. This may explain the lack of difference found in the "anterior" portion of the corpus callosum in many studies comparing healthy elderly with AD patients. If the ROI is contaminated with premotor and supplementary motor fibers, which are affected only at the latest stages of the disease, then FA values will be artificially higher than if only prefrontal fibers were included in the ROI.

5.9.d Meta-Analysis of DTI studies of AD. Roughly 20 empirical studies investigating changes in diffusion parameters in AD patients have been published over the past two decades, with over two-thirds of them appearing in the literature since 2000. As evident from the discussion above, the importance of white matter changes in the pathogenesis of Alzheimer's disease (AD) remains unresolved. To date, the results of studies applying DTI to AD (detailed above) have been inconsistent, with some indicating greater loss of white matter integrity in posterior than anterior regions,

and others reporting an anterior-posterior gradient of degeneration. The rapid technological advances and consequent changes in acquisition and processing approaches makes a quantitative meta-analysis of these studies problematic, as does the inconsistent definition of regions of interest. Therefore, a subset of studies with comparable methodology were selected for inclusion in a meta-analysis (Horne, Bangen, Delano-Wood, & Bondi, 2007) in an effort to facilitate hypothesis generation and power analysis for the current project.

Studies were selected according to the following criteria: 1) studies employing an ROI approach were included to facilitate calculation of the effect size (*d*); 2) only DTI (as opposed to DWI) studies were considered; and 3) studies had to include both an AD group and an age-matched control group. Ten studies published between 2000 and 2006 met criteria for inclusion. Results from 147 patients with AD and 130 age-matched healthy older adults were included (see Table 1 below).

Table 1. Participant characteristics across all studies included in meta-analysis

	Mean (*SD*)	Minimum	Maximum
Alzheimer's disease			
N	14.70 (6.15)	7	25
Age	70.97 (5.40)	60.7	77.0
MMSE (*N* = 9)	20.30 (4.18)	13.0	27.0
Normal elderly			
N	13.00 (5.68)	7	25
Age	69.58 (5.48)	58.9	77.0
MMSE (*N* = 7)	28.96 (0.65)	28.0	30.0

Note. MMSE = Mini-Mental State Examination.

Effect sizes (*d*) derived from various regions of interest revealed evidence of large differences in diffusion parameters between AD patients and healthy elderly across studies (see Table 2). Although effect sizes revealed an anterior-posterior gradient when comparing separate lobar WM measures, large effects were also found in selected posterior regions (e.g., splenium, posterior cingulate bundle, superior longitudinal fasciculus). Results suggest that the pattern of microstructural WM changes in AD follows the retrogenesis model, and future DTI studies should predict differences in both anterior and posterior regions depending upon the vulnerability of the specific white matter fiber bundle vis-à-vis retrogenesis. Knowledge of the expected magnitude and pattern of microstructural WM changes in AD will inform future investigations of at-risk groups (e.g., MCI, APOE ε4) and thus aid in the early detection of AD.

Table 2. Regional effect sizes across studies included in meta-analysis.

	Fractional Anisotropy			Mean Diffusivity			Other		
	N	Mean *d*	(*SD*)	*N*	Mean *d*	(*SD*)	*N*	Mean *d*	(*SD*)
Total WM	1	-1.53	---						
Frontal lobe	3	-1.60	(0.50)	4	1.95	(2.40)	1[b]	-	
Superior frontal WM	1	-0.90	---	1	1.02	---			
Inferior frontal WM	1	-0.84	---	1	0.14	---			
Temporal lobe	4	-1.35	(0.67)	5	1.84	(1.41)	1[b]	+	
Parietal lobe	3	-1.08	(-0.96)	5	2.03	(1.45)	1[b]	-	
Occipital lobe	3	-0.05	(0.06)	5	0.47	(0.37)	1[b]	-	
Corpus Callosum									
Average across genu & splenium	4	-1.17	(0.76)	5	2.60	(2.75)			
Anterior corpus callosum	3	-0.66	(0.13)	4	1.01	(1.27)	1[b]	-	
Posterior corpus callosum	3	-1.41	(1.64)	4	4.40	(5.20)	2[a,b]	-5.81/+	---
Cingulum	1	-0.44	---	1	3.77	---			
Left cingulum							1[a]	-4.22	---
Right cingulum							1[a]	-2.11	---
Anterior cingulate bundle							1	+	
Posterior cingulate bundle	1	-1.39	---	1	0.77	---	1	+	
Left posterior cingulate bundle	1	-1.52	---	1	0.89	---			
Right posterior cingulate bundle	1	-1.26	---	1	0.64	---			
Internal Capsule	2	-0.19	(0.05)	1	1.61	(2.27)	1[b]	-	
Anterior limb IC	1	0.18	---	1	0.91	---			
Posterior limb IC	1	0.48	---	1	1.51	---	1[a]	0.00	---
Superior longitudinal fasciculus							1[a]	-4.83	---
Hippocampus							1[c]	-2.62	---
Entorhinal cortex							1[c]	-1.16	---
Perforant pathway							1[c]	-3.15	---

Note. IC = internal capsule, WM = white matter.
[a] lattice index (Rose et al., 2000).
[b] study of origin (Takahashi et al., 2002) did not report data sufficient for effect size calculation. + denotes a significant effect was reported; - indicates a significant effect was not found for that region.
[c] intervoxel coherence (Kalus et al., 2006)

5.9.e Sample size estimates and statistical power. Studies investigating WM microstructural differences between AD patients and age-matched control groups (summarized in sections 5.9.b and 5.9.d) revealed several brain sites where FA was lower in the AD group than in the normal control group. In many of these regions the effect size was large (i.e., Cohen's d > .8, Cohen, 1988). As shown in Table 3, projected sample size estimates based on *d* values from representative studies range

from 12-24 subjects at a power of approximately .80, depending upon the region of interest (determined through G-Power; Faul, Erdfelder, Lang, & Buchner, 2007). It is assumed that the MR acquisition protocol and post-processing methods used in the current study are at least as sensitive to group differences as those employed in previously published studies.

Table 3. Regional effect sizes across studies and corresponding power analysis.

	Fractional Anisotropy			Power Analysis (for β > .80)
	N	Mean *d*	(SD)	*N* needed
Total White Matter	1	-1.53	---	14
Frontal lobe	3	-1.60	(0.50)	12
Temporal lobe	4	-1.35	(0.67)	16
Parietal lobe	3	-1.08	(-0.96)	24
Occipital lobe	3	-0.05	(0.06)	
Corpus Callosum				
Anterior corpus callosum	3	-0.66	(0.13)	60
Posterior corpus callosum	3	-1.41	(1.64)	16
Cingulum	1	-0.44	---	130
Anterior cingulate bundle				
Posterior cingulate bundle	1	-1.39	---	16
Internal Capsule	2	-0.19	(0.05)	

Chapter 6. Cognitive correlates of DTI

6.1 Cognitive Correlates of DTI in Normal Aging

Like studies examining the relationship between WMH and cognition (discussed in section 4.1.c), the integrity of WM tracts as measured by DTI has also been used to examine the relationship of changes in WM to cognitive decline, with promising results.

In one of the first studies to indicate the potential for DTI parameters to be sensitive to age-related changes in performance measures, Sullivan et al. (2001) showed that FA values in the splenium and parietal pericallosal regions were significantly correlated with scores from an alternating finger tapping task in a sample of 49 adults (ages 23-79), and these regions correlated more strongly with this task than with age. Madden et al. (2004) demonstrated that age can also affect the regional relationship of FA values to performance by comparing the relationship between FA values in various ROIs and reaction time on an oddball task in younger and older adults. Their results demonstrated that FA values of the splenium predicted a significant amount of variance in reaction time in younger, but not older adults, whereas the anterior limb of the internal capsule predicted a significant amount of variance in older, but not younger adults.

Consistent with the proposed anterior-posterior gradient of age-related changes in WM microstructure and the "disconnection" model of cognitive aging (see sections 2.3 and 3.2, respectively), researchers hypothesize that a predilection for disruption of anterior fibers likely drives age-related cognitive declines (O'Sullivan, 2001; Sullivan,

2006; Raz, 2005). Results from a study by O'Sullivan et al. (2001) support this hypothesis. They examined correlations (corrected for age, sex, WM volume, premorbid intelligence and MMSE score) between tests of executive function (WCST, Trail Making Test, Verbal Fluency) and FA and MD in anterior, middle, and posterior ROIs in 20 older adults. Mean diffusivity of anterior WM was significantly correlated with the difference between Trail Making Test A and B ($r = .61$, $p < .05$). In addition, FA in the middle ROI, which was stated to contain fibers of the arcuate fasciculus, was significantly correlated with verbal fluency ($r = .61$, $p < .05$).

Sullivan et al. (2006) correlated performance on the Stroop Color-Word Test (Stroop, 1935) with regional WM microstructure of the corpus callosum as delineated by fiber tracking in a group of 10 older adults. The number of words read in the simple word reading condition correlated with several regional DTI parameters, including FA in the premotor/precentral ($r = .59$, $p < .04$) and postcentral ($r = .68$, $p < .02$) callosal bundles, ADC in the premotor/precentral bundle ($r = .59$, $p < .04$), and number of fibers in the posterior parietal ($r = 0.60$, $p < 0.04$) and superior temporal ($r = 0.62$, $p < 0.03$) bundles. The authors concluded that these results provide support for a relationship between cognitive performance and the selective vulnerability of anterior WM fibers with age (although both anterior and posterior regions were correlated with cognitive performance). In addition, simple color naming was significantly correlated with fiber length in the superior temporal bundle ($r = .59$, $p < .04$). Finally, the number of words read correctly in the incongruent color-word condition, but not the interference score, was significantly correlated with fiber length in the postcentral

bundle ($r = 0.62$, $p < 0.03$). The authors note that these correlations were located in the callosal body, as opposed to the anterior or posterior extremes (prefrontal and inferior temporal/occipital callosal bundles), which is inconsistent with the hypothesis that loss of integrity of WM tracts selectively in prefrontal areas underlies age-related cognitive decline. They point out that the absence of a significant correlation between any DTI metric and the inferior frontal callosal bundles was surprising, and argue that perhaps a different task that is more sensitive than the Stroop may be needed.

Charlton et al. (2006) utilized histogram analysis to measure whole-brain WM FA and MD characteristics, ROIs for regional FA and MD values, and magnetic resonance spectroscopy (MRS) to evaluate the underlying neuropathologic basis for any identified changes in WM in 106 healthy adults (ages 50 to 90). In addition, they administered an extensive and well-selected battery of neuropsychological tests to cover three cognitive domains and an estimate of premorbid intelligence. This study will be described in detail due to the overlap of their selected cognitive tests and those proposed for use in the present study design. Performance on the National Adult Reading Test (NART) represented premorbid intelligence. Executive function was measured by selected indices from several DKEFS tests (Trail Making Test number-letter switching minus motor speed; total achievement for the Tower Test; FAS total correct; animals and boys' names total correct; Color-Word Interference total correct) and number of categories on the WCST. Digit span backwards and letter-number sequencing (WMS-III total correct) comprised the working memory domain. Information processing was represented by Digit Symbol (WAIS-R number

completed), Grooved Pegboard Test (time to completion), and Adult Memory and Information Processing Speed Battery (AMIPB; total completed for information processing speed). Raw scores were converted into *z*-scores and a composite score for each domain was computed. Anterior, middle, and posterior ROIs were drawn on a slice that passed through the WM of the centrum semiovale and the periventricular region and were described as being localized to the prefrontal cortex, frontal lobe, and posterior to the splenium, respectively. Bivariate Pearson correlations showed that both MD and FA (derived from both post-processing approaches) correlated significantly with the three cognitive domains of interest. However, when these analyses were followed up with partial correlations (controlling for age and premorbid intelligence), only working memory continued to show a relationship with DTI parameters. Specifically, for MD, the anterior, middle, and posterior ROIs were negatively related to working memory (r = -.299, -.235, -.258, respectively; all *p*'s < .05), and, for FA, the middle and posterior ROIs were positively related to working memory (r = .292, .199, respectively; all *p*'s < .05). The authors suggested that a significant correlation of NAA/creatine (a marker of axonal loss) with FA, even after controlling for age, provides evidence that axonal loss may underlie the reported changes in WM microstructural integrity with age. They further conclude that the demonstrated relationship between DTI parameters and cognitive domains thought to decline with age provides support for the "disconnection" hypothesis of cognitive aging (discussed in section 3.2).

6.2 Cognitive Correlates of DTI in Alzheimer's Disease

6.2.a MMSE. Studies examining the cognitive correlates of DTI parameters in individuals with AD have lagged behind investigations of normal aging, as a limited set of cognitive tests have been utilized. The majority of studies have only looked at correlations with the Mini-Mental State Examination (MMSE, Folstein, Robins, & Helzer, 1983), and two have examined DTI correlates of verbal memory performance.

Among those studies that have examined the relationship between DTI parameters and MMSE, it is important to note that the composition of samples has varied across studies. Specifically, only three studies have looked at correlations within an AD group (Bozzali et al., 2002; Takahashi et al., 2002; Yoshiura et al., 2002), with two of the three studies reporting a significant relationship between MMSE scores and DTI parameters. Yoshiura et al. (2002) found that MD (r = -.53, p < .005) of the posterior cingulate (only ROI studied) was negatively correlated with MMSE scores, but FA was not significantly related. Bozzali et al. (2002) reported significant correlations of MMSE scores with overall WM MD (r=-.92, p<.001) and FA (r=.78, p=.002) among AD patients. Several studies have collapsed across NC and AD groups (Duan et al., 2006; Naggara et al., 2006; Rose et al., 2006) or across NC, MCI, and AD groups (Kalus et al., 2006). Kalus et al. (2006) showed that a measure of intervoxel coherence of the perforant pathway and hippocampus were significantly correlated with MMSE scores, whereas volumetric measurements of these structures were not. Duan et al. (2006) reported that FA values of multiple structures, including the splenium, and WM of the frontal, temporal and parietal lobes, were positively

correlated with MMSE scores, and two of these structures (splenium and parietal WM) were also negatively correlated with MD. Neither FA nor MD of the genu, occipital WM, and anterior and posterior limbs of the internal capsule were significantly correlated with MMSE scores in this study. Rose et al. (2006) reported a significant correlation (r = .77) between a measure of anisotropy of the splenium and MMSE scores. Naggara et al. (2006) failed to find any significant correlations between MMSE scores and FA or MD of seven ROIs. They contributed their null results to the small range of MMSE scores within their sample due to inclusion of only mild AD patients.

