# Age-Related Changes in Prefrontal White Matter Measured by Diffusion Tensor Imaging

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**ABSTRACT: Age-related degeneration of brain white matter (WM) has received a great deal of attention, with recent studies demonstrating that such changes are correlated with cognitive decline and increased risk for the development of age-related neurodegenerative disease. Past studies have used magnetic resonance imaging (MRI) to measure the volume of normal and abnormal tissue signal as an index of tissue pathology. More recently, diffusion tensor MRI (DTI) has been employed to obtain regional measures of tissue microstructure, such as fractional anisotropy (FA), providing better spatial resolution and potentially more sensitive metrics of tissue damage than traditional volumetric measures. We used DTI to examine the regional basis of age-related alterations in prefrontal WM. As expected from prior volumetric and DTI studies, prefrontal FA was reduced in older adults (OA) compared to young adults (YA). Although WM volume has been reported to be relatively preserved until late aging, FA was significantly reduced by middle age. Much of prefrontal WM showed reduced FA with increasing age. Ventromedial and deep prefrontal regions showed a somewhat greater reduction compared to other prefrontal areas. Prefrontal WM anisotropy correlated with prefrontal WM volume, but the correlation was significant only when the analysis was limited to participants over age 40. This evidence of widespread and regionally accelerated alterations in prefrontal WM with aging illustrates FA's potential as a microstructural index of volumetric measures.**

**KEYWORDS: aging; Alzheimer's disease; white matter; prefrontal; MRI; DTI**

## BRAIN AGING

Great effort has been put toward characterizing alterations that occur in the brain with healthy or "successful" aging. This issue is particularly important because the risk for a number of neurological diseases increases with increasing age, and

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knowledge of expected, nondisease-related changes would help to distinguish healthy individuals from those with impending disease. Thus, contemporary studies of brain aging extend across research domains and methods, from histological research in rats to *in vivo* neuroimaging of humans and nonhuman primates. Through these studies, it has become clear that the prefrontal region of the brain shows significant age-related alteration in various indices of tissue integrity, ranging from reduced brain volume[1] to layer-specific reduction in the size of dendritic fields.[2]

## NEUROIMAGING STUDIES OF GRAY AND WHITE MATTER

Neuroimaging technologies have greatly enhanced the ability to perform studies on large numbers of well-characterized individuals *in vivo*, and magnetic resonance imaging (MRI) has been particularly important due to this technology's ability to perform high-resolution scanning noninvasively. Early MRI studies noted the obvious appearance of alterations in white matter (WM) tissue signal with aging (i.e., WM hyper/hypointensities),[3,4] a finding known from prior computed tomography studies. Importantly, changes were observed in cognitively healthy individuals. These changes were not apparent in individuals under the age of 45 or even in every older individual examined.[4] Thus, such changes are not an early or inevitable consequence of brain aging.

In addition to abnormal WM signal, gray matter (GM) and WM atrophy are apparent in MR scans of older adults (OA). Prior studies have reported disparate results, with some investigators emphasizing loss of GM[5–8] and others emphasizing alterations of WM[9,10] as the prominent feature of brain aging. For example, a recent study by Raz and colleagues measured regional GM and WM volumes throughout the brain in 148 adults aged 18 to 77 years.[1] Their results demonstrated that the most dramatic age-related loss was in prefrontal cortical volume, where the loss surpassed that in prefrontal WM volume and in all other WM and GM volumes. In contrast, Guttmann and colleagues examined 72 adults aged 18–81 and found that WM volume was significantly reduced in OA with minimal loss of GM.[11] This finding held when controlling for the presence WM abnormalities (hyperintensities), demonstrating that WM volume loss is independent of WM abnormalities. Procedural differences, including participant sample, scan type and resolution, volumetric method employed, and the type of statistical analysis, all contribute to discrepancies among prior reports. A growing consensus now exists that both GM and WM volumes decline with aging. Such loss may be regionally and temporally selective, with prefrontal GM volume declining early in the age span,[1] and WM volume loss most prominent sometime after age 40.[12] WM likely shows an age-related increase in volume prior to this middle-age (MA) period, that is, in adolescents and young adults (YA).[12–14]

