Published in final edited form as:

J Alzheimers Dis. 2019 ; 70(4): 965–981. doi:10.3233/JAD-181210.

Relationships Between Diffusion Tensor Imaging and Cerebrospinal Fluid Metrics in Early Stages of the Alzheimer's Disease Continuum

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Abstract

Recently, the field of Alzheimer's disease (AD) research has adopted a new framework that places the progression of AD along a continuum consisting of a preclinical stage, followed by conversion to mild cognitive impairment, and ultimately dementia. Important neuropathological changes occur in the preclinical phase, necessitating the identification of metrics that can detect such early changes. While cerebrospinal fluid (CSF) measures of amyloid and tau are generally accepted as biomarkers of AD pathology, neuroimaging measures used to index white matter alterations throughout the brain remain less widely endorsed as candidate biomarkers. To explore the relationship between white matter alterations and AD pathology, we review the literature on multimodal studies that assessed both CSF markers and white matter indices, derived from diffusion tensor imaging (DTI) methods, across cohorts primarily in the early phases of AD. Our review indicates that abnormal CSF measures of $A\beta_{42}$ and tau are associated with widespread alterations in white matter microstructure throughout the brain. Furthermore, white matter variability is related to individual differences in behavior and can aid in tracking longitudinal changes in cognition. Our review advocates for the utilization of DTI metrics in investigations of early AD and suggests that the combined use of DTI and CSF markers may better explain individual differences in cognition and disease progression. However, further research is needed to resolve certain mixed findings.

Keywords

Alzheimer's disease; biomarkers; cerebrospinal fluid; diffusion tensor imaging; mild cognitive impairment

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia and is currently estimated to affect one in ten Americans over the age of 65 [1]. It is the sixth-leading cause of death in the United States and the only top ten leading cause of death for which the progression

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Authors' disclosures available online (<https://www.j-alz.com/manuscript-disclosures/18-1210r2>).

cannot be prevented, slowed, or cured [1,2]. Given that none of the FDA-approved drugs for AD to date have been shown to slow or stop the progression of the disease, it is possible that dementia encapsulates a stage of AD in which neurodegeneration has become too significant to observe any noticeable response to interventions. Prior research [3–6] suggests that pathological changes can be observed decades before the onset of AD dementia, resulting in a disease continuum ranging from a preclinical, asymptomatic phase to mild cognitive impairment (MCI) and dementia [7]. This redefined framework of an AD continuum has prompted researchers to target earlier phases in the hopes of maximizing the potential impact of pharmaceutical interventions.

One approach to defining the stages along the continuum is based on evidence of certain *in vivo* neuropathological changes, as measured by biomarkers of AD pathology [8], where a biomarker refers to physiological, biochemical, or anatomical variables that are used to diagnose or predict specific pathological changes that occur as a consequence of the disease [9]. The key pathological features in AD, amyloid plaques and neurofibrillary tangles, are only observed at autopsy; therefore, biomarkers aim to measure *in vivo* changes or abnormalities that are representative of the underlying neuropathology. Cerebrospinal fluid (CSF) measures are often used as *in vivo* biomarkers of amyloid- β ($A\beta_{42}$) and tau (total tau or phosphorylated tau). $A\beta_{42}$ abnormalities indicate amyloid plaque deposition, while phosphorylated tau abnormalities are linked to neurofibrillary tangles, and total tau is linked to more general neuronal injury. As reviewed below, abnormalities in these measures can be found throughout the AD continuum and have repeatedly been able to predict the likelihood of progression from cognitively normal to MCI to AD dementia. These CSF markers have been well-validated in the literature.

In contrast, changes in white matter have been less studied as potential biomarkers. It is well-known that pronounced white matter damage occurs by the time AD has progressed to dementia. One hypothesis suggests that observed white matter damage is simply a consequence of gray matter atrophy. The Wallerian degeneration model posits that deterioration of connected gray matter regions leads to degradation of the white matter pathways connecting those regions [10]. In this model, white matter damage is secondary to gray matter loss. However, evidence from pathology studies suggests that white matter damage is often independent of gray matter atrophy, and more recent neuroimaging studies have begun to report the presence of microstructural white matter abnormalities in the earliest phases of AD [10, 11]. Together, these findings cast doubt on the Wallerian degeneration hypothesis. It is possible that Wallerian degeneration may still be a mechanism of white matter atrophy in later stages of AD, with a separate mechanism accounting for earlier alterations. Indeed, it seems that the earliest manifestations of white matter damage may be subtle, and therefore only apparent in the microstructural properties of the brain. Thus, methods that can capture these microstructural changes may provide opportunities for detecting important early brain changes related to AD pathology.