6.2.b Verbal memory. As previously mentioned, studies investigating AD have yet to systematically investigate the relationship between DTI parameters and specific cognitive domains, and only two studies (Fellgiebel et al., 2005; Kalus et al., 2006) have examined verbal delayed recall (CERAD). Both of these studies collapsed across normal elderly control, MCI, and AD groups and performed Spearman's rank correlational analysis. Kalus et al. (2006) found that verbal delayed recall was positively correlated with intervoxel coherence of the left perforant pathway (r = .49, p = .006) and both right (r=.59, p=.001) and left (r = .49, p = .006) hippocampi. Fellgiebel et al. (2005) found that delayed verbal recall performance correlated positively with FA and negatively with MD in both the left (r = .37, p = .003; r = -.35, p = .005) and right (r = .33, p = .009; r = -.30, p = .018) posterior cingulate bundles. The authors conclude that a disconnection of neural circuits necessary for optimal

memory performance, which includes the posterior cingulate bundle, contributes to poorer episodic memory performance in MCI and AD.

As evident from the paucity of cognitive measures discussed above, no published studies investigating the relationship between DTI parameters and cognition in Alzheimer's disease have employed measures of working memory, processing speed, or executive function. This is unfortunate, because these cognitive domains have been shown to correlate with DTI parameters in other diseased populations (Nestor et al., 2004; O'Sullivan, Barrick, Morris, Clark, & Markus, 2005; O'Sullivan et al., 2001; Rovaris et al., 2002) and in normal aging (Charlton et al., 2006; O'Sullivan et al., 2005; O'Sullivan et al., 2001; Sullivan et al., 2006). Clearly, this is an area in need of further investigation.

Chapter 7. Aims and Hypotheses

7.1 Aims

7.1.a Across-group comparison of WM integrity. This study aimed to resolve current discrepancies in the literature by applying the retrogenesis model of AD. Unlike prior studies that have expected a purely anterior-posterior gradient when applying this model, group differences were predicted in both anterior and posterior regions, depending upon the vulnerability of the specific WM fiber pathway. In addition, group differences were further examined after covarying for possible confounds, including total gray matter volume, total WM volume, and white matter lesion burden (i.e., WMH volume). Finally, ROIs placed in the genu and splenium of the corpus callosum facilitated comparison of expectant results to the current literature.

7.1.b Relationship between cognition and WM integrity. By expecting decreased WM integrity in patients with AD, a "disconnection" syndrome can be expected. Therefore, it necessarily follows that higher cognitive functions that are dependent upon the synchronization of distributed neural networks (e.g., multi-modal functions) are expected to be the most vulnerable to the effects of AD. Support for this model was evaluated by examining the correlation between WM structural integrity and composite cognitive scores. The relationship between WM structural integrity and dementia severity (as measured by the DRS) was also examined.

7.2 Hypotheses

7.2.a Across-group comparison of WM integrity. Greater loss of WM microstructural integrity (lower FA) was predicted in patients with AD relative to normal healthy elderly in late-myelinating vulnerable WM fiber pathways, whereas early-myelinating fiber pathways were predicted to be relatively spared. Specifically, group differences in late-myelinating tracts were expected. These include tracts within the allocortex (e.g., fornix) and corticocortical tracts connecting association areas of the neocortex (e.g., superior longitudinal fasciculus, inferior longitudinal fasciculus, uncinate fasciculus), and commissural fibers (e.g., forceps minor, forceps major). Group differences are not expected in early-myelinating tracts (e.g., internal capsule, cerebral peduncles).

7.2.b Relationship between cognition and WM integrity. Neuropsychological test performance is predicted to correlate with loss of WM microstructural integrity. Specifically, neuropsychological test performance will be positively correlated with FA (e.g., poorer performance will be associated with lowered FA values).

Chapter 8. Method

8.1 Participants

The study was approved by the institutional review boards at San Diego State University and the University of California San Diego. Written informed consent was obtained from all participants and surrogate consent was obtained for any participant suspected of questionable decisional capacity. Participants were selected without regard to ethnicity or race.

Eighteen individuals diagnosed with possible or probable AD and 16 elderly normal control (NC) participants were selected for this study from the larger cohort of research volunteers of the Alzheimer's Disease Research Center (ADRC) at the University of California San Diego. Two AD patients and two normal control participants were excluded (see reasons below), thus the final sample included 30 participants (16 AD and 14 NC). The two groups did not differ significantly on age ($F_{1,28} = .003$, $p = .96$, $\eta_p^2 = .00$; NC group range 66-93; AD group range 60-91), education ($F_{1,28} = .25$, $p = .62$, $\eta_p^2 = .01$; NC group range 8-19; AD group range 12-18), or stroke risk ($F_{1,28} = .09$, $p = .77$, $\eta_p^2 = .00$; NC group range 5-19; AD group range 4-20). Gender (proportion) did not differ significantly across groups ($\chi^2 = .53$, $p = .47$). As expected, DRS total score for the AD group was significantly lower than that for the NC group ($F_{1,28} = 69.64$, $p < .001$, $\eta_p^2 = .71$; NC group range 128-143; AD group range 107-134). To facilitate comparison of our results to other studies, MMSE score was also examined and was significantly lower in the AD group compared to the NC group ($F_{1,28} = 26.31$, $p < .001$, $\eta_p^2 = .48$; NC group range 28-30; AD group range

15-29). Please see Table 4 for demographic descriptive statistics. Descriptive statistics of all cognitive variables are presented in Appendix A. Briefly, group comparisons across normal control and AD participants in the current study closely adhere to the cognitive profile of AD described in the literature (see section 3.5). Specifically, AD participants showed significantly poorer performance on all memory measures (and these indices produced the largest effect sizes), tests of language (confrontation naming and category fluency), most measures of executive functions, and they showed significantly less ability to complete instrumental activities of daily living compared to normal control participants.

Table 4. Demographic data for Alzheimer's patients and normal elderly.

	NC (n = 14)	**AD** (n = 16)	η_p^2
Age	77.4 (8.1)	77.3 (9.0)	.00
Education	15.3 (2.9)	15.8 (2.1)	.01
Gender % Female (M/F)	64% (5/9)	50% (8/8)	
Framingham Stroke Risk Profile	13.1 (4.0)	13.6 (4.9)	.00
Mattis Dementia Rating Scale*	141.1 (4.0)	124.0 (6.7)	.71
Mini-Mental State Exam	29.29 (.73)	24.44 (3.46)	.48

* $p < .05$

AD patients received a diagnosis of possible or probable AD by two senior staff neurologists according to the criteria developed by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the

Alzheimer's Disease and Related Disorders Association (McKhann et al., 1984). Individuals were excluded from this study if they had causes of dementia other than AD (e.g., stroke, hypothyroidism, vitamin B12 deficiency, electrolyte imbalance), a history of severe head injury, alcoholism, or serious psychiatric disturbance. Persons with significant cerebrovascular disease (as indexed by modified Rosen ischemic scores greater than 4, Rosen, Terry, Fuld, Katzman, & Peck, 1980) were excluded. All ADRC participants receive (a) annual neurological, medical, and psychiatric examinations; (b) global cognitive screening (e.g., Mattis Dementia Rating Scale, DRS, Mattis, 1976); and (c) the ADRC Core Neuropsychological Battery (assesses basic cognitive domains such as attention, memory, language, visuospatial skill, problem solving and abstraction, and motor coordination). For a detailed description of the tests that comprise this battery, see Salmon and Butters (1992).

All participants in this study received an MRI scan and underwent neuropsychological testing. Any participant who did not have an adequate MRI examination (e.g., persons who are unable to undergo the MRI examination without complications such as movement or claustrophobia) was excluded. To help optimize success with the scanning procedure, very mild or mild AD participants were targeted for recruitment (i.e., those with a DRS score of 115 or greater, total score possible = 144 points). Two participants with DRS scores below 115 were included in the study (DRS = 109, 110) due to power requirements. Two individuals with AD had to be excluded due to incomplete scans (one stopped the scan early due to anxiety and the other's head did not fit within the head coil). Two normal control participants were

also excluded due to problematic scans (one stopped the scan early due to anxiety and the other had excessive head movement).

8.2 Measures

Participants were scanned within 3.8 months, on average, of their ADRC annual evaluation (SD = 2.2; range 0-9 months). In addition, a short battery of neuropsychological tests of approximately one-hour duration was administered on the same day as the scan. Several factors guided selection of this test battery. First, because we predicted that higher-order, multimodal tasks will be most sensitive to change in WM microstructural integrity, tests that have indices that examine the unique contribution of higher-order functions (above and beyond the contribution of lower-order functions) were chosen. For example, contrast scores from the two Delis-Kaplan Executive Function System (DKEFS, Delis, Kaplan, Kramer, 2001) subtests; the dual task decrement for the dual task condition. Secondly, variants of neuropsychological measures (e.g., DKEFS Color-Word Interference, DKEFS Trail Making Test) or tests representing cognitive domains (e.g., Letter-Number Sequencing for working memory) that have been shown to significantly correlate with DTI parameters in studies of other populations were preferred. Lastly, tests already administered by the ADRC (e.g., California Verbal Learning Test, CVLT, Delis, Kramer, Kaplan, & Ober, 1987) were ruled out to avoid overlap and practice effects across the two testing sessions. Cognitive abilities assessed by each test are listed in parentheses.

1. DKEFS Color-Word Interference (processing speed for base trials, executive function, set-switching)
2. DKEFS Trail Making Test (visual scanning, motor speed, executive function, set-switching)
3. Wechsler Adult Intelligence Scale – Third Edition (WAIS-III, Wechsler, 1997) Letter-Number Sequencing (divided attention, working memory)
4. Benton Facial Recognition Test (Benton, 1994, visuospatial)
5. Right-Left Orientation Test (Benton, 1994, body-part identification, mental rotation)
6. Dual Performance Task (Della Sala, Baddeley, Papagno, & Spinnler, 1995, simple auditory attention, motor speed, divided attention, central executive function)

In the dual performance task (Della Sala et al., 1995), there are two basic tasks that are performed separately in the first two trials, and then a dual task trial where both tasks are performed simultaneously. Participants first complete a digit span task by administering progressively lengthening strings of digits to determine how many digits the participant can recall reliably (e.g., they must get two of three trials correct to advance to the next span length). Once a digit span length is established, a two-minute trial is completed using digit spans of the set length. Next, participants are instructed to place a cross in a trail of boxes arrayed on a response sheet, as quickly as possible, for two minutes. The final two-minute trial involves doing both tasks simultaneously. Previous studies have shown that individuals with AD demonstrate a

greater decrement in performance during the dual task than normal controls (Della Sala et al., 1995; Greene, Hodges, & Baddeley, 1995). The following indices were examined (per Greene, Hodges, & Baddeley, 1995): proportion of digit span sequences correct in single task, number of boxes filled in single task, proportion of digit span sequences correct in dual task, number of boxes filled in dual task, and dual task decrement ((120 sec/number of boxes dual task)/(proportion of digit span sequences correct on dual task) – (120 secs/number of boxes single task)/(proportion of digit span sequences correct on single task)). The dual task decrement represents how many extra seconds are required to fill one box during the dual task compared to the single task, adjusting for proportion of digit span sequences correct.

8.2.a Normative data. Mayo's Older Americans Normative Studies (MOANS) data were employed for several tests. Age-corrected scaled scores were derived from MOANS data for FAS total score, Trail Making Test parts A and B, WAIS-R Vocabulary, WAIS-R Digit Symbol, WMS-R Digit Span, and WMS-R Logical Memory (Ivnik, Malec, Smith, Tangalos, & Petersen, 1996; Ivnik et al., 1992a, 1992b). Normative data from Lucas et al. (1998), which was based on the same normative sample as MOANS data, was used to derive age-corrected scaled scores for DRS total score and subscale scores. An age-corrected scaled score was derived from the WAIS-III manual for Letter-Number Sequencing. Age-corrected scaled scores were derived for all DKEFS test indices from the DKEFS manual.

8.2.b Stroke risk assessment. The Framingham Stroke Risk Profile (FSRP, D'Agostino, Wolf, Belanger, & Kannel, 1994) was developed to predict a 10-year

probability or risk of stroke (Truelsen, Lindenstrom, & Boysen, 1994). The risk profile is based on the following stroke risk factors: age, systolic blood pressure (SBP), antihypertensive medication, diabetes, cigarette smoking status, history of cardiovascular disease (CVD), atrial fibrillation (AF), and left ventricular hypertrophy (LVH) as determined by electrocardiogram (ECG). This self-report measure was used to predict stroke risk for each participant. Because Rosen's modified Hachinski scale was used for exclusionary criteria, the FSRP was used as a separate indicator of cerebrovascular status for analyses. Although some overlap exists between items that comprise both scales (e.g., evidence of cardiovascular disease), the FSRP provides a greater range of scores (0-30 points) than the modified Hachinski scale (0-12).

8.3 Imaging Protocol

Participants were scanned in a 3-Tesla GE Signa Infinity MRI scanner equipped with quantum gradients providing echo planar capability. The scanner is housed at the UCSD Center for Functional Imaging on the UCSD La Jolla campus. Automated shimming is used to enhance field homogeneity. We obtained both mid-sagittal and axial localizer slices to confirm the adequacy of head placement.

Structural MRI sequences were as follows:

- T1: MPRAGE, TR=7msec, TE=min full, flip angle=8 degrees, inversion recovery prepared: inversion time 900 msec, bandwidth 31.25 kHz, FOV=26cm, slice thickness 1.2mm, Locs per slab=170, number of slabs=1, Plane=sagittal, SPGR, Freq=256, Phase=256, (matrix size 256x256), NEX=1, Phase FOV=.94, Frequency/direction=Superior/inferior, Auto center

frequency=water, coil=8 channel phased array, scan time was approximately nine minutes.

- T2-weighted axial fluid-attenuated inversion recovery (FLAIR): TR=8650, TE=136, Inverse Time=2250, FOV=24, NEX=1, Phase=224, Frequency=352, Bandwidth = 31.25, Slice thickness=4mm, spacing=0, number of slices=27, Auto Center=water, scan time was approximately 4.5 minutes.
- Two field maps were collected to correct for distortions in DTI images due to susceptibility artifact: TE=minimum full (1^{st} field map) or 5.5 (2^{nd} field map), TR=1,000, FOV=24, spacing=0, NEX=1, flip angle=60, bandwidth=31.25, slick thickness=3mm, frequency=128, phase=128, phase fov=1, frequency/direction=1.
- DTI images were collected in the axial plane with a double spin echo EPI acquistion (eddy current compensated), TR = 11,000ms, TE = minimum, FOV = 24 cm, slice thickness = 3 mm, spacing = 0, matrix size 128 X 128, in-plane resolution = 1.875 x 1.875. Approximately 36 slices were acquired with 15 non-collinear diffusion directions and 4 averages (*b* value = 1500 s/mm^2). Total DTI acquisition time with field mapping was approximately 16 minutes.