## PREFRONTAL TISSUE INTEGRITY MEASURED WITH VOLUMETRIC MRI

A number of studies have indirectly examined prefrontal integrity through measures of age-related changes in the volume of the corpus callosum (e.g., refs. 15–19). This structure is particularly informative in this regard because of its topographical

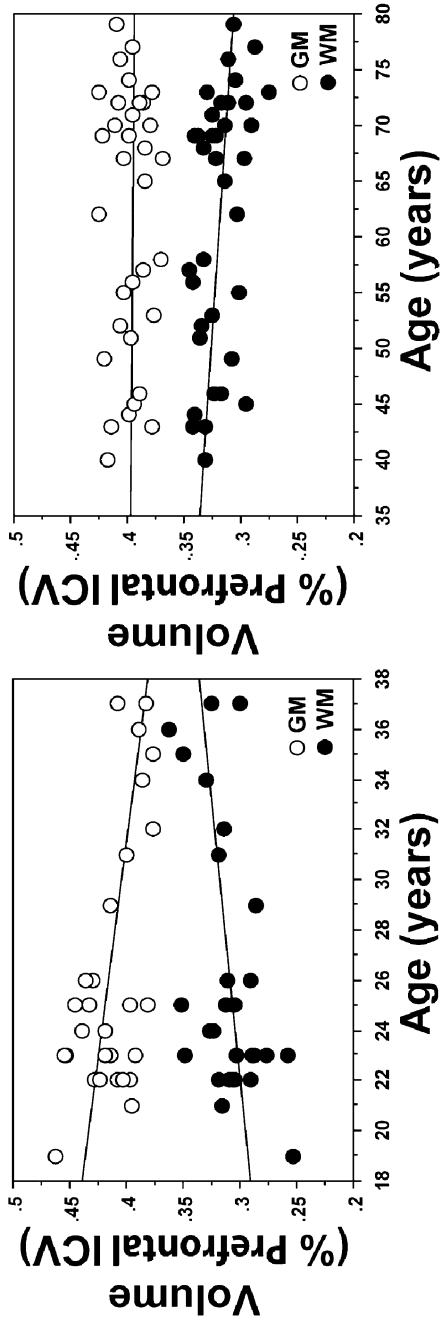


**FIGURE 1.** Prefrontal GM and WM volume across the adult age span. Adults younger than 40 years of age showed a reduction in prefrontal GM volume with an increase in prefrontal WM volume (*left panel*). In contrast, adults older than 40 showed a reduction in prefrontal WM volume with only modest reductions in prefrontal GM volume (*right panel*).

organization, with frontal commissural fibers projecting through the anterior portion, the genu, and occipital fibers projecting through the posterior portion, the splenium.[20] Thus, regional division of the corpus callosum provides an index of tissue integrity on a functional and/or lobar level. Examination of age-related changes in the corpus callosum shows that the genu and anterior portions decrease in volume with increasing age, whereas the splenium and posterior sections of the callosum are relatively preserved.[15–19] These findings support the view that anterior tissue changes are more prominent than posterior changes with aging.

Age-related reduction in prefrontal GM and WM volume has also been directly measured with MRI (e.g., refs. 1 and 21). As reviewed above, discrepancies as to which tissue is most affected could be explained by the population sample: cortical loss appears to be more prominent in the adolescent to middle age range, with WM loss occurring later. This pattern of early reduction in cortical volume and later loss of WM volume is apparent in prefrontal tissue. Investigators have demonstrated that orbitofrontal cortical volume[1] and superior frontal GM density[13] show a strong reduction in early adulthood, with minimal decline in middle to late aging. Similarly, we find a decrease in total prefrontal GM and an increase in prefrontal WM in participants less than 40 years of age, and a decline in WM volume with only modest reductions in cortical volume in participants older than 40 years of age (FIG. 1). Other studies show a trend for volume loss in more posterior frontal GM with later aging (e.g., ref. 12), and we see similar reductions in posterior frontal cortical thickness that continue later in the age span.[22] The finding of increased WM volume in early adulthood is supported by recent studies demonstrating a curvilinear pattern of WM volume across the adult age span (e.g., ref. 12); the finding of early cortical volume reduction is supported by recent studies in adolescents[14,23] and young adults.[22]