Diffusion tensor imaging (DTI) provides a method for quantifying the microstructural properties of white matter pathways *in vivo*. As summarized below, the growing literature using this method has identified a number of consistent findings with respect to microstructural changes throughout the course of AD. In fact, there are suggestions that

microstructural white matter alterations may precede gray matter atrophy detected by MRI [11]. Similar evidence in the non-demented stages of AD has been observed in pathology studies of individuals who exhibit post-mortem AD pathology but no clinical symptoms of AD. These subjects exhibited widespread white matter damage, consistent with damage seen in AD dementia, but relatively preserved gray matter [12]. Based on these findings, a review by Sachdev and colleagues [11] concluded that microstructural abnormalities arise early in the course of AD progression and do seem to contribute to the pathological progression of AD.

Although white matter alterations are not specific to underlying AD pathology, they may still convey important information regarding early brain changes and prediction of future cognitive decline. Since CSF measures are well-validated as biomarkers approximating *in vivo* AD-specific pathology, this review aims to provide an overview of studies that have examined CSF biomarkers and white matter indices in tandem in order to investigate the relationship between DTI measures and AD pathology and to examine the potential value added by incorporating both white matter measures and CSF markers into studies of early AD. Given our particular interest in early detection, the present review specifically focused on studies that included cognitively normal or MCI cohorts. Specifically, we sought to examine the following questions: 1) Do combined studies of CSF and DTI metrics yield consistent group differences? 2) Are there reliable correlations between CSF and DTI indices? 3) Are there relationships between DTI measures and behavior? 4) Does the combination of CSF markers with DTI data yield more accurate prediction models of AD progression?

In subsequent sections, we will first provide an overview of DTI methods, measures, and findings related to AD, followed by a brief overview of the primary CSF measures and associated findings. We will review current studies that have utilized a multi-modal approach with respect to combining CSF and DTI indices as potential biomarkers of AD. Finally, we highlight some limitations of the current literature and discuss how these considerations may shape future investigations.

DTI BIOMARKERS

White matter pathways make up the structural connections linking disparate brain regions. On a coarse scale, these pathways can be observed on typical structural MRI scans; however, only macrostructural measures, such as volume, shape, and potentially morphology, can be derived at this level of analysis. In order to examine more fine-grained underlying properties of the white matter, a different imaging method is needed. Diffusion-weighted MR imaging (DW-MRI) enables the quantification of microstructural properties of white matter pathways, including myelination, axonal diameter, axonal density, and membrane permeability [13]. DW-MRI utilizes the diffusion properties of water molecules to differentiate types of brain tissue. In unrestricted compartments, such as the ventricles or gray matter, water molecules diffuse in an isotropic fashion, such that random diffusion occurs relatively equally in all directions. However, in the myelinated axons that make up white matter tracts, the direction of diffusion is restricted due to the presence of myelin sheaths. DW-MRI captures the degree of restriction, called anisotropy, and provides

measures of the microstructural properties of white matter, such as the orientation and magnitude of diffusion within each voxel of the brain [14–17].

Fractional anisotropy (FA) and mean diffusivity (MD) are the most commonly reported indices. FA ranges from 0 to 1 and reflects a scaled index of the degree of anisotropy, where an FA value of 0 represents perfectly isotropic diffusion, while an FA value of 1 indicates anisotropic diffusion completely restricted along one axis. MD measures the overall diffusion within a voxel. Higher MD values indicate more random diffusion, reflecting a less directional neuronal structure. With respect to detecting white matter abnormalities, FA is very sensitive to microstructural changes in general, but it provides less information about the particular type of change in diffusivity. Therefore, additional metrics should ideally be reported in conjunction with FA analyses [17]. Changes in MD can indicate presence of tissue damage, reflected by increased free diffusion [18].