8.4 Image Processing

8.4.a T1. Bias correction of field inhomogeneities was performed with N3 (Sled, Zijdenbos, & Evans, 1998). UCSD Laboratory of Cognitive Imaging (LOCI) and Bioinformatics Research Network (BIRN) groups have developed optimal methods for skull stripping that were applied to the T1 images. Specifically, the T1

image was skull stripped with Hybrid Watershed algorithm (Gootjes et al., 2004; Segonne et al., 2004), Brain Surface Extractor (BSE, Sandor & Leahy, 1997; Shattuck & Leahy, 2001), or both, as these two programs have been shown to be more effective than others (e.g., BET, 3dIntracranial) in patients with AD (Fennema-Notestine et al., 2006). Any remaining edits were performed manually.

Tissue segmentation (e.g., separating gray matter, white matter, and CSF) was then performed using the Oxford Centre for Functional Magnetic Resonance Imaging of the BRAIN (FMRIB)'s Automated Segmentation Tool (FAST, Zhang, Brady, & Smith, 2001) in order to derive gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) volumes. GM and WM volumes were then divided by the whole-brain volume (GM+WM+CSF) to generate proportionalized (e.g., percentage) GM and WM volumes that were corrected for variable head size. I will hereon refer to these proportionalized volumes as GM and WM volumes.

8.4.b FLAIR. Hyperintense regions (i.e., WMH), defined as circumscribed areas of increased signal intensity within the WM, were manually outlined as regions of interest for each subject on axial slices beginning at the most inferior slice on which the inferior horn of the lateral ventricles could be seen. These tracings were performed by one operator (HP) and then verified and edited as needed by a second operator (LDW), who had previous experience and training with these ROIs (Delano-Wood et al., 2008). Total WMH volume was then calculated by multiplying the number of voxels within the ROIs by the voxel size (0.469mm x 0.469mm x 4.00mm = 0.879844mm^3).

It should be noted that the FLAIR of one AD participant was contaminated by head movement (e.g., blurred gray matter and WM boundaries), thus all analyses involving WMH do not include this individual.

8.4.c DTI. Diffusion weighted images were submitted to FMRIB's Utility for Geometrically Unwarping EPIs (FUGUE) and Phase Region Expanding Labeller for Unwrapping Discrete Estimates (PRELUDE) programs, which unwarp echo-planar imaging (EPI) and DTI images to help correct phase variations in field map data due to field inhomogeneity and subtle subject movements. Next, eddy current correction was applied using the FMRIB's Software Library (FSL) program eddy correct to further adjust for the effects of head movement and eddy currents through affine registration. Then, the B0 volume (e.g., no diffusion weighting) was registered to the T1 volume using FMRIB's Linear Image Registration Tool (FLIRT) with six degrees of freedom and this registration algorithm was subsequently applied to the 15 diffusion directions so that the T1, B0, and all direction volumes were registered. The AFNI (Analysis of Functional NeuroImages) program 3dDWItoDT calculated the diffusion tensor and FA map from the diffusion weighted images using nonlinear estimation of the diffusion tensor model (Pierpaoli & Basser, 1996). The FA map was then extracted to prepare for TBSS analysis. From the FA map, color-coded FA images were created to facilitate ROI drawings (see below).

8.4.d Tract-Based Spatial Statistics. Tract-Based Spatial Statistics (TBSS, Smith et al., 2006), part of FSL (Smith et al., 2004) is a novel tool for the post-processing and analysis of multisubject DTI data that contains the strengths of

traditional VBM analysis (e.g., avoids user bias and the necessity of limiting the investigation to a small number of regions) because, like VBM, it is an automated, whole-brain approach. At the same time, many of the weaknesses of VBM, namely alignment and smoothing, are greatly attenuated in TBSS.

First, a target image was selected to serve as a target for all nonlinear registrations. As the target subject ideally is the "most typical" subject of the group, a normal control subject whose percentage brain volume (according to FAST segmentation) was at the median split for the entire sample was selected (per Smith et al., 2006, the final skeleton is quite comparable when different target subjects are used). All subjects' FA data were then aligned into a common space using the nonlinear registration Image Registration Toolkit (IRTK, Rueckert et al., 1999) and then affine-transformed into 1 x 1 x 1 mm^3 MNI152 space. The aligned FA images were then averaged to create a mean FA image. The process of resolution upsampling and averaging across subjects rendered the mean FA image relatively smooth, obviating the need for additional smoothing. The mean FA image was subsequently thinned to create a mean FA skeleton by using a local search for each voxel in the tract perpendicular direction, identifying the voxel with the highest FA as the center of the tract. The resultant mean FA skeleton represents the central portion of all the fiber pathways throughout the brain that are common to the group. A threshold FA value of .2 was then applied to exclude voxels that are primarily GM or CSF. Each individual subject's aligned FA data is then probabilistically projected onto this skeleton using a searching algorithm. The same perpendicular tract direction that was used to create the

original mean FA skeleton is used to search each individual's FA image to find the maximum FA value and assign this value to the skeleton voxel. Searching constraints are placed to ensure the value assigned is closer to that skeleton voxel than any other part of the skeleton, with priority given to more proximate voxels (see Smith et al., 2006), In this way, each individual's FA skeleton should contain the center of their unique WM tracts, adjusted to the alignment of the group.

8.4.e TBSS Regions of Interest. Regions of interest (ROIs) were drawn on the mean FA skeleton (overlaid on mean FA map). ROIs were created to represent two early-myelinating pathways and two late-myelinating pathways. The early-myelinating pathways included the posterior limb of the internal capsule (ICp) and the cerebral peduncles (CP). The late-myelinating pathways included the superior longitudinal fasciculus (SLF) and the inferior longitudinal fasciculus (ILF). Two FSL white-matter atlases (ICBM-DTI-81 WM labels atlas and JHU WM tractography atlas) guided the placement of the ROIs and they were further verified using a DTI color map atlas and neuropathological data from the rhesus monkey (Mori, Wakana, Nagae-Poetscher, & van Zijl, 2005; Schmahmann & Pandya, 2006). These atlases were also used to determine the location of significant voxels in the voxelwise group comparison. It should be noted that the ILF may also include voxels from the inferior fronto-occipital fasciculus (congruent with the ICBM-DTI-81 WM labels atlas that does not differentiate between these two tracts).

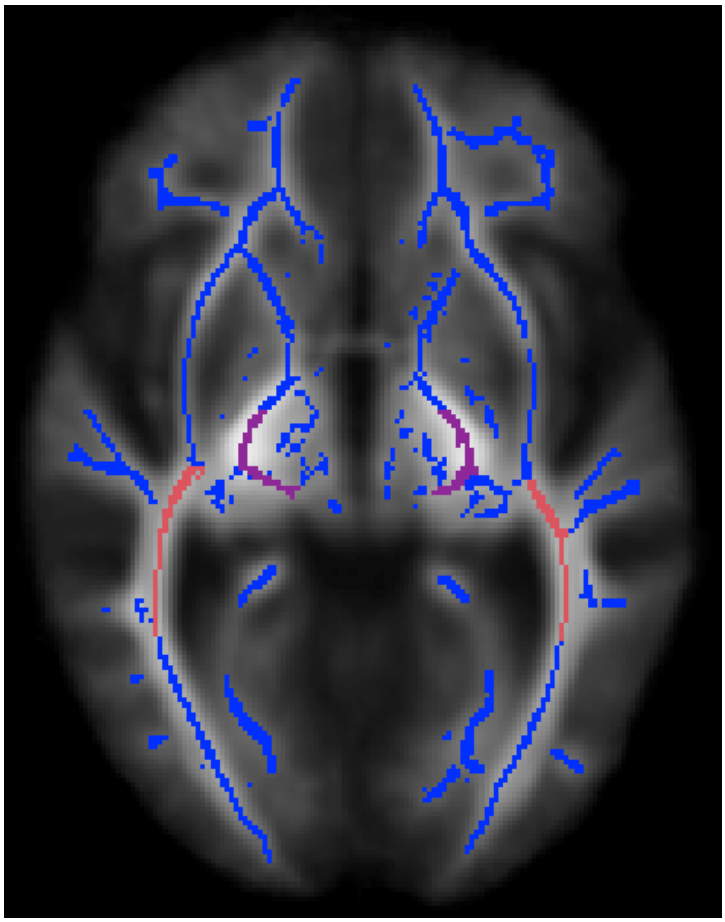

Figure 2. Regions of interest: cerebral peduncles (in purple) and inferior longitudinal fasciculus (in pink).

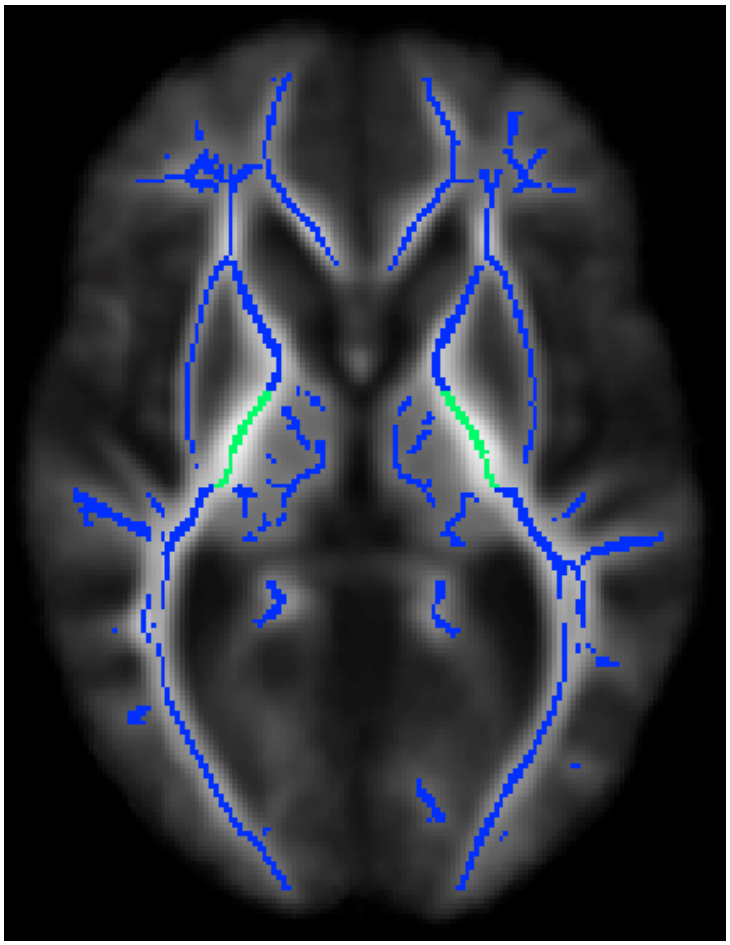

Figure 3. Region of interest: posterior limb of the internal capsule (in green).

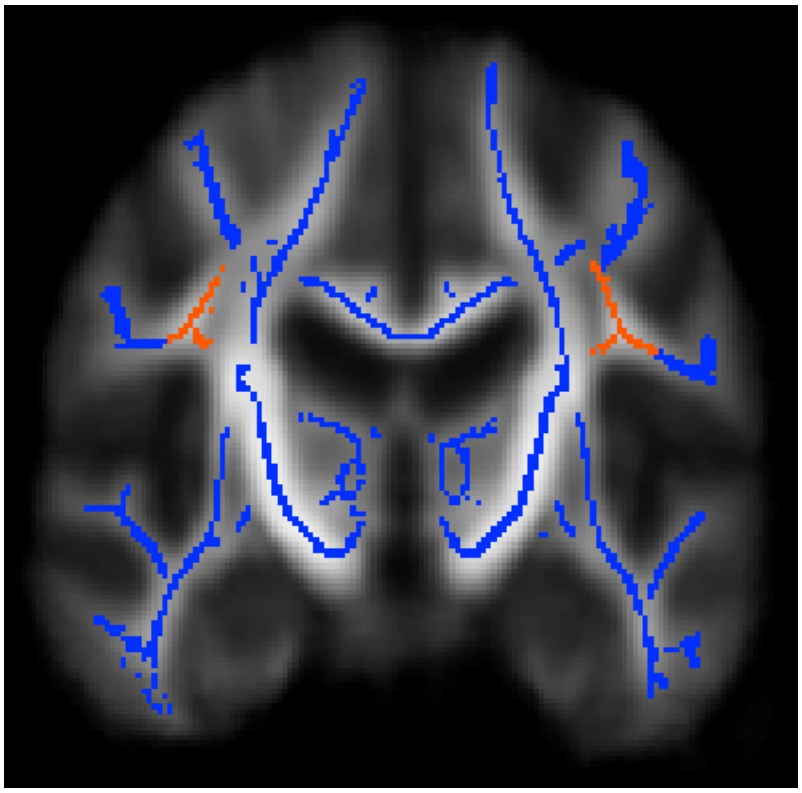

Figure 4. Region of interest: superior longitudinal fasciculus (in orange).

ROIs were also drawn on the mean FA skeleton to delineate the genu and splenium of the corpus callosum. Hofer and Frahm's (2006) recently proposed classification scheme for vertical partitioning of the corpus callosum was used to guide placement of these ROIs. Using this scheme, ROIs were drawn for Region I (genu; defined as the anterior one-sixth of the corpus callosum) and Region V (splenium; defined as the posterior one-fourth of the corpus callosum). Hofer and Frahm reported that their fiber-tracking results showed that Region I contains fiber bundles connecting prefrontal regions and that Region V contains fiber bundles connecting temporal, parietal, and occipital regions. Average FA values for each ROI were subsequently derived for each individual subject.

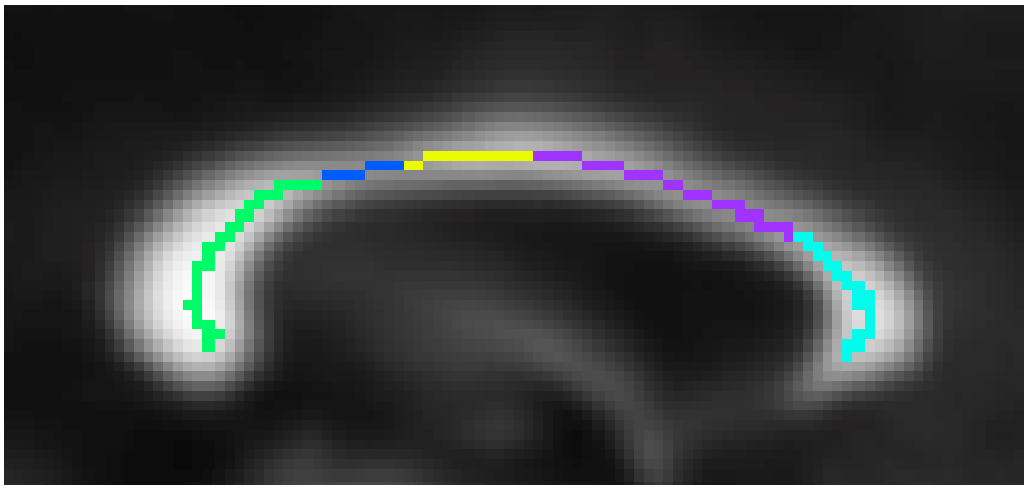

Figure 5. Regions of interest: genu (in light blue) and splenium (in green) of the corpus callosum.