Our prior work specifically examined how prefrontal tissue volume is altered with very late aging.[21] A younger group comprised adults 60–75 years of age, while an older group consisted of individuals 85 years and older. In addition, the study included a group of patients with Alzheimer's disease (AD) who were age and demographically matched to the "younger" group. This investigation addressed two important questions: (i) is late aging accompanied by a preferential decline in GM or WM volume?; (ii) does the pathology of AD look like "accelerated aging" (i.e., do AD patients show the same pattern of volume loss in prefrontal tissue as the >85-year-old adults)? Contrary to expectations at the time, we found minimal prefrontal cortical volume loss with late aging, whereas a profound decline in WM volume emerged.[21] Additionally, although AD patients showed a reduction in cortical volume, the loss of prefrontal WM was highly variable, suggesting that certain patients have a propensity towards WM loss, while other patients are relatively spared from these changes. Thus, prefrontal WM changes are more prominent than GM loss with late aging, and prefrontal WM loss could be an important contributor to clinical heterogeneity in AD patients.

Importantly, volumetric reductions in WM occurred in the absence of significant abnormal prefrontal WM signal in these participants (abnormalities occupied less than 1% of the total prefrontal WM volume). Thus, similar to the results of Guttmann and colleagues, this finding clarifies that volumetric loss in brain WM is not simply due to a change in the amount of tissue being classified as "abnormal". Instead, volumetric loss likely represents a process that is related to microstructural alterations in tissue, ultimately resulting in gross volume reduction. A method for measuring

such microstructural changes *in vivo* would facilitate sorting out the various components contributing to the diminution in WM integrity.

## DTI AS A TOOL TO MEASURE TISSUE PATHOLOGY

DTI is one technique that could, in the least, quantify alterations in tissue structure regardless of pathophysiological mechanism and, much more ambitiously, differentiate among pathologies and specify affected fiber pathways. Diffusion imaging in humans using MRI has existed for over 15 years (e.g., ref. 24), but recently has gained significant popularity due to new acquisition and analysis techniques. Specifically, a strong interest has been developed in the use of diffusion data to describe normal and abnormal brain anatomy through anisotropy, tensormap, and tractography techniques that provide information about the anatomical orientation and microstructure of major brain fasciculi. Although these new technologies have been applied in a number of recent clinical investigations, the precise biophysical basis of anisotropy measured by DTI techniques is still being explored (e.g., ref. 25) and the histological bases of alterations in this signal due to age or disease are yet to be defined.

## REGIONAL CHANGES IN PREFRONTAL WHITE MATTER MEASURED WITH DTI

DTI has allowed an indirect assessment of prefrontal tissue through measurement of "fractional anisotropy" (FA)[26] in callosal tissue (e.g., ref. 27). The FA metric is a summary measure of the restrictional microenvironment of brain water diffusion, and this measure changes regionally in the brain with age and disease. Similar to volumetric results, the anterior regions of the callosum are most susceptible to alterations in tissue microstructure (e.g., refs. 27–30). These findings support the view that anterior tissue is preferentially affected by age-related alterations. Further, they give credence to the theory that DTI measures represent a microstructural index of tissue volume. Still, it is unclear from studies of the callosum alone whether FA changes are due to altered prefrontal WM or a result of alterations in cortex. Recent DTI experiments in our lab and others have more directly uncovered preferential alterations in frontal WM relative to other areas of the brain[29–33] (FIG. 2).