Although less commonly reported in earlier DTI studies, it is also important to consider axial diffusivity (DA) and radial diffusivity (RD), as these measures (along with MD) have been shown to be more sensitive to specific microstructural changes. This sensitivity has been demonstrated in AD-related white matter changes, particularly in early stages where the microstructural differences are likely to be subtle [19]. DA (also called parallel diffusivity) represents the degree of diffusion parallel to the primary axon bundle, while RD (also called perpendicular diffusivity) represents diffusion perpendicular to the primary axon bundle. RD may be more sensitive to alterations in myelination, while changes in DA may reflect axonal injury [20].

Given the presence of pronounced white matter alterations observed in AD dementia [10, 21, 22], there has been a recent push to investigate whether these white matter differences, albeit potentially more subtle, also emerge in earlier stages, such as in MCI patients or even asymptomatic samples. Several recent reviews have summarized these findings [19, 23–28]. Briefly, white matter differences between patients with MCI and healthy controls are most consistently observed in the corpus callosum, along with limbic pathways, including the cingulum, fornix, and uncinate fasciculus. Studies additionally often report altered white matter microstructure in the parietal lobes, particularly the precuneus. This pattern is consistent with patterns demonstrated in individuals at risk for AD due to family history and/or the presence of an apolipoprotein E4 allele. Specifically, these at-risk groups have been shown to exhibit microstructural aberrations in the cingulum, parahippocampus, uncinate fasciculus, and corpus callosum [28]. Longitudinal changes have been observed in the corpus callosum [29] and fornix [30, 31]; however, only in the fornix was the rate of change significantly different between MCI patients and controls.

There is also a general consensus that white matter alterations occur in the hippocampus, both in differentiating MCI patients from controls and in predicting conversion from MCI to AD dementia. In fact, a meta-analysis by Clerx and colleagues [27] reported that in studies examining MD differences, hippocampal MD was the best differentiator between MCI patients and controls, and the hippocampal MD effect size was larger than the effect size for the same contrast using hippocampal volume. Looking across the AD continuum, Teipel and colleagues [19] posit that the current DTI findings converge on a timeline of microstructural

white matter changes that begin in the limbic tracts, subsequently extend to more lateral temporoparietal association tracts, and ultimately progress to long-range frontal fiber pathways. They also note that the limbic tract alterations are the most severe and are detected years before cognitive deficits and gray matter deterioration. Together, these findings demonstrate an important link between microstructural white matter changes and AD progression.

CSF BIOMARKERS

There is now a vast literature demonstrating that certain neuro-pathophysiological changes associated with AD manifest up to decades before any cognitive symptoms emerge [3–6, 32]. Arguably, the most widely studied metrics in this literature are two classes of CSF biomarkers, which serve as proxies for measures of neurological changes related to the two hallmark features of AD: accumulation of amyloid plaques and neurofibrillary tangles made up of hyperphosphorylated tau [33, 34]. The three most common CSF biomarkers align with these hallmark features; specifically, $A\beta_{42}$ is used to index amyloid- β ($A\beta$) protein deposition, while total tau (t -tau) and phosphorylated tau (p -tau) are measures associated with the pathological build-up of tau proteins [8, 35]. Importantly, $A\beta_{42}$ is thought to directly reflect the presence of amyloidosis, while p -tau reflects tau pathology (i.e., neurofibrillary tangles), and both are therefore more specific to AD than t -tau [36]. Whereas elevated p -tau has only been found in relation to AD, high levels of t -tau are present across a number of neurodegenerative disorders, suggesting that t -tau is less specific to AD and instead signifies general neuronal injury [8, 35].

These biomarkers have repeatedly shown the ability to differentiate patient groups along the AD continuum [37]. They also predict conversion from MCI to dementia and conversion from preclinical stages to MCI [37]. In general, low levels of $A\beta_{42}$ indicate amyloidosis, while elevated levels of t -tau and p -tau indicate neuronal injury [7, 8, 38]. Post-mortem studies provide evidence that CSF $A\beta_{42}$ correlates negatively with brain $A\beta$ load at autopsy, and CSF tau correlates positively with hyperphosphorylated tau neurofibrillary tangles, corroborating CSF findings that low levels of $A\beta_{42}$ and high levels of tau reflect underlying AD neuropathology [36].