8.5 Data Analysis

8.5.a Group differences. To test for localized differences across groups, voxelwise statistics were performed for each point on the common FA skeleton. A permutation-based approach (Nichols & Holmes, 2001) that accounts for "familywise errors" was used to control for multiple comparisons. This approach tests the desired test statistic (e.g., voxel *t* value, cluster size, or cluster mass) against a null distribution (created by multiple random permutations of subject ID order with respect to the model) of maximum (across space) values of the test statistic (Smith et al., 2006). Specifically, permutation-based inference cluster size ($t > 1$, $p < .05$) was used to test whether FA is significantly reduced in AD patients compared with NC participants.

An average FA value of the voxels on the skeleton that were significantly different across groups (FA_D) was derived and submitted to Analysis of Covariance

(ACNOVA) to test whether these group differences remain when covarying for each of the following variables: age, GM, WM, and WMH volume.

An average FA value was extracted for each ROI (e.g., SLF, ILF, CP, ICp, genu, splenium). ANOVA was used to examine differences across groups and derive effect sizes (partial eta squared). In addition, Repeated Measures ANOVA was used to test whether there was a significant interaction between region (early- and late-myelinating) and group (NC and AD).

8.5.b Relationship between FA and cerebral health indices. An average FA value was extracted for each individual subject by averaging across the entire FA skeleton (average FA). This average FA value was used to examine correlations with age and stroke risk as well as test partial correlations (controlling for age) with GM, WM, and WMH volume.

8.5.c Relationship between FA and neuropsychological data. Pearson correlations were used to examine the relationship between FA_D and composite neuropsychological scores. Composite scores were created for four neuropsychological domains previously shown to be sensitive to microstructural WM integrity in normal aging and/or AD using the average of age-corrected scaled scores across tests hypothesized to measure that domain. The **executive functions** composite score included letter fluency (FAS), Trail Making Test Part B, DKEFS Color-Word Inhibition-Switching trial, and DKEFS Trail Making Test Number-Letter Switching trial. The **processing speed** composite score included DKEFS Trail Making Test Number Sequencing and Letter Sequencing composite score, DKEFS Color-Word

Interference Color Naming and Word Reading composite score, Trail Making Test Part A, and WAIS-R Digit Symbol. The **attention/working memory** composite score included WMS-R Digit Span and WMS-III Letter-Number Sequencing. The **memory** composite score included WMS-R Logical Memory Immediate Recall, WMS-R Logical Memory Delayed Recall, and the DRS Memory subscale. Tests within each cognitive domain were submitted to a principle components analysis (PCA) to verify that all tests within a domain loaded on only one factor, which was the case for each domain. Further, a factor score from each PCA was saved for the separate cognitive domains and this score was submitted to correlation analyses. Because results of the correlation between FA_D and the factor scores and FA_D and the composite scores were nearly identical, only analyses using the composite scores are presented.

Four subjects had missing data on one score included in the composite scores (one control subject was missing Trails A, one control subject was missing Logical Memory Delayed Recall, one AD subject was missing Trails B, one AD subject was missing DKEFS color-word inhibition/switching). For these four subjects, composite scores were averaged across their remaining available data. The results were essentially identical with and without these subjects' data included in the composite scores, thus only results with data from all subjects (N = 30) were reported for composite score analyses.

Hierarchical linear regression models determined whether FA_D accounted for additional variance above and beyond more traditional brain measures. Specifically, for each dependent variable (each neuropsychological composite score and total DRS

age-corrected scaled score), the first model contained GM, WM, and WMH as independent variables. The second model added FA_D and tested whether the additional change in variance was significant.

Since most of the neuropsychological tests selected for use in this study have not been previously related to FA values in AD patients, individual test indices were also examined in an exploratory fashion by testing Pearson correlations between average FA, FA_D, FA of the six ROIs and selected neuropsychological test indices. Nine variables (gray matter volume, WMH volume, splenium FA, DRS Memory SS, DRS Initiation/Perseveration SS, DRS Construction SS, dual task decrement, BNT, and DKEFS trail making test motor SS) had non-normal distributions as defined by a skewness or kurtosis statistic twice its standard deviation. Spearman correlations are reported for these variables.

Chapter 9. Results

9.1 Voxelwise Comparison

Independent samples t-tests corrected for multiple comparisons using permutation-based inference (T. E. Nichols & Holmes, 2002, cluster-forming threshold $t = 1$, corrected cluster size $p < .05$) was used to test for voxelwise group differences in FA. Voxelwise analyses revealed significantly lower FA values in AD patients compared to healthy older adults in late-myelinating association fiber pathways, including the uncinate fasciculus, ILF, and SLF. Significant differences were also observed in the fornix/stria terminalus, cingulum, splenium of the corpus callosum, and forceps major. No significant differences were seen in early-myelinating pathways.

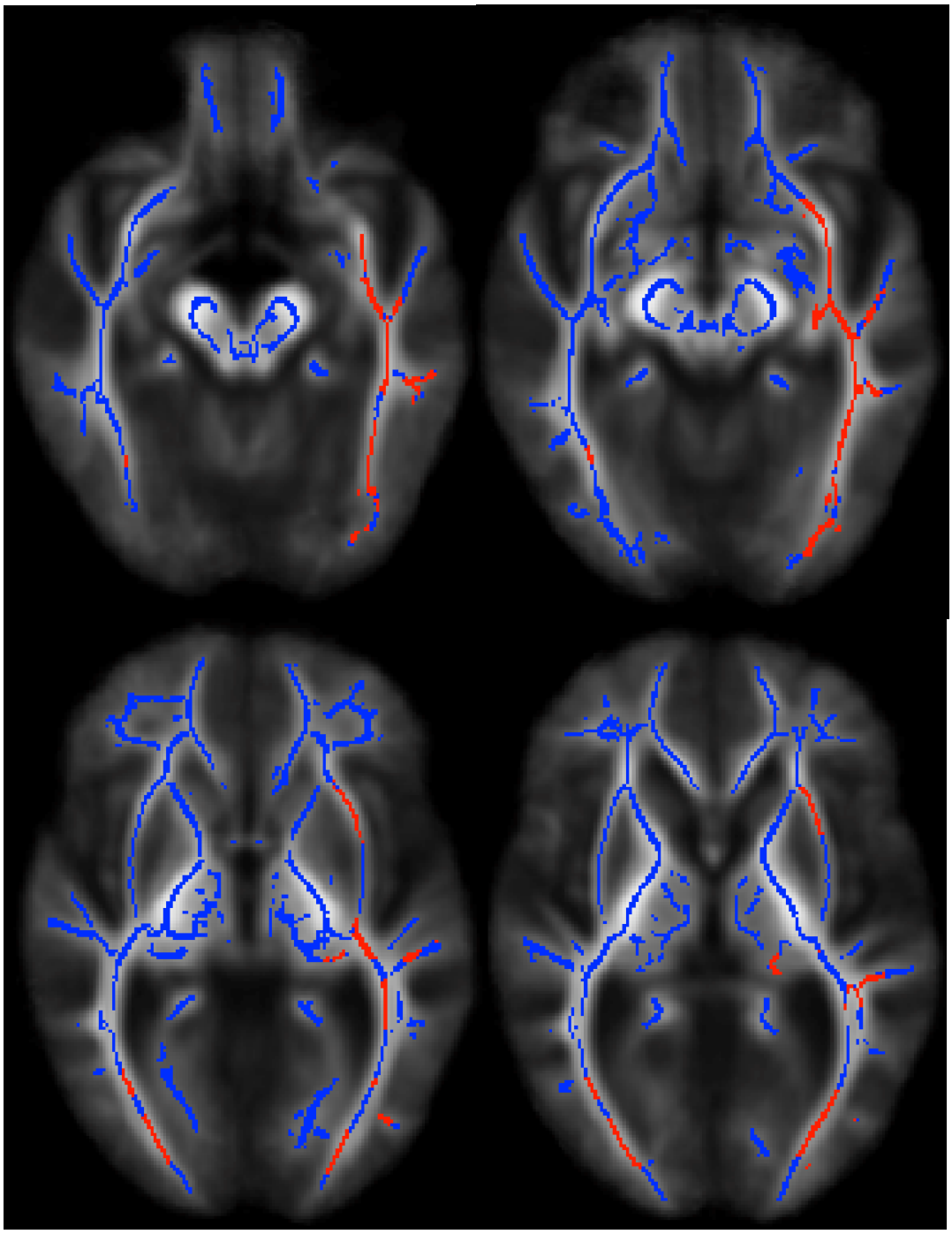

Figure 6. Voxelwise group differences in the uncinate fasciculus, inferior longitudinal fasciculus, and fornix (in red) overlaid on mean FA skeleton (in blue).

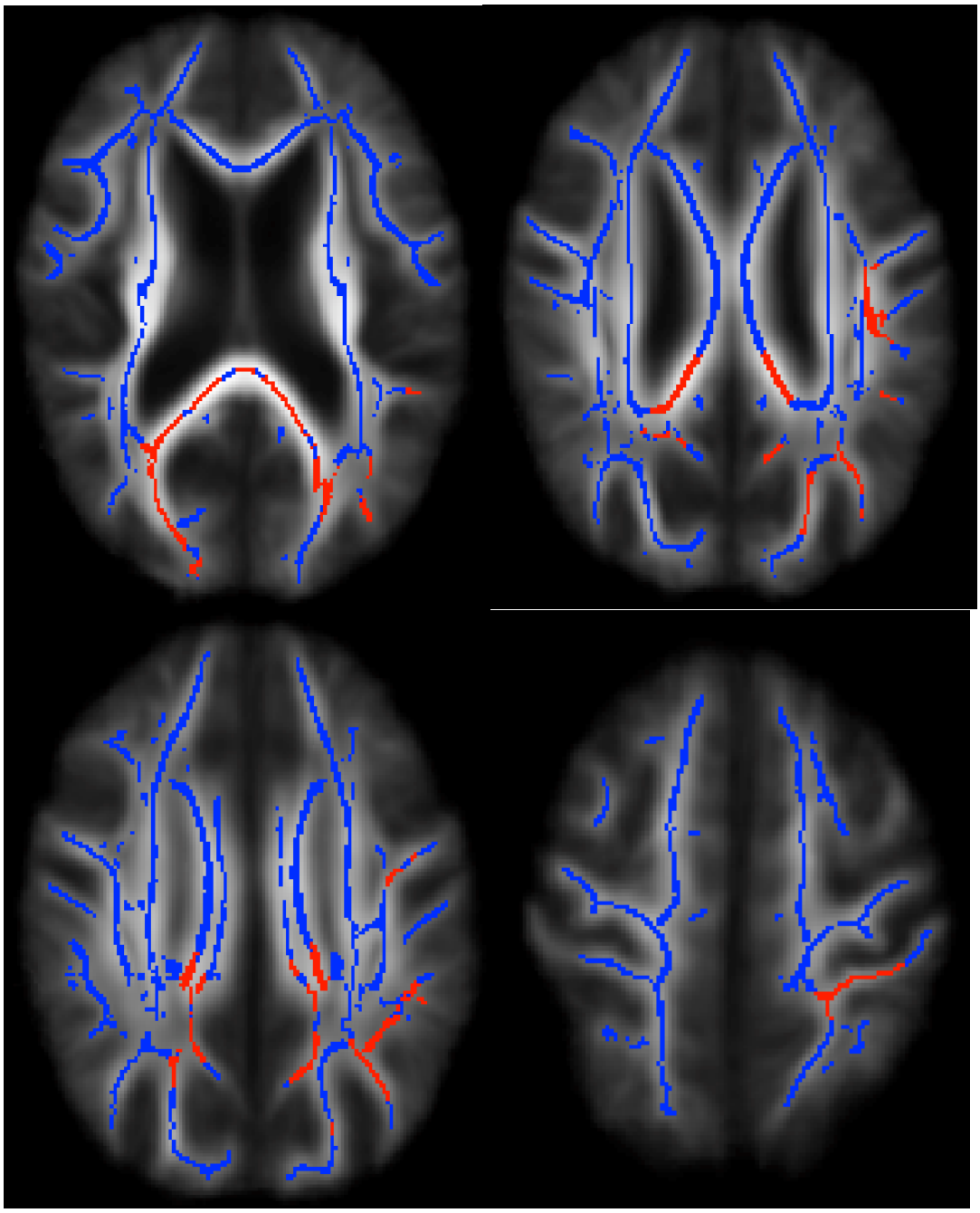

Figure 7. Voxelwise group differences in the splenium, cingulum, forceps major and superior longitudinal fasciculus (in red) overlaid on mean FA skeleton (in blue).

An average FA value was derived for each individual in those voxels on the FA skeleton that were significantly different across groups (FA_D). As expected, the AD group showed lower FA than the NC group ($F_{1,28} = 17.69$, $p < .001$, $\eta_p^2 = .39$). The group difference remained highly significant when controlling for age, GM volume, WM volume, and total WMH ($F_{1,24} = 14.38$, $p = .001$, $\eta_p^2 = .38$).

9.2 Group Comparison of Average FA and Brain Volume Indices

An average FA of the entire WM skeleton was derived for each individual. The difference between groups on average FA approached significance ($F_{1,28} = 3.66$, $p = .07$, $\eta_p^2 = .12$), with the AD group showing lower overall WM microstructural integrity than the NC group. The group difference also approached significance for gray matter volume ($F_{1,28} = 3.65$, $p = .07$, $\eta_p^2 = .12$). The AD group had lower whole brain volume than the NC group ($F_{1,28} = 9.31$, $p = .005$, $\eta_p^2 = .25$). WM volume ($F_{1,28} = 1.67$, $p = .21$, $\eta_p^2 = .06$) and total WMH volume ($F_{1,27} = 1.16$, $p = .29$, $\eta_p^2 = .04$) did not differ significantly across groups. See Table 5 for means and standard deviations.

Table 5. Group comparison of average FA and brain volume indices.