DTI may also be useful for characterizing the regional nature of changes within prefrontal WM because FA is calculated on a voxel by voxel basis throughout the volume. Our prior work examined age-related changes in FA across all brain WM and in a number of regions of interest (ROIs) across the adult age span (adults aged 21–76).[30] Alterations within prefrontal WM were heterogeneous, with ventromedial and "deep" prefrontal WM particularly affected, and WM in the inferior frontal gyrus not statistically affected. More recently, we have used tensormapping techniques to define regional boundaries for ROI measurements. We placed ROIs in the WM of each of the major frontal gyri and, using the tensor information, attempted to sample from within a homogeneous region of WM and from homologous regions across participants. This procedure showed a statistical reduction in FA in all regional measures, except for a trend in middle frontal WM (FIG. 3). In certain regions, such as ventromedial prefrontal WM, an accelerated decline in FA with age was apparent

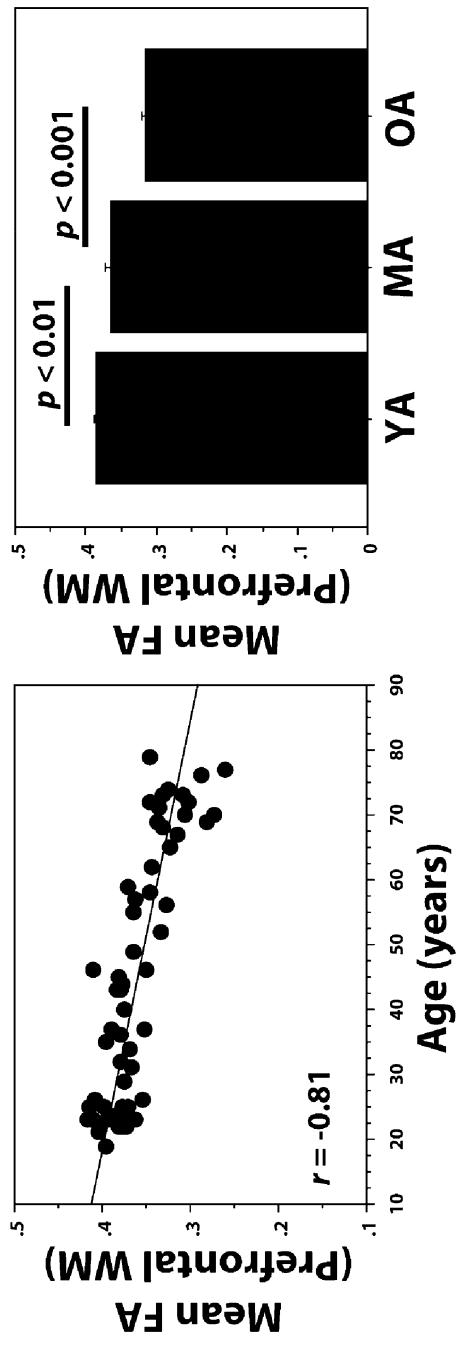


**FIGURE 2.** Age-related reduction in prefrontal WM FA. We found a strong reduction in the FA of prefrontal WM with increasing age (*left panel*), with significant reductions in MA (40- to 59-year-old adults) compared to YA (18- to 39-year-old adults), and in OA (60- to 80-year-old adults) compared to MA (*right panel*).