More recent studies have begun to combine CSF biomarkers, and one meta-analysis [37] reported that a combination of $A\beta_{42}$ and tau markers yielded the best predictive sensitivity and specificity. Specifically, calculation of a p -tau/ $A\beta_{42}$ ratio measure provided the best differentiation of AD dementia patients from healthy controls and MCI from AD dementia. These findings are in line with the redefined clinical research criteria for MCI, in which a combination of low $A\beta_{42}$ with high tau has been determined to yield the highest likelihood of progression to AD dementia [38]. The enhanced predictability gleaned from combining $A\beta_{42}$ and tau markers is consistent with the argument that the presence of $A\beta$ plaques alone is not sufficient to produce AD dementia, as evidenced by converging findings from CSF and autopsy studies revealing that approximately 30–40% of cognitively normal older adults exhibit significant $A\beta$ plaque deposition without ever manifesting cognitive or clinical symptoms of AD [39–43].

Recent models have postulated different time-lines for the appearance of abnormal A β ₄₂ and tau biomarkers, suggesting that A β ₄₂ abnormalities appear first, followed by later increases in tau. Both are thought to precede MRI markers and cognitive manifestations [9,44]. CSF A β ₄₂ and tau also appear to have different rates of change throughout progression along the AD continuum. Low A β ₄₂ levels become apparent early, but then those low levels tend to stay relatively stable over time. By contrast, *t*-tau and *p*-tau abnormalities become increasingly abnormal over time [3].

Increasing importance is being placed on these CSF biomarkers. In fact, in the 2018 updated research framework [8], definition of the AD continuum is based on the *in vivo* presence of biomarkers. This framework adopts the A/T/N profile system [35], where “A” refers to biomarkers of A β , “T” refers to biomarkers of phosphorylated tau, and “N” refers to biomarkers of neurodegeneration or neuronal injury (e.g., *t*-tau or neurodegeneration on MRI). When combined with cognitive profiles, individuals who are cognitively unimpaired but exhibit abnormal A profiles, abnormal A and T profiles, or abnormal A, T, and N profiles are considered to be in the preclinical phase of AD. Given that amyloid positivity is present in each of the preclinical stages, it seems to be a key potential component in determining risk for later progression of MCI or AD dementia.

COMBINED USE OF DTI AND CSF BIOMARKERS

The present review focused on multimodal studies that included both DTI and CSF measures in their investigations. Articles were retrieved from Google Scholar and PubMed using the keywords “diffusion imaging”, “DTI”, “CSF”, “biomarkers”, “Alzheimer’s disease”, “preclinical AD”, “MCI”, and “multimodal”. Only studies that included both DTI and CSF metrics in cognitively normal or early AD samples (e.g., preclinical AD, subjective cognitive decline, MCI) were included.

Investigating group differences

A number of the studies in the current review examined group differences in DTI indices by partitioning subject groups based on CSF biomarkers. The most common variable used to divide groups was CSF A β ₄₂, such that participants with levels of A β ₄₂ below a certain threshold (which differed by study) were considered to have A β ₄₂ abnormalities, often referred to as amyloid positivity. Microstructural white matter differences were found between amyloid positive and amyloid negative groups consisting of cognitively normal asymptomatic older adults [45, 46], as well as patients with subjective cognitive decline (SCD) or MCI [47]. In the asymptomatic samples, amyloid positive individuals exhibited significantly lower FA [45] and higher DA [46] in the fornix compared to individuals with higher CSF levels of A β ₄₂. They also showed increased DA in the corpus callosum, corona radiata, internal capsule, superior longitudinal fasciculus, uncinate fasciculus, and inferior fronto-occipital fasciculus [46]. In patients with MCI, the amyloid positive group demonstrated lower FA and higher MD, DA, and RD in the splenium of the corpus callosum relative to the amyloid negative group [47].