	NC (n=14)	**AD (n=16)**	*p*	η_p^2
Average FA skeleton	.395 (.022)	.379 (.021)	.07	.12
FA_D	.445 (.033)	.399 (.027)	<.001*	.39
Gray Matter (%)	.444 (.031)	.425 (.021)	.07	.12
White Matter (%)	.338 (.017)	.326 (.028)	.21	.06
Whole Brain (%)	.781 (.026)	.752 (.026)	.005*	.25
Total WMH (mm^3)	6497 (6939)	9856 (9544)	.29	.04

Note. FA_D = FA skeleton voxels that were significantly different across groups in voxelwise analysis, WMH = white matter hyperintensity volume.
* $p < .01$

9.3 ROI Group Comparisons

No significant differences across groups were found in early-myelinating regions (CP, $F_{1,28} = .10$, $p = .75$, $\eta_p^2 = .00$; ICp, $F_{1,28} = .42$, $p = .52$, $\eta_p^2 = .02$). No significant differences were found across groups in the genu ($F_{1,28} = .27$, $p = .61$, $\eta_p^2 = .01$) or splenium ($F_{1,28} = 1.42$, $p = .24$, $\eta_p^2 = .05$). A significant difference was found for late-myelinating regions ($F_{1,28} = 4.49$, $p = .04$, $\eta_p^2 = .14$), with the AD group showing lower FA than the NC group. When the two late-myelinating ROIs were tested separately, the ILF showed a significant difference ($F_{1,28} = 6.15$, $p = .02$, $\eta_p^2 = .18$), again with the AD group showing lower FA than the NC group, but the SLF did not ($F_{1,28} = .74$, $p = .40$, $\eta_p^2 = .03$). To follow up on these findings, repeated measures ANOVA was performed to test for an interaction between region (early vs. late) and

group (NC vs. AD). When testing the aggregate ROI results of early- versus late-myelinating regions, the region (early/late) by group (NC/AD) interaction approached significance ($F_{1,28} = 2.81$, $p = .11$, $\eta_p^2 = .09$). This analysis was then tested separately for each late-myelinating ROI. For the SLF, the region (early/SLF) by group (NC/AD) interaction was not significant ($F_{1,28} = .13$, $p = .72$, $\eta_p^2 = .01$). For the ILF, the region (early/ILF) by group (NC/AD) interaction was significant ($F_{1,28} = 4.28$, $p = .05$, $\eta_p^2 = .13$).

Table 6. Average FA across groups for each ROI.

	NC (n=14)	**AD (n=16)**	*p*	η_p^2
Early-Myelinating	.644 (.023)	.638 (.031)	.58	.01
CP	.620 (.026)	.617 (.029)	.75	.00
ICp	.667 (.028)	.659 (.039)	.52	.02
Late-Myelinating*	.435 (.027)	.414 (.028)	.04	.14
SLF	.403 (.027)	.394 (.030)	.40	.03
ILF*	.467 (.036)	.434 (.037)	.02	.18
Commissural				
Genu	.573 (.047)	.565 (.038)	.61	.01
Splenium	.684 (.031)	.666 (.046)	.24	.05

Note. CP = cerebral peduncles, ICp = posterior limb of the internal capsule, SLF = superior longitudinal fasciculus, ILF = inferior longitudinal fasciculus.
*$p < .05$.

9.4 Relationship Between Average FA and Cerebral Health Indices

Age was significantly related to average FA (r = -.51, p = .004), FA_D (r = -.50, p = .005), genu (r = -.54, p = .002), splenium (r = -.38, p = .04), and ILF (r = -.46, p = .01). Stroke risk was significantly related to average FA (r =-.51, p = .004), FA_D (r = -.45, p = .01), genu (r = -.46, p = .01), splenium (r = -.41, p = .02), and ILF (r = -.36, p = .05). The SLF and both early-myelinating ROIs (cerebral peduncles and posterior limb of the internal capsule) were not significantly related to either age or stroke risk (p's > .05; see Appendix B).

The following are partial correlations, controlling for the effect of age. Average FA skeleton was significantly correlated with gray matter volume (r = .42, p = .02) and total WMH volume (r = -.50, p = .007), but not with WM volume (r = -.04, p = .86). FA_D was significantly correlated with gray matter volume (r = .56, p = .002) and total WMH volume (r = -.53, p = .003), but not with WM volume (r = .03, p = .88). The ILF was significantly correlated with gray matter volume (r = .58, p = .001) and total WMH volume (r = -.59, p < .001), but not with WM volume (r = -.16, p = .40). The SLF was significantly correlated with WMH volume (r = -.37, p = .05), but not with gray matter volume (r = .21, p = .28) or WM volume (r = -.02, p = .92). The genu, splenium, cerebral peduncles and the posterior limb of the internal capsule were not significantly correlated with total WMH volume, gray matter volume, or WM volume (p's > .05; see table 7).

Table 7. Partial correlation coefficients: relationship of white matter microstructural integrity and brain volume indices.

	Gray Matter	White Matter	Total WMH
Avg FA skeleton	.42* (.02)	-.04 (.86)	-.50* (.007)
FA_D	.56* (.002)	.03 (.88)	-.53* (.003)
SLF	.21 (.28)	-.02 (.92)	-.37* (.05)
ILF	.58* (.001)	-.16 (.40)	-.59* (.001)
CP	-.05 (.79)	.09 (.64)	-.17 (.39)
ICp	.13 (.50)	-.04 (.85)	-.29 (.14)
Genu	.20 (.29)	.18 (.35)	.03 (.88)
Splenium	.33 (.08)	-.06 (.77)	.06 (.78)

Note. WMH = white matter hyperintensity volume, FA_D = FA skeleton voxels that were significantly different across groups in voxelwise analysis, SLF = superior longitudinal fasciculus, ILF = inferior longitudinal fasciculus, CP = cerebral peduncles, ICp = posterior limb of the internal capsule.
* $p < .05$

9.5 Relationship Between Cognition and FA

9.5.a A priori composite score correlations. Lower FA_D was significantly related to poorer performance on memory, executive functions, and processing speed ($p < .05$, composite scores), but not attention/working memory. GM volume was significantly related to executive functions and memory ($p < .05$), but not processing speed or attention/working memory. WMH volume and WM volume did not show significant correlations with any of the composite scores.

Table 8. Pearson (and Spearman) correlation coefficients: relationship of composite neuropsychological scores, dementia severity and brain measures.

	Executive Functions	Processing speed	Attention/ Working Memory	Memory	Total DRS SS
FA_D	.49 (.01)	.44 (.02)	.25 (.18)	.49 (.01)	.53 (.002)
WMH (r_s)	-.03 (.90)	.18 (.35)	.09 (.64)	-.04 (.86)	.16 (.42)
GM (r_s)	.50 (.005)	.32 (.08)	.24 (.21)	.45 (.01)	.38 (.04)
WM	-.06 (.77)	.21 (.27)	-.08 (.66)	.12 (.52)	.22 (.25)

Note. DRS SS = Dementia Rating Scale age-corrected scaled score, FA_D = FA skeleton voxels that were significantly different across groups in voxelwise analysis, WMH = white matter hyperintensity volume, GM = gray matter volume, WM = white matter volume, r_s denotes Spearman correlation coefficient.
* $p < .05$

9.5.b Hierarchical linear regression models. Hierarchical linear regression models were built to examine whether FA_D explains a significant amount of variance in each composite score and DRS above and beyond GM, WM, and WMH volumes (see Appendix C). The addition of FA_D to the model led to a significant change in R^2 for executive functions (R^2 change = .13, $F_{1,24}$ change = 5.31, p = .03), processing speed (R^2 change = .14, $F_{1,24}$ change = 6.04, p = .02), attention/working memory (R^2 change = .17, $F_{1,24}$ change = 5.56, p = .03), and DRS (R^2 change = .15, $F_{1,24}$ change = 7.45, p = .01), but not for memory (R^2 change = .08, $F_{1,24}$ change = 3.23, p = .09). When all variables were present within the model, for executive functions, processing

speed, attention/working memory, and DRS, the WMH volume and FA_D coefficients were both significant ($p < .05$), but GM and WM volume were not ($p > .05$). For memory, no single coefficient was significant, but the overall model was significant ($p = .02$). The overall models for executive functions, processing speed, and DRS were significant ($p < .05$). However, the overall model for attention/working memory was not significant ($p = .09$).

9.5.c Exploratory correlations between FA indices and individual test indices. Exploratory analyses revealed that lower FA_D was significantly associated with poorer performance on several measures of executive function (DRS Initiation/Perseveration, DKEFS color word inhibition-switching, DKEFS color word inhibition-switching versus combined naming and reading contrast score, DKEFS color word inhibition-switching versus inhibition contrast score, DKEFS trail making test number-letter switching, and Trails B). Lower FA_D was significantly associated with poorer performance on three measures with a motor or processing speed component (DKEFS trail making test number and letter sequencing composite score, DKEFS trail making test motor speed, and dual task's simple motor component). Lower FA_D was significantly associated with poorer performance on several measures of memory (Logical Memory immediate recall, Logical Memory delayed recall, CVLT 1-5 total, CVLT long-delay free-recall, and DRS Memory subscale). Lower FA_D was significantly associated with poorer performance on visuospatial measures (facial recognition and DRS Construction) and language (Boston Naming Test; BNT). Lower FA_D was significantly associated with both cognitive and functional dementia

severity. Specifically, lower FA_D was significantly associated with poorer performance on DRS total score and higher FAQ score (i.e., more impairment on instrumental activities of daily living, *p*'s < .05).

Average FA (across whole WM skeleton) showed a similar pattern of correlations but demonstrated a weaker effect size. Seven of the 17 significant correlations reported above remained significant. Lower average FA was significantly associated with poorer performance on facial recognition, one measure with a motor or processing speed component (DKEFS trail making test number and letter sequencing composite score), two measures of executive function (DKEFS color word inhibition-switching versus combined naming and reading contrast score, DKEFS color word inhibition-switching versus inhibition contrast score), and three memory indices (CVLT 1-5 total, CVLT long-delay free-recall, DRS Memory; all *p*'s < .05).

Lower splenium FA was significantly associated with poorer performance on one measure of executive function (DKEFS trail making test number-letter switching). Lower splenium FA was significantly associated with higher FAQ (all *p*'s < .05).

Lower SLF FA was significantly associated with higher DKEFS trail making test number-letter sequencing versus number and letter sequencing composite score contrast scaled score ($p < .05$; i.e., less WM integrity in SLF was associated with less of a difference in performance across higher order trails switching task and lower order sequencing trials).

Lower ILF FA was significantly associated with poorer performance on three executive function indices (DKEFS color word inhibition-switching, DKEFS color

word inhibition-switching versus combined naming and reading contrast score, DKEFS color word inhibition-switching versus inhibition contrast score) and three memory indices (CVLT 1-5 total, CVLT long-delay free-recall, and DRS Memory subscale; all p's < .05).

Genu FA was not significantly correlated with any cognitive indices. Early myelinating regions (ICp and CP) were not significantly correlated with any cognitive indices (all p's > .05).

Only cognitive variables with significant correlations are presented in Tables 9-12 for ease of interpretation. Please see the Appendix C for a complete table of all correlation coefficients.

Table 9. Pearson (and Spearman) correlation coefficients: relationship of executive functions and white matter microstructural integrity.

Executive Functions	Avg FA	FA_D	Splenium (r_s)	SLF	ILF
CW Inhibition/ Switching SS		.47 (.01)			.45 (.01)
CW Inhib/Switch vs Combined Naming+Reading	.40 (.03)	.49 (.006)			.61 (.000)
CW Inhib/Switch vs Inhibition Contrast SS	.44 (.02)	.48 (.009)			.55 (.002)
TMT Number-Letter Switching SS		.41 (.02)	.36 (.05)		
TMT No.-Letter Switch vs No. + Letter composite				-.47 (.01)	
Trails B SS		.40 (.03)			
DRS Initiation/ Perseveration SS (r_s)		.36 (.05)			

Note. FA_D = FA skeleton voxels that were significantly different across groups in voxelwise analysis, SLF = superior longitudinal fasciculus, ILF = inferior longitudinal fasciculus, SS = age-corrected scaled score, CW = Color-Word Interference Test (DKEFS), TMT = Trail Making Test (DKEFS), DRS = Mattis Dementia Rating Scale, r_s denotes Spearman correlation coefficient.

Table 10. Pearson (and Spearman) correlation coefficients: relationship of motor and processing speed measures and white matter microstructural integrity.

Motor/Processing Speed	Avg FA	FA_D
TMT Number + Letter Sequencing Composite	.37 (.05)	.51 (.004)
TMT Motor SS (r_s)		.37 (.04)
Simple Task motor score raw		.42 (.02)

Note. FA_D = FA skeleton voxels that were significantly different across groups in voxelwise analysis, SS = age-corrected scaled score, TMT = Trail Making Test (DKEFS), r_s denotes Spearman correlation coefficient.

Table 11. Pearson (and Spearman) correlation coefficients: relationship of memory and white matter microstructural integrity.

Memory	Avg FA	FA_D	ILF
Memory Composite Score		.49 (.006)	
LM Immediate SS		.38 (.04)	
LM Delay SS		.44 (.02)	
CVLT 1-5 raw	.38 (.04)	.61 (.000)	.45 (.01)
CVLT long-delay free-recall raw	.38 (.04)	.59 (.001)	.38 (.04)
DRS Memory SS (r_s)	.38 (.04)	.58 (.001)	.38 (.04)

Note. FA_D = FA skeleton voxels that were significantly different across groups in voxelwise analysis, ILF = inferior longitudinal fasciculus, SS = age-corrected scaled score, LM = Logical Memory (WMS-R), CVLT = California Verbal Learning Test, DRS = Mattis Dementia Rating Scale, r_s denotes Spearman correlation coefficient.

Table 12. Pearson (and Spearman) correlation coefficients: relationship of language, visuospatial skills, and dementia severity and white matter microstructural integrity.

	Avg FA	FA_D	Splenium (r_s)
Language			
BNT raw score (r_s)		.52 (.003)	
Visuospatial			
Facial Recognition	.39 (.03)	.44 (.02)	
DRS Construction SS (r_s)		.38 (.04)	
Dementia Severity			
DRS Total SS		.53 (.002)	
FAQ		-.55 (.002)	-.38 (.04)

Note. FA_D = FA skeleton voxels that were significantly different across groups in voxelwise analysis, SS = age-corrected scaled score, BNT = Boston Naming Test (30-item), DRS = Mattis Dementia Rating Scale, FAQ = Functional Activities Questionnaire, r_s denotes Spearman correlation coefficient.

Chapter 10. Discussion

The present study aimed to (1) resolve current discrepancies in the literature on white matter changes in AD by applying the retrogenesis model and (2) determine whether the pattern of relationships between cognition and WM microstructural changes support the view of AD as a disconnection syndrome. A novel methodology for analyzing DTI data was employed that allows for systematic whole-brain analysis of WM microstructural changes while minimizing individual differences due to varying degrees of atrophy.

In this study, two distinct analyses of the DTI data were performed: whole brain voxelwise analysis and a priori ROI analysis. As predicted, both methods of analysis produced results that were largely consistent with the retrogenesis model of AD. However, the ROI analysis also found differential results in late myelinating pathways that suggest that the observed group differences may be due to a combination of retrogenesis and Wallerian degeneration (WM degeneration secondary to neuronal loss).