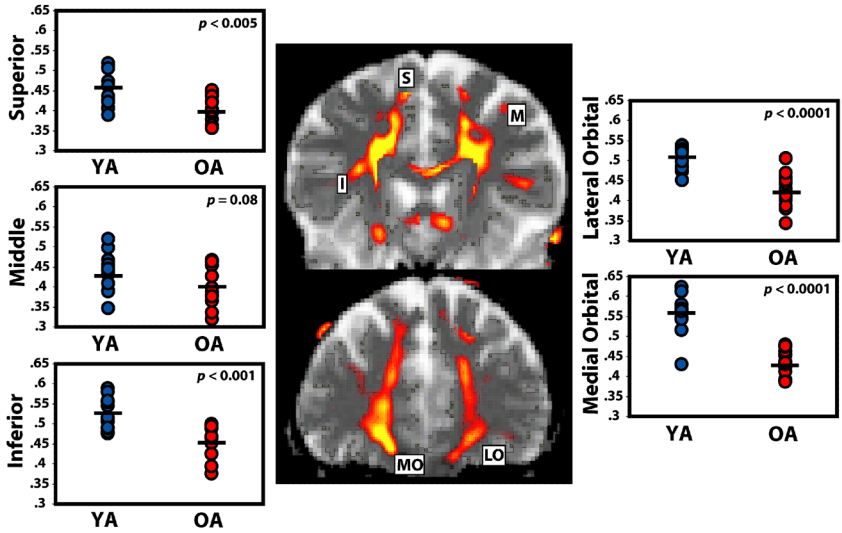


**FIGURE 3.** Regional measures of prefrontal FA. ROIs were placed in superior (S), middle (M), inferior (I) (*left panel*), lateral orbital (LO), and medial orbital (MO) (*right panel*) WM in YA (18- to 39-year-old adults) and OA (60- to 80-year-old adults). FA was statistically reduced in OA in all regions, except for a trend in the middle frontal ROI. ROI measures and voxel-based statistical maps (*center panel*) suggested that ventromedial prefrontal WM showed accelerated reduction in FA with aging.

(FIG. 4). We find similar results with whole-brain voxel-based comparisons of FA in YA and OA. Thus, although alterations in prefrontal WM are widespread, certain regions, such as ventromedial WM, appear to show an accelerated decline in FA.

To further test whether prefrontal fibers generally show greater alteration than more posterior fiber systems, we also placed ROIs within the anterior and posterior limb of the internal capsule, expecting alteration of the frontally projecting fibers of the anterior limb and preservation of the posterior limb, which is associated with primary motor function. In fact, we found the opposite result. The posterior limb showed a significant age-related reduction in FA, while the anterior limb was relatively preserved (FIG. 5). This finding was particularly interesting given recent data demonstrating a reduction in thickness of the precentral gyrus,[22] where fibers of the posterior limb are believed to originate. Additionally, although prefrontal WM shows an appreciable decline in FA, these results suggest that the loss is selective and does not generalize to all or entire fiber systems projecting to and from prefrontal cortex.

## IS FA A MICROSTRUCTURAL INDEX OF WM VOLUME?

An important question in the application of these innovative technologies is how they relate to traditionally employed imaging measures. For example, although FA is believed to be an index of tissue microstructure, it is currently unknown how FA