Following a similar approach, groups can be based on partitions of CSF tau levels. Our review revealed only one study utilizing this approach. Stenset et al. [48] assessed white

matter differences across healthy age-matched controls, SCD, or MCI patients with normal tau levels, and SCD or MCI patients with pathological tau levels. The authors reported that the microstructure of the cingulum was significantly altered in the pathological tau group compared to both the normal tau group and healthy controls, as evidenced by decreased FA and increased RD. Additional differences emerged between the pathological tau and healthy control groups in the forceps major (lower FA, higher RD in the pathological tau group) and the genu of the corpus callosum (higher RD in the pathological tau group).

Finally, our review identified two studies that utilized multiple biomarker measures to assess group differences. First, Lim and colleagues [49] stratified early MCI patients into groups based on a p -tau/ $A\beta_{42}$ ratio and found that compared to the high-ratio group, the low-ratio group exhibited higher RD in the corpus callosum, forceps minor, superior longitudinal fasciculus, and inferior longitudinal fasciculus. Moreover, these low-ratio early MCI patients also demonstrated “widespread” increases in MD, DA, and RD when compared to healthy controls. Second, a recent study by Pereira et al. [50] utilized a multimodal approach and categorized cognitively normal older adults based on two markers: 1) $A\beta_{42}$ and 2) a neurodegeneration marker derived based on cortical thickness of medial temporal lobe regions and hippocampal volume. They performed whole brain tractography and then applied graph theory methods to the DTI data to demonstrate that when comparing participants with relatively normal $A\beta_{42}$ levels and no markers of neurodegeneration to participants with markers indicating both abnormal $A\beta_{42}$ and neurodegeneration, the amyloid/neurodegeneration positive participants showed abnormal local connectivity increases and longer path lengths between remote brain regions, indicating less efficient structural networks. These participants were also found to have reduced FA in a number of the specific structural connections identified by graph theory.

Together, these studies identify several white matter pathways with altered microstructure in individuals that display abnormal CSF biomarkers. Of the white matter tracts consistently reported, the fornix, uncinate fasciculus, and cingulum have been most implicated in episodic memory function. The fornix connects the hippocampus to the mammillary bodies, and is therefore known to be critically important in facilitating episodic memory function. Fornix microstructure has been shown to correlate with episodic memory performance in both cognitively normal older adults [51] and across the AD continuum [52, 53]. Similarly, the uncinate fasciculus connects the anterior and medial temporal lobes, including portions of entorhinal, parahippocampal, and perirhinal cortex, to the orbitofrontal cortex and has been previously implicated in episodic memory function in cognitively normal participants [51], as well as MCI patients [54, 55]. In fact, in one study, uncinate FA at baseline positively correlated with memory performance three years later [55]. The cingulum, particularly the posterior segment, has also consistently been associated with episodic memory function. The posterior division of the cingulum connects inferior parietal cortex to the hippocampus and parahippocampus and has been shown to correlate with memory performance in MCI and AD dementia patients [56] and non-demented older adults [51,57].

While less directly involved in memory, the corpus callosum is critically important in facilitating many cognitive functions, as it is the major fiber bundle connecting the left and right hemispheres. It is also one of the tracts that has most consistently shown alterations in

AD dementia and MCI [21]. The cingulum, corpus callosum, and uncinate fasciculus all also follow some of the most protracted developmental trajectories, with FA not reaching its peak values until 35 or 40 years of age [58]. Coupled with the microstructural changes identified in early phases of the AD progression, this fits with one mechanistic model of white matter degeneration in AD which posits that the latest developing or myelinating tracts are the first to begin degenerating in AD [10].

It is important to note that these findings were above and beyond the general effect of aging. At the very least, each study used age-matched groups, and many further controlled for age and a number of other factors (e.g., sex, education) in their analyses. Therefore, the differences in microstructure do not seem to be merely the result of aging. In the case of the fornix, Gold and colleagues [45] additionally controlled for the volumes of both the hippocampus and the fornix in their analyses, indicating that 1) microstructural differences were not simply the result of volumetric differences and 2) white matter differences were independent of gray matter atrophy. This signifies that alterations in the microstructure of the fornix may follow a different trajectory, possibly appearing earlier than macrostructural or gray matter alterations. In assessing the efficacy of potential DTI biomarkers, fornix microstructure may