10.1 Whole Brain Voxelwise Analysis

Voxelwise analysis revealed less WM microstructural integrity (i.e., lower FA) in AD patients compared to healthy older adults in vulnerable, late-myelinating fiber pathways. Association pathways have been identified as the latest-myelinating fiber pathways in the brain (Kinney, Brody, Kloman, & Gilles, 1988; Yakovlev & Lecours, 1967), thus according to the retrogenesis model these will be the most vulnerable to insult. In our results, differences were found in association pathways that connect

association areas of the neocortex (uncinate fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus). As expected, the findings suggest that early-myelinating fiber pathways may be spared.

In addition, less WM microstructural integrity was found in AD patients compared to normal control participants in the fornix/stria terminalus, cingulum, splenium of the corpus callosum, and forceps major. These fiber pathways have connections to brain regions affected early by AD pathology (Braak & Braak, 1996b). For example, the cingulum has projections to several areas afflicted early by AD pathology (e.g., entorhinal cortex, presubiculum, parahippocampal gyrus). Although these areas can also be viewed as relatively late-myelinating, they are not as vulnerable as corticocortical association pathways (e.g., they myelinate before corticocortical association pathways). Changes in these structures in AD may reflect Wallerian degeneration. As an example, early neuronal death in the entorhinal cortex may lead to distal changes in the microstructural WM integrity of the cingulum because of its connections to these cells within the entorhinal cortex that are afflicted by AD neuropathology and subsequent deprivation of required nutrients and microtubule destabilization (Ehlers, 2004). Therefore, the results of our voxelwise analysis suggest that both retrogenesis and Wallerian degeneration are mechanisms of white matter change in AD.

These results are consistent with a recent VBM study by Tiepel et al. (2007) that used a multivariate approach (principle components analysis) to examine the relative differences in FA across groups. They found that, compared to normal

controls, AD patients had relatively lower FA in intracortical projecting (i.e., later-myelinating) fiber pathways (anterior corpus callosum, WM of the parahippocampal gyrus and fornix, and WM of the frontal, temporal, and occipital lobes) and relatively higher FA in extracortical projecting (i.e., early-myelinating) fiber pathways (WM of the pre- and postcentral gyrus, the centrum semiovale and the superior frontal gyrus, anterior and posterior parts of the internal capsule, thalamus and putamen, the anteromedial midbrain, and the cerebellum). Although results from Tiepel et al. (2007) are based on Talairach and Tournoux coordinates (as opposed to focusing on specific fiber pathways as in the current study), and different processing methods and statistical approaches were used, the consistent pattern of results across these two studies offers encouraging support for the utility of the retrogenesis model in AD when a whole-brain analysis is performed.

10.2 WM Microstructural Differences Remain after Covarying for Volumetric MR Measures

Because the difference across groups remained after covarying for age, gray matter, white matter, and WMH, our results also suggest that the changes in WM microstructural integrity observed in AD are not entirely explained by contributions from volumetric MR measures. Consistent with these results, other studies have attested that DTI is sensitive to widespread changes in WM that are not fully captured by macrostructural measures of WM (Kalus et al., 2006; Taylor et al., 2007). Also, some studies have demonstrated that DTI parameters significantly improve prediction of group members compared to volumetric measures alone (Kantarci et al., 2005;

Zhang et al., 2007). This finding offers additional support for the retrogenesis model of AD because, even after controlling for atrophy, microstructural WM integrity is decreased in AD. If Wallerian degeneration were the only mechanism of change, it would be expected that the variance due to atrophy would account for the change in microstructural WM integrity, and there would no longer be a statistically significant group difference.

10.3 Strengths and Weaknesses of Whole Brain Voxelwise Analysis

The whole-brain voxelwise analysis facilitates the investigation and interpretation of results from multiple areas, and does not limit the analysis to a small number of ROIs. However, short of running the same analysis multiple times with differing alpha levels, voxels that surpass the significance threshold are observed, but it is unclear to what extent other areas approached significance. In order to provide a more direct test of the retrogenesis hypothesis (i.e. testing under conditions where an effect size can be calculated), an analysis of a priori ROIs was also performed (see sections 5.7 and 10.8 for further discussion of strengths and limitations of both approaches).

10.4 ROI Analyses

To perform a more direct test of the retrogenesis model, ROIs were created for two early-myelinating pathways (cerebral peduncles, posterior limb of the internal capsule) and two late-myelinating pathways (inferior longitudinal fasciculus, superior longitudinal fasciculus). This provides a more direct test because it allows us to test an interaction and ROIs were selected a priori according to order of myelination, thus

fewer comparisons were performed, reducing the likelihood of Type I error. We found that an interaction between region (early- and late-myelinating pathways) and group (NC and AD) approached significance. Further, when only the ILF was used to represent late-myelinating pathways, the interaction between region and group was significant.

10.4.a Late-myelinating fiber pathways. Follow-up analysis of individual late-myelinating fiber pathways revealed that the ILF was driving this interaction. Although both the ILF and SLF are vulnerable late-myelinating pathways, in the ROI analyses the ILF showed significantly less WM microstructural integrity in AD patients than in normal healthy elderly, whereas the SLF did not.

Wallerian degeneration may explain the difference across groups in the ILF because of its connections to medial temporal areas affected early in the AD neuropathological process (Braak & Braak, 1996b). The ILF courses through the WM of the temporal, parietal, and occipital lobe and is the predominant path connecting the temporal and occipital lobes. In addition to connections with the occipital lobe, the ILF also conveys fibers from the posterior cingulate gyrus, the inferior parietal lobules and the superior temporal gyrus to the parahippocampal gyrus within the temporal lobe. The SLF, which did not show significant group differences, does not have connections to the temporal lobe and instead links the parietal lobe with the frontal lobe (Schmahmann & Pandya, 2006). Although parietal and frontal cortices are also affected in AD, this occurs later in the disease process relative to temporal lobe pathology (Braak & Braak, 1996b). Therefore, in our sample of patients with mild-to-

moderate disease severity, it may be that the changes in the SLF that were seen on voxelwise group comparison may not be as widespread or severe as those in the ILF. Consequently, when averaging across a number of voxels, as in ROI analysis, any changes that were present may not have been large enough to produce a significant group difference.

10.4.b Early-myelinating fiber pathways. Consistent with the retrogenesis model, there were no significant differences across groups in the cerebral peduncles or the posterior limb of the internal capsule. Other studies have also used these structures to represent early-myelinating fiber pathways and have similarly found sparing of these areas in AD patients (Naggara et al., 2006; Rose et al., 2000; Rose, Janke, & Chalk, 2008; Xie et al., 2006; Zhang et al., 2007), all of which represents an important methodologic validation of our techniques.

10.4.c Commissural fiber pathways. ROIs were placed in the genu and splenium primarily because these regions are the most consistently studied and we aimed to use these regions to help link our results to the existing literature. We used a novel classification scheme based on fiber tractography of the corpus callosum in humans to manually delineate the genu and splenium on the FA skeleton (Hofer & Frahm, 2006). Like the superior longitudinal fasciculus, the splenium showed incongruent results across voxelwise and ROI analyses. Qualitatively, the voxelwise analysis revealed strong, clear group differences within the splenium. However, when taking an average across this area for each subject in the ROI analyses, the AD group did not show significantly lower FA compared to the healthy elderly. This result was

unexpected because most studies that have performed ROI analysis of the splenium have shown group differences between AD patients and control groups (Duan et al., 2006; Naggara et al., 2006; Rose et al., 2000; Takahashi et al., 2002; but see Choi et al., 2005; Head et al., 2004).

One possible explanation for this finding is that our ROIs were extracted from TBSS data (i.e., the FA skeleton), whereas most studies place circular or rectangular ROIs within a WM region for each individual. Because the FA skeleton represents the central WM within each fiber pathway (by using an algorithm that searches for the highest FA value along a specified path to place on each voxel of the FA skeleton), ROI analysis using this method may be less sensitive compared to other approaches (but likely more robust). The lack of differences across groups in the genu in both the voxelwise and ROI analyses is highly consistent with other studies that have consistently failed to find group differences in this region (Choi et al., 2005; Duan et al., 2006; Head et al., 2004; Naggara et al., 2006; Takahashi et al., 2002; but see Teipel et al., 2007). Therefore, although our ROI results were not entirely consistent with the current literature, the pattern of results in the corpus callosum on voxelwise analysis was highly congruent with the current literature and likely best reflects the generalizability of these results.

10.5 Aim 1: Discrepancies in the Literature and the Retrogenesis Model

In most studies of AD employing DTI, it has been concluded that changes in WM in AD patients are found predominantly in posterior regions (Medina et al., 2006), as would be predicted based on the spatiotemporal progression of

neurofibrillary tangles throughout the brain in AD via Wallerian degeneration. As discussed in section 5.9.c, researchers finding differences in the diffusion properties of WM in AD patients relative to normal elderly in frontal WM regions or the genu have argued for an anterior-posterior gradient of degeneration in AD (Choi et al., 2005; Duan et al., 2006; Naggara et al., 2006), similar to most studies of normal aging (Head et al., 2004; O'Sullivan et al., 2001; Pfefferbaum, Adalsteinsson, & Sullivan, 2005; Raz et al., 2005; Sullivan, Adalsteinsson, & Pfefferbaum, 2006; Van Petten et al., 2004). This anterior-posterior gradient of AD degeneration is generally thought to be more consistent with the retrogenesis model of AD (although this is likely an oversimplification). Possible resolutions of these two contradictory camps could lie in theories related to disease process, disease severity of the sample, and/or the methodology used. We will look at each of these in turn.

10.5.a Theory. When WM degeneration in aging and AD is conceptualized as reverse myelination as in the retrogenesis model (Bartzokis, 2004; Braak & Braak, 1996a; Reisberg et al., 1999), these two seemingly discrepant patterns of greater posterior than anterior involvement versus a proposed anterior-posterior gradient of degeneration can coexist (as discussed in 5.9.c). This is because the anterior-posterior gradient theory of degeneration is often presented simultaneously with retrogenesis. That is, if one assumes that the degeneration of WM follows an inverse pattern of myelogenesis, then it can be further specified that it is those regions that continue to develop myelin into the fourth and fifth decades of life (that are characterized by small-diameter myelinated fibers and multiple myelinated axons being supported by a

single oligodendrocyte) that will first show loss of WM integrity with age or with disease processes such as AD (Bartzokis, 2004; Reisberg et al., 1999).

However, the cycles of normal myelination within the brain are complicated and represent an entire area of research that continues to develop. Vulnerability of WM fibers depends not only on when myelination begins, but also on how protracted myelination is within a region (i.e., how long the process of myelination continues). Because of the complexity of the regional progression of myelination, several general rules have been proposed. Kinney et al. (1988) delineated that, "proximal pathways myelinate earlier and faster than distal pathways, sensory pathways myelinate before motor pathways, projection before associative pathways, central telencephalic sites before poles, and occipital before fronto-temporal poles. No single rule acts alone; rather, there is a complex interplay in which one may supersede another to dictate the sequence of myelination within or across an axonal system" (p. 228). Despite Kinney et al.'s assertion that no one rule explains the process of myelination, understandably, researchers have used these rules individually to explain results. Most notably, the rule that the occipital poles myelinate before fronto-temporal poles has likely lead to the generalization that posterior regions myelinate before anterior regions, which has been propagated by studies reporting an anterior-posterior gradient of change in normal aging (where it is typically concluded that this occurs because frontal regions are the last to myelinate).

An alternative and perhaps more unifying approach than looking for anterior vs. posterior gradients of change is to predict WM changes in vulnerable late-

myelinating fiber bundles, as done in the current study. This is consistent with Salat et al.'s (2005) argument that WM changes in normal aging are regionally selective depending on the vulnerability of particular fiber bundles as opposed to being exclusively restricted to a regional location. A more general principle of myelination that coincides with this approach is that myelination of functional systems that are critical early in life (e.g., sensorimotor systems) begins earlier and progresses more rapidly than functional systems that are not necessary until later in childhood or that is a higher evolutionary function (e.g., language, executive functions; Barkovich, 2005; Yakovlev & Lecours, 1967).

10.5.b Disease severity. Another possible explanation for the discrepant results in the literature is due to differences in dementia severity of the AD sample across studies. Naggara et al. (2006) suggested that studies including only mild AD patients may result primarily in an age-related pattern of decline in WM microstructural integrity and those with higher disease severity will additionally show the posterior involvement associated with the more advanced disease process. However, results from studies investigating MCI argue against this possibility. For example, Medina et al. (2006) found highly consistent regions of reduced WM integrity in both MCI and AD groups relative to the control group. Only the posterior cingulate bundle showed additional decline in the AD group. In addition, studies that investigated patients with mild AD (Head et al., 2004; Medina et al., 2006) show a similar pattern of results to studies of samples with a higher degree of dementia severity based on MMSE score (Bozzali et al., 2002; Duan et al., 2006; Takahashi et

al., 2002). The similarities across different stages of AD suggests that WM microstructural changes may be detectable even earlier in the disease process and thus may provide a useful marker for predicting progression to AD in at-risk groups (e.g., individuals with the apolipoprotein ε4 allele).

10.5.c Methodology. Use of an ROI approach has dominated past DTI studies, with the choice of which WM regions to measure varying considerably across studies. Further, regions that are targeted across studies frequently have incongruent ROI identification procedures. For example, several studies have drawn ROIs in each of the four lobes (Duan et al., 2006; Huang, Friedland, & Auchus, 2007; Naggara et al., 2006), and although the placement of the ROIs is generally described, the specific fiber pathway(s) being sampled are not named. In addition, although an analysis using a priori ROIs can provide a good way to test specific hypotheses, it does not allow for a thorough evaluation of the regional pattern of WM changes. Consequently, it is more difficult to determine whether results are consistent with retrogenesis. As Pfefferbaum, Adalsteinsson, and Sullivan (2005) point out, "to make claims about the selective vulnerability of frontal brain regions to aging, frontal sites must be examined within the context of the rest of the brain" (p. 892). If studies are placing ROIs in arbitrarily selected regions within each lobe to represent anterior and posterior change, then conclusions drawn may be an artifact of ROI placement.

This potential for discrepant findings was illustrated in the current study, as the voxelwise analysis and ROI analyses produced different results. On voxelwise analysis, numerous voxels within the splenium and the superior longitudinal fasciculus

showed significantly lower FA across groups. However, when averaging across voxels within these regions to derive one average FA score for each individual and then comparing these regions across groups, the differences were no longer significant. Thus, in the current study, voxelwise analysis of the FA skeleton was more sensitive to group differences than the ROIs.