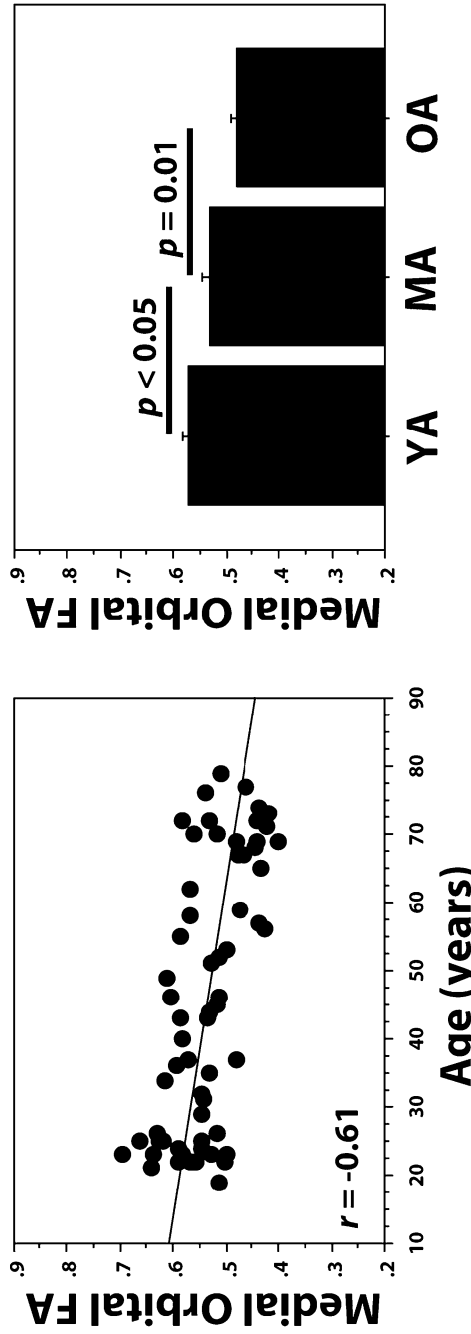


**FIGURE 4.** Age-related reductions in medial orbital (ventromedial) prefrontal FA. We found a strong statistical reduction in FA in the ventromedial prefrontal ROI. This effect was apparent when examining participants across the age span (*left panel*), and was significant by middle age when examining participants grouped into YA (18- to 39-year-old adults), MA (40- to 59-year-old adults), and OA (60- to 80-year-old adults) (*right panel*).

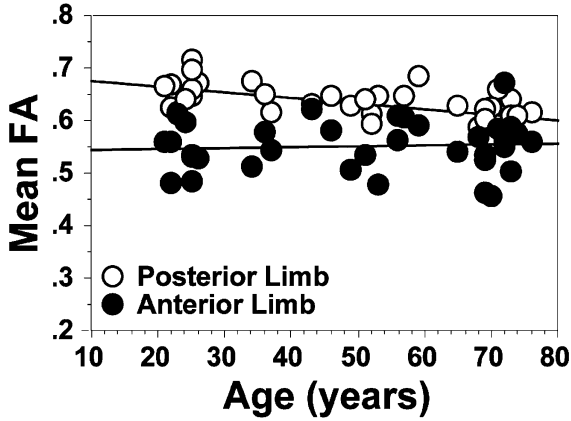


**FIGURE 5.** Regional measurements of FA in the anterior and posterior limbs of the internal capsule. We obtained regional measurements by sampling a line of voxels through the center of each limb in a single axial slice. The results showed a significant age-related reduction in FA in the posterior limb, with relative preservation of the anterior limb.

relates to WM volume, a classic imaging metric of tissue integrity. We addressed this issue by examining the relation between prefrontal WM FA and prefrontal WM volume. Mean prefrontal WM FA was correlated with total prefrontal volume, but only when the analyses were limited to adults over age 40 (FIG. 6). This result could be expected given the findings that FA is reduced during the YA to MA period, a time when WM volume in this region is still increasing. Thus, FA could provide a meaningful metric that is potentially a microstructural index of volumetric measures. One would need to interpret this index with caution, however, because FA and volume could be temporally shifted such that FA begins to decline significantly earlier than gross effects measured through volume. Our prefrontal GM and FA measures were not correlated within any segment of the age span. We suggest that this finding is due to the fact that FA is measuring a meaningful property of WM as opposed to more generic, global brain changes. A clear description of the full relation between WM FA and volume awaits future research.

## WHAT CONTRIBUTES TO AGE-RELATED CHANGES IN PREFRONTAL FA?

Evidence suggests that changes in FA with aging are due to microstructural alterations that are antecedent to WM hyperintensities or volume loss commonly measured in MR studies. Regionally, we find reduced FA in brain areas that have high hyperintensity distribution.[34] Prior studies have shown that these patches are heterogeneously pathologic, resulting from infarction, gliosis, demyelination, or cysts.[35] Many OA, however, are relatively free from WM abnormalities, yet still show marked decline in WM FA and volume. Additionally, changes in FA occur in regions such as the corpus callosum, where hyperintensities are not typically found. These

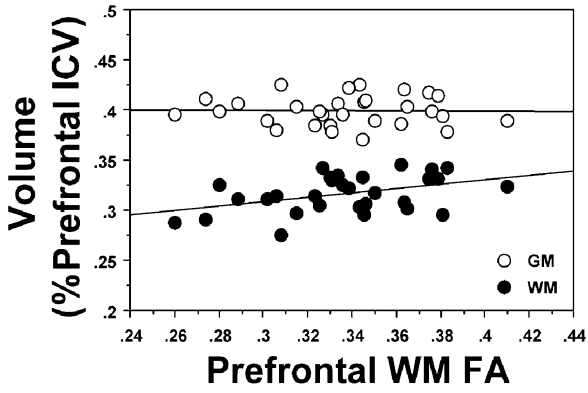


**FIGURE 6.** Correlation between prefrontal GM and WM volume and prefrontal WM FA. Greater prefrontal WM volume was related to higher prefrontal WM FA, but only when limiting the analysis to adults over age 40. In contrast, prefrontal GM volume was not related to prefrontal WM FA.

facts suggest that large signal abnormalities are not a hallmark of aging, but stem from medical conditions with increased incidence in the aging population, such as hypertension and cerebrovascular risk. Thus, FA provides information about additional alterations in WM independent of obvious abnormalities. It is possible that these reductions in FA could even be related to subclinical cerebrovascular risk. Recent research demonstrates that untreated as well as treated hypertension can result in negative changes in prefrontal brain structure,[36] supporting a role for subclinical cerebrovascular risk in accelerating brain pathology. Alternatively, FA reduction may represent an independent and distinct process from hyperintensity formation or cerebrovascular risk. Decreases in normal WM volume are found in well-characterized, healthy adults. Thus, whatever the basis of age-related reduction in FA, it is not necessarily associated with current or impending disease.

## ARE FA MEASURES OF WM INTEGRITY CLINICALLY SIGNIFICANT?

DTI as described in this chapter will be useful as a clinical technique only if one can demonstrate that the measures are related to cognitive and other symptomology. The clinical significance of WM changes has been difficult to establish because of the pathologic, regional, and quantitative variability associated with WM damage. Studies appearing in the literature suggest that DTI can contribute to clinical diagnosis. One impressive study demonstrated a strong relation between DTI measures in the temporal stem WM and disease severity in patients with AD.[37] Preliminary data from our laboratory and published reports from others suggest that DTI measures predict functional capacity in patients with Huntington's disease[38] and cognitive abilities in OA.[39] In fact, our data even suggest that regional anisotropy and cognitive performance are related within young healthy participants.[40] Functional MRI (fMRI) studies (e.g., refs. 41–44) demonstrated age-related alterations in

frontal lobe neural activity, and a promising future endeavor will be the combination of DTI with fMRI measures to determine the significance of WM alterations on brain function. Thus, although requiring further study and evaluation, recent data indicate that DTI measures are an important clinical index of regional pathology.

## CAVEATS AND FUTURE DIRECTIONS

A number of caveats exist in the use of diffusion imaging to address questions about age-related tissue degeneration. The most common current methods do not allow for whole brain acquisition with much higher resolution than 2 $mm^3$. Thus, sampling from appreciable regions of WM without partial volume contamination from GM or cerebrospinal fluid is difficult, particularly when examining participant populations where WM atrophy is expected. Although partial voluming affects measures of FA, recent studies demonstrated that it does not account for the entire effect found in studies of aging.[30,45] A confounding factor to comparing regional measurements arises because some regions can be measured and spatially normalized more reliably than others. Similarly, FA is strongly influenced by the orientational homogeneity of the fiber system being measured. It is likely that measurements from regions comprising less homogeneous fiber systems have inherently reduced statistical power to detect significant alterations. Further, ROI and voxel-based studies will be affected by image distortions common to fast imaging. Thus, DTI must overcome these significant hurdles to advance as a research tool with clinical applicability. Novel methods in data acquisition and analysis will be critical towards attaining this goal.[46,47] In spite of these limitations, DTI has been, and will continue to be, an important research method for examining brain aging and age-related disease.

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