Like ROIs, studies reporting voxelwise results often fail to specify what specific fiber pathways were implicated. Instead of reporting results according to their MNI or Talairach coordinates for proximate gray matter structures or simply reporting general group differences within the frontal, parietal, temporal, or occipital lobe, an effort should be made to specify in what fiber pathway changes are occurring. Specific fiber pathways can be more readily identified as early or late-myelinating or as connecting certain cortical areas. In addition, when researching a population that has significant atrophy (as in AD), reporting MNI or Talairach coordinates can be misleading, because a given patient sample's average brain may not overlay sufficiently on these template atlases to produce reliable results. This was certainly the case in the present study, and additional steps were taken to determine those pathways wherein significant results were found. This latter procedure was accomplished by closely examining viewable atlases within the FSL program and verifying those results with external atlases (Mori et al., 2005; Schmahmann & Pandya, 2006).

Further investigation of specific fiber pathways is needed to test hypotheses about retrogenesis and/or Wallerian degeneration. Fiber tractography may provide a more sophisticated method of investigating specific fiber pathways. For example,

Taoka et al. (2006) performed tractography of three WM pathways within the temporal stem in 15 patients with AD and 15 control subjects. They found results congruent with the retrogenesis model; AD patients showed significantly lower FA (and higher ADC) bilaterally in the uncinate fasciculus and the inferior fronto-occipital fasciculus relative to controls. No differences in either FA or ADC were found in Meyer's loop, which is part of the optic tract. Thus, consistent with the results from the present study, they found group differences in late-myelinating association tracts whereas an early-myelinating tract involved in sensory processing was not affected. However, like traditional ROI analysis, tractography is limited in that it does not allow for evaluation of whole-brain regional patterns.

10.6 Aim 2: The Relationship Between Cognition and WM Integrity

Studies of normal aging have recently begun to focus on a disconnection model of neurocognitive aging. A "disconnection" syndrome can ensue if WM connectivity is interrupted. Thus in the disconnection model of neurocognitive aging, loss of WM integrity is thought to be the mechanism underlying changes in cognition with age (Bartzokis, 2004; O'Sullivan et al., 2001; Pfefferbaum et al., 2005; Raz, 2005). Similarly, decreased WM integrity in patients with AD may lead to a "disconnection" syndrome. Therefore, higher cognitive functions that are dependent upon the synchronization of distributed neural networks are expected to be the most vulnerable to the effects of AD (Bartzokis, 2004). However, studies examining the cognitive correlates of DTI measures in individuals with AD are limited; only correlations with the MMSE and verbal memory have been reported.

We found significant relationships between WM integrity and dementia severity, a priori composite scores, and individual test indices. These findings support the application of the disconnection model of AD as a means of conceptualizing the mechanism of the relationship between WM integrity and cognition, because, as discussed below, the relationship between WM integrity and cognition cannot be entirely explained by volumetric MR measures.

Like studies that have shown a significant relationship between white matter integrity and MMSE score (Bozzali et al., 2002; Duan et al., 2006; Kalus et al., 2006; Rose et al., 2006; Yoshiura et al., 2002), using a more sensitive measure of global cognition (the Mattis Dementia Rating Scale) we found that lower WM integrity was significantly associated with increased dementia severity in the current study. We also extended this finding to show that lower WM integrity was also significantly associated with decreased functional capacity (Functional Activities Questionnaire).

Using a priori composite scores, we found that executive functions, processing speed, and memory were significantly related to WM integrity. These findings support the disconnection model of AD that predicts that higher cognitive functions will be most sensitive to changes in WM integrity. Although these results represent a novel finding in a sample of AD and normal healthy participants, these findings are consistent with studies of normal aging, schizophrenia, chronic head injury, acute mild TBI, ischaemic leukoaraiosis, and CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) that have also found significant correlations between WM integrity and measures of executive functions

(Bazarian et al., 2007; Grieve, Williams, Paul, Clark, & Gordon, 2007; Nestor et al., 2004; O'Sullivan et al., 2005; O'Sullivan et al., 2001; O'Sullivan et al., 2004), memory (Nestor et al., 2004; O'Sullivan et al., 2001; Salmond et al., 2006), and processing speed (Bazarian et al., 2007; Madden et al., 2004). However, we did not find a significant relationship between WM integrity and attention/working memory, which is inconsistent with other studies (Charlton et al., 2006; Karlsgodt et al., 2008).

Congruent with the literature that shows inconsistent relationships between cognition and WMH volume in AD, WMH volume was not significantly related to cognition in the current study. WM volume also showed no significant correlations with cognition. The lack of significant correlations with cognition and these two traditional MR variables highlights that measuring the microstructural integrity of WM with DTI is more sensitive than these macrostructural WM measures. Correlations between gray matter and neuropsychological performance revealed the same pattern of results as did the correlations with WM microstructural integrity (for dementia severity and composite scores). This raised the question of whether DTI explains any additional variance above and beyond traditional MR measures. We showed that, even when accounting for gray matter, WM, and WMH volumes, changes in the microstructural integrity of WM continued to be significantly related to dementia severity, executive functions and processing speed. In addition, a significant relationship between WM integrity and attention/working memory emerged.

These results are consistent with experimental studies of cognition (Festa et al., 2005; Lakmache et al., 1998; Mohr et al., 1990) as well as electrophysiological studies

using EEG and MEG (Berendse et al., 2000; Leuchter et al., 1992) in AD that have also provided support for the disconnection model of AD (Bartzokis, 2004; Delbeuck, Van der Linden, & Collette, 2003). Unexpectedly, WM integrity did not predict a significant amount of variance in memory performance after controlling for volumetric MR measures (although it approached significance). This may suggest that memory is more related to generalized atrophy, whereas executive functions, processing speed, and attention/working memory are more related to WM microstructural integrity.

10.7 Relationship Between Cerebral Health and WM Integrity

In addition to addressing the principal aims proposed, the data analysis also provided further information on the relationship between measures related to cerebral health and measures of WM integrity. The retrogenesis model also provides a template for discussing these results, particularly across different neurodegenerative diseases and aging.

10.7.a Age and stroke risk. Studies of normal aging have consistently shown robust relationships between FA and age (Kochunov et al., 2007; Lehmbeck, Brassen, Weber-Fahr, & Braus, 2006; Pfefferbaum et al., 2005; Pfefferbaum & Sullivan, 2003); Salat et al., 2005). We found that age and stroke risk were both significantly related to average FA, FA_D, genu, splenium, and ILF. The SLF and both early-myelinating ROIs (cerebral peduncles and posterior limb of the internal capsule) were not significantly related to either age or stroke risk. These results are in agreement with another study by our group (Delano-Wood et al., submitted) completed on a 1.5 T scanner that found

a significant relationship between stroke risk and both genu and splenium FA in a sample of patients with MCI and normal healthy elderly. A number of studies have concluded that anterior areas, particularly the genu, show a stronger relationship with age than posterior areas (Sullivan et al., 2005; Pfefferbaum et al., 2005), although Salat et al. (2005) de-emphasize the predominance of anterior changes with aging and instead argue that specific regional fiber bundles may be vulnerable to age-related changes, regardless of their anterior or posterior location. Despite our focus on AD, our results are consistent with these studies of normal aging. It is interesting to note that the only significant relationships that emerged with the genu were with age and stroke risk, consistent with the fact that this structure does not contain fibers that provide a direct link to areas affected early by AD pathology but does contain prefrontal fibers that are vulnerable to the effects of age and vascular risk factors.

10.7.b Volumetric Indices of Cerebral Health. Studies of normal aging (Kochunov et al., 2007; Taylor et al., 2007), AD (Sydykova et al., 2007) and other neurodegenerative disorders (Cader et al., 2007; Ciccarelli et al., 2003) have found significant relationships between DTI parameters and volumetric indices of cerebral health. Consistent with these studies, we found that, independent of age, lower gray matter volume was significantly related to less WM microstructural integrity globally and within the inferior longitudinal fasciculus. Lower gray matter volume was not related to the superior longitudinal fasciculus, commissural or early-myelinating ROIs in the current study (although the splenium approached significance). In addition, higher WMH volume was significantly related to less WM microstructural integrity

globally and within our late-myelinating ROIs (inferior longitudinal fasciculus and superior longitudinal fasciculus), independent of age. Higher WMH was not related to commissural or early-myelinating ROIs, and WM volume was unrelated to microstructural WM integrity in the current study. Similar to our study, Kochunov et al. (2007) employed TBSS to investigate the relationship of WM integrity and cerebral health indices in normal aging and found that, independent of age, FA values were significantly related to average gray matter thickness ($r = .46$) and WMH volume ($r = -.41$). Also congruent with our findings, they reported that late-myelinating fiber pathways had higher associations with cerebral health indices than early-myelinating fiber pathways.

The similarity of relationships between WM microstructural integrity and cerebral health indices across different study populations suggests that there may be similar mechanisms underlying these WM changes in normal aging, AD, and other neurodegenerative diseases (consistent with the assertion of Bartzokis, 2004). Retrogenesis is likely one such mechanism and can be used to explain similar patterns of results from studies of various patient populations. Discrepant result patterns can likely be attributed to disease-specific pathology (e.g., neurofibrillary tangles in AD, white matter lesions in MS). Integrating both overlapping and unique mechanisms of change into hypothesis generation and the explanation of results across different study populations will help further our understanding of the process of neurodegeneration across disorders and help to elucidate what processes are specific to certain disorders.

10.8 Limitations and Future Directions.

As is the case with most imaging studies, this study is limited by a small sample size. However, even with limited power, we were able to detect group differences that were congruent with our a priori hypotheses and with the extant literature, which speaks to the validity of our post-processing approach. This is the first study to use TBSS to investigate changes in WM integrity in AD patients compared to normal healthy elderly, thus these results should be regarded as preliminary. Although TBSS circumvents some of the limitations of VBM that can lead to partial voluming (e.g., improved registration, does not require spatial smoothing, as discussed in section 5.7), these problems remain for smaller tracts. Specifically, if the tract width is smaller than the original voxel size, the voxel may include gray matter (Smith et al., 2006). We aimed to minimize this potential problem by applying an initial FA threshold that removes all voxels with an FA value less than .2, but care should be taken when interpreting group differences in small WM tracts (e.g., the fornix).

Another possible limitation of the TBSS approach is that because FA images are used to define the FA skeleton and to determine the "center" of the WM tract by searching for the highest FA value along a predefined path, analyses are carried out on WM voxels with only the highest FA values. As discussed in section 10.4.c, this may lower sensitivity to group differences. However, this also greatly enhances the registration procedure and thereby reduces the likelihood for partial voluming, thus the possible decrease in sensitivity is worth the improved confidence in the robustness of

our data. Future studies should incorporate other diffusion parameters (e.g., DA, DR; see section 5.5) that were not used in the initial creation of the skeleton and that may garner additional information that would better inform pathological inference (see section 5.6). To be able to make more direct conclusions about how underlying pathology may explain the current results, future studies may incorporate the use of axial diffusivity (DA) and radial diffusivity (DR). DR is thought to reflect loss of myelin, whereas DA is more likely to implicate axonal damage (Song et al., 2003; Song et al., 2002; Sun et al., 2005).

As mentioned in section 10.5.c, future studies may benefit from using fiber tractography to answer questions regarding specific fiber pathways and to allow investigation of connectivity between gray matter structures. The current study has an inherent degree of uncertainty in identifying and labeling specific fiber pathways (as discussed in 10.5.c). This is because the TBSS approach utilizes information from the entire group to determine what WM fiber pathways are common to the group and then information about the integrity of the WM pathways are represented by 2-D summary indices (e.g., FA). Such an approach is necessary for voxelwise analysis. While fiber tractography does not lend itself to voxelwise analysis, it may provide richer data. For example, tractography can be used to determine the number of fibers within a WM pathway, the length of those fibers, and seeding can be used to determine the connections between gray matter structures. This approach may offer another way to test underlying mechanisms of WM degeneration in AD. For example, Wallerian degeneration could be investigated by seeding WM fiber pathways from the medial

temporal lobe region to examine correlations between the extent of MTL atrophy (which would likely be determined from T1 images) and indices derived from fiber tractography. Fiber tractography suffers some of the same limitations as the traditional ROI approach in that it is highly time-consuming and only a limited number of pathways can be investigated.

One advantage of the ROI approach employed in the current study is that drawing the ROI on the FA skeleton mask eliminates the possibility for systematic bias and greatly reduces the time required because the ROIs are drawn only once (thus the same voxels are represented for each subject and the drawing is independent of group status) and then the average FA is extracted for each individual through use of an automated calculation program. Other inherent weaknesses of the ROI approach remain (discussed in section 5.7), namely, only a small number of ROIs are chosen and the operational definition of the ROIs may vary across studies. This is currently the only study to use this approach in AD and basing our ROIs on available atlas tools (see 8.4.e) will hopefully increase the reproducibility of these results (see Karisgodt et al., 2007 for an example of this approach in patients with Schizophrenia).

Another limitation of the current study is that differences in WM integrity across groups could be related to factors other than AD pathology, such as the possible contributions of cerebrovascular disease. Our groups did not differ significantly on stroke risk or on total WMH volume, but this does not guarantee that vascular processes did not underlie some of the results. The relationship between WM microstructural integrity and vascular risk factors warrants further study and may

prove to be a moderating factor in the development of AD. Future longitudinal studies of at-risk groups that implement multiple imaging modalities will best address this issue.

10.9 Summary.

In summary, this prospective DTI study using 3.0 Tesla MR is the first to employ TBSS to investigate changes in WM microstructural integrity in patients with AD relative to normal healthy elderly and the first to examine the relationship of WM integrity to multiple higher-order cognitive domains. Our results demonstrated that patients with AD show changes in vulnerable WM fiber pathways that likely reflect both retrogenesis and Wallerian degeneration. Further, these group differences remained even when controlling for grey matter, WM, and white matter hyperintensity volumes, suggesting that DTI captures unique variance that traditional MR measures may miss. WM integrity was associated with changes in higher-order cognition, supporting the view that some of the cognitive changes seen in AD may be secondary to a disconnection syndrome. Again, the majority of these associations remained significant even when the variance from traditional MR volumetric measures was removed. Knowledge of the pattern of WM microstructural changes in AD and its underlying mechanisms may contribute to earlier detection and intervention in groups at risk for AD (e.g., MCI, APOE ε4).

Appendix A

Mean (*SD*) of cognitive variables for normal control participants and Alzheimer's patients.

	NC (n=14)	**AD (n=16)**	*p*	η_p^2
Executive Functions				
Executive Functions composite score	12.07 (2.92)	6.82 (1.62)	<.001	.55
CW Inhibition SS	11.71 (2.89)	7.38 (3.83)	.004	.28
CW Inhibition/Switching SS	10.50 (4.83)	4.53 (4.03)	.002	.31
CW Inhib/Swich vs Combined Naming+Reading	8.36 (2.98)	5.40 (3.48)	.04	.16
CW Inhib/Swich vs Inhibition Contrast SS	8.64 (3.30)	6.40 (4.34)	.20	.06
TMT Number-Letter Switching SS	12.14 (3.26)	5.88 (3.32)	<.001	.46
Trails N-L Switching vs Number + Letter Composite	7.79 (2.33)	7.69 (4.42)	.92	.00
Trails N-L Switching vs Motor Contrast	9.64 (2.31)	6.00 (3.18)	.001	.38
Trails B SS	12.79 (2.89)	7.47 (2.50)	<.001	.52
FAS SS	12.86 (3.82)	9.44 (2.76)	.01	.23
DRS Initiation/Perseveraton SS (r_s)	11.86 (.95)	7.69 (3.05)	<.001	.46
DRS Conceptualization SS (r_s)	12.57 (1.09)	10.00 (2.56)	<.001	.40
Dual Task Decrement (r_s)	2.42 (4.39)	0.82 (1.39)	.20	.06
Attention/Working Memory				
Attention/Working Memory Composite Score	12.14 (2.46)	8.22 (1.91)	<.001	.46
Digit Span SS	12.86 (3.21)	8.81 (2.34)	<.001	.36
Letter-Number Sequencing SS	11.43 (2.53)	7.63 (2.19)	<.001	.41

	NC (n=14)	**AD (n=16)**	*p*	η_p^2
Simple Task Digit Span % correct	.74 (.17)	.73 (.19)	.93	.00
DRS Attention SS	12.43 (1.83)	10.56 (2.10)	.02	.19
Motor/Processing Speed				
Processing Speed Composite Score	12.93 (2.17)	8.38 (2.08)	<.001	.54
Digit Symbol SS	13.07 (3.63)	8.06 (2.44)	<.001	.40
Trails A SS	12.08 (2.43)	8.25 (3.19)	.001	.32
CW Naming + Reading Composite	12.14 (2.35)	9.00 (3.56)	.008	.23
TMT Number + Letter Sequencing Composite	14.36 (2.59)	8.19 (3.35)	<.001	.51
TMT Motor SS (r_s)	12.50 (1.65)	9.88 (3.26)	.02	.20
Simple Task Motor Raw	145.2 (37.2)	126.6 (42.9)	.27	.04
Memory				
Memory Composite Score	13.15 (2.37)	4.94 (1.98)	<.001	.84
LM Immediate Recall SS	13.79 (3.33)	5.44 (2.48)	<.001	.73
LM Delayed Recall SS	14.62 (2.57)	5.81 (2.48)	<.001	.76
CVLT 1-5 raw	50.5 (13.4)	21.6 (7.8)	<.001	.68
CVLT long-delay free-recall raw	10.4 (4.2)	1.7 (2.0)	<.001	.74
DRS Memory SS (r_s)	11.57 (1.70)	3.56 (2.42)	<.001	.83
Language				
BNT raw score (r_s)	28.14 (2.38)	20.75 (7.23)	.001	.32
Category fluency total raw	44.9 (14.5)	28.7 (9.7)	.001	.32

	NC (n=14)	**AD (n=16)**	*p*	η_p^2
Visuospatial				
Benton Facial Recognition	44.79 (5.29)	41.56 (4.99)	.10	.10
DRS Construction SS (r_s)	9.21 (2.01)	8.13 (1.89)	.14	.08
Dementia Severity				
DRS Total SS	13.71 (1.94)	5.81 (1.97)	<.001	.81
FAQ	.64 (1.39)	16.13 (6.38)	<.001	.74

Note. FA_D = FA skeleton voxels that were significantly different across groups in voxelwise analysis, SLF = superior longitudinal fasciculus, ILF = inferior longitudinal fasciculus, ICp = posterior limb of the internal capsule, CP = cerebral peduncles, FSRP = Framingham Stroke Risk Profile, WMH = white matter hyperintensity volume, GM = gray matter volume, WM = white matter volume, SS = age-corrected scaled score, CW = Color-Word Interference Test (DKEFS), TMT = Trail Making Test (DKEFS), FAS = letter fluency, DRS = Mattis Dementia Rating Scale, LM = Logical Memory (WMS-R), CVLT = California Verbal Learning Test, BNT = Boston Naming Test (30-item), FAQ = Functional Activities Questionnaire.

Appendix B

Hierarchical linear regression models.

	FA_D		WMH		GM		WM		R^2	ΔR^2
	β	*p*	β	*p*	β	*p*	β	*p*		
DRS SS	.69*	.01	.57*	.007	.15	.40	.25	.27	.51*	.15*
Executive Functions	.64*	.03	.59*	.01	.29	.25	-.08	.68	.42*	.13*
Processing Speed	.66*	.02	.62*	.006	.21	.38	.11	.56	.45*	.14*
Attention/Working Memory	.73*	.03	.55*	.03	-.05	.85	-.32	.15	.27	.17*
Memory	.51	.09	.41	.07	.34	.19	.11	.59	.39*	.08

Note. GM, WM, and WMH volumes were entered into the first model. The change in R^2 the additional variance accounted for after the addition of FA_D to the model, R^2 reflects the variance accounted for by the full model. FA_D = FA skeleton voxels that were significantly different across groups in voxelwise analysis, WMH = white matter hyperintensity volume, GM = gray matter volume, WM = white matter volume, DRS SS = Mattis Dementia Rating Scale age-corrected scaled score.

* $p < .05$

Appendix C

Pearson (and Spearman) correlation coefficients: relationship of cognition and white matter microstructural integrity.

	Avg FA	FA_D	Genu	Splenium (r_s)	SLF	ILF	ICp	CP
Cerebral Health								
Age	-.51 (.004)	-.50 (.005)	-.54 (.002)	-.38 (.04)	-.14 (.47)	-.46 (.01)	-.14 (.47)	.01 (.95)
FSRP total score	-.51 (.004)	-.45 (.01)	-.46 (.01)	-.41 (.02)	-.26 (.18)	-.36 (.05)	-.18 (.33)	-.07 (.72)
GM volume (r_s)	.58 (.001)	.72 (.000)	.25 (.18)	.46 (.01)	.15 (.42)	.69 (.000)	.16 (.41)	-.08 (.68)
WM volume	-.02 (.93)	.04 (.84)	.17 (.38)	.09 (.63)	-.02 (.93)	-.13 (.49)	-.03 (.86)	.09 (.63)
Whole brain volume	.51 (.004)	.64 (.001)	.52 (.003)	.53 (.003)	.21 (.27)	.51 (.004)	.14 (.47)	.03 (.89)
WMH volume (r_s)	-.53 (.003)	-.60 (.001)	-.27 (.17)	-.29 (.13)	-.34 (.07)	-.64 (.001)	-.34 (.07)	-.09 (.65)
Executive Functions								
Executive Functions composite score	.22 (.25)	.49 (.006)	-.01 (.99)	.31 (.09)	.06 (.76)	.32 (.09)	.05 (.78)	-.07 (.72)
CW Inhibition SS	-.03 (.88)	.25 (.18)	-.05 (.79)	-.03 (.90)	-.07 (.72)	.13 (.50)	-.19 (.31)	-.34 (.06)
CW Inhib/Switch SS	.25 (.19)	.47 (.01)	.02 (.92)	.19 (.34)	.14 (.47)	.45 (.01)	.11 (.58)	-.14 (.46)
CW Inhib/Swich vs Combined naming+reading	.40 (.03)	.49 (.006)	.15 (.43)	.26 (.17)	.22 (.26)	.61 (.000)	.32 (.08)	.09 (.64)
CW Inhib/Swich vs Inhib contrast SS	.44 (.02)	.48 (.009)	.17 .37	.30 (.11)	.22 (.25)	.55 (.002)	.31 (.10)	.16 (.41)
TMT No.-Letter switching SS	.11 (.56)	.41 (.02)	-.01 (.94)	.36 (.05)	-.10 (.60)	.21 (.27)	-.07 (.73)	-.10 (.59)
TMT N-L switch vs N+L composite	-.31 (.10)	-.09 (.64)	-.22 (.23)	.15 (.42)	-.47 (.01)	-.11 (.55)	-.34 (.07)	-.32 (.08)
TMT N-L switch vs motor	-.07 (.72)	.22 (.25)	-.10 (.61)	.12 (.52)	-.18 (.35)	.15 (.44)	-.02 (.92)	-.14 (.45)
Trails B SS	.20 (.29)	.40 (.03)	-.12 (.54)	.26 (.17)	.15 (.43)	.17 (.39)	.15 (.44)	.21 (.27)
FAS SS	.14 (.45)	.28 (.14)	.06 (.75)	.07 (.70)	.07 (.71)	.14 (.47)	.04 (.84)	-.09 (.64)
DRS Initiation/ Perseveraton SS (r_s)	.12 (.52)	.36 (.05)	.16 (.41)	.30 (.11)	-.04 (.86)	.18 (.34)	.03 (.87)	-.18 (.34)
DRS Conceptual-ization SS (r_s)	.14 (.48)	.32 (.08)	-.12 (.53)	-.10 (.59)	.14 (.48)	.23 (.22)	.15 (.42)	.00 (.99)
Dual Task Decrement (r_s)	.28 (.14)	.26 (.17)	.04 (.82)	.26 (.17)	.11 (.56)	.15 (.44)	.08 (.69)	.18 (.36)

	Avg FA	FA_D	Genu	Splenium (r_s)	SLF	ILF	ICp	CP
Attention/Working Memory								
Attn/WM Composite Score	-.04 (.85)	.25 (.18)	-.05 (.81)	.03 (.87)	-.07 (.72)	.21 (.28)	.06 (.77)	-.16 (.39)
Digit Span SS	-.05 (.78)	.20 (.28)	-.10 (.59)	-.08 (.66)	-.04 (.84)	.19 (.32)	.03 (.86)	-.10 (.61)
Letter-Number Sequencing SS	-.01 (.96)	.26 (.17)	.03 (.90)	.17 (.38)	-.09 (.63)	.19 (.33)	.07 (.71)	-.21 (.27)
Simple Task Digit Span % correct	.10 (.61)	.05 (.80)	-.16 (.41)	-.16 (.39)	.18 (.34)	-.09 (.65)	.21 (.26)	.24 (.19)
DRS Attention SS	.29 (.12)	.34 (.06)	.17 (.38)	.24 (.20)	.11 (.56)	.34 (.07)	.14 (.47)	.20 (.28)
Motor/Processing Speed								
Processing Speed Composite Score	.22 (.24)	.44 (.02)	.01 (.94)	.19 (.31)	.13 (.51)	.20 (.30)	.06 (.76)	.01 (.95)
Digit Symbol SS	.15 (.44)	.33 (.08)	-.10 (.61)	.17 (.37)	.06 (.76)	.16 (.41)	.15 (.43)	.07 (.71)
Trails A SS	.17 (.38)	.28 (.14)	.00 (.99)	.22 (.25)	.13 (.52)	.05 (.80)	-.01 (.98)	.15 (.44)
CW Naming + Reading Composite	.005 (.98)	.28 (.14)	-.05 (.81)	.05 (.80)	-.08 (.70)	.07 (.71)	-.24 (.21)	-.35 (.06)
TMT N+L seq composite	.37 (.05)	.51 (.004)	.17 (.37)	.32 (.09)	.29 (.13)	.31 (.10)	.21 (.27)	.16 (.41)
TMT motor SS (r_s)	.30 (.10)	.37 (.04)	-.05 (.80)	.34 (.07)	.11 (.57)	.22 (.25)	.08 (.68)	.08 (.69)
Simple Task motor raw	.35 (.06)	.42 (.02)	.15 (.42)	.26 (.17)	.10 (.62)	.21 (.26)	-.05 (.81)	-.05 (.80)
Memory								
Memory Composite Score	.23 (.23)	.49 (.006)	.17 (.54)	.27 (.15)	.08 (.67)	.32 (.09)	.04 (.84)	.03 (.87)
LM Immed SS	.10 (.59)	.38 (.04)	.00 (.98)	.17 (.38)	.04 (.82)	.23 (.23)	-.04 (.84)	-.05 (.81)
LM Delay SS	.21 (.29)	.44 (.02)	.06 (.75)	.31 (.11)	.09 (.64)	.30 (.12)	.04 (.82)	.06 (.76)
CVLT 1-5 raw	.38 (.04)	.61 (.000)	.05 (.81)	.28 (.15)	.20 (.29)	.45 (.01)	.14 (.47)	.12 (.55)
CVLT long-delay free-recall raw	.38 (.04)	.59 (.001)	.15 (.45)	.32 (.09)	.25 (.19)	.38 (.04)	.15 (.45)	.11 (.57)
DRS Memory SS (r_s)	.38 (.04)	.58 (.001)	.23 (.22)	.34 (.06)	.08 (.69)	.38 (.04)	.02 (.92)	.04 (.84)
Language								
BNT raw score (r_s)	.31 (.10)	.52 (.003)	-.04 (.84)	.14 (.47)	.19 (.31)	.27 (.15)	-.02 (.93)	.14 (.46)
Category fluency total raw	.06 (.75)	.35 (.06)	.02 (.94)	.24 (.20)	.05 (.78)	.15 (.42)	-.08 (.69)	-.28 (.14)

	Avg FA	FA_D	Genu	Splenium (r_s)	SLF	ILF	ICp	CP
Visuospatial								
Facial Recognition	.39 (.03)	.44 (.02)	.30 (.10)	.32 (.09)	.23 (.21)	.26 (.16)	.10 (.61)	-.02 (.93)
DRS Construction SS (r_s)	.21 (.27)	.38 (.04)	.20 (.29)	.21 (.26)	-.14 (.48)	.21 (.26)	.01 (.95)	.01 (.98)
Dementia Severity								
DRS total age SS	.25 (.18)	.53 (.002)	.15 (.43)	.22 (.25)	.07 (.72)	.34 (.06)	.09 (.65)	-.02 (.92)
FAQ	-.29 (.13)	-.55 (.002)	-.09 (.64)	-.38 (.04)	.02 (.93)	-.33 (.07)	.02 (.90)	.06 (.76)

Note. FA_D = FA skeleton voxels that were significantly different across groups in voxelwise analysis, SLF = superior longitudinal fasciculus, ILF = inferior longitudinal fasciculus, ICp = posterior limb of the internal capsule, CP = cerebral peduncles, FSRP = Framingham Stroke Risk Profile, WMH = white matter hyperintensity volume, GM = gray matter volume, WM = white matter volume, SS = age-corrected scaled score, CW = Color-Word Interference Test (DKEFS), TMT = Trail Making Test (DKEFS), FAS = letter fluency, DRS = Mattis Dementia Rating Scale, LM = Logical Memory (WMS-R), CVLT = California Verbal Learning Test, BNT = Boston Naming Test (30-item), FAQ = Functional Activities Questionnaire, r_s denotes Spearman correlation coefficient.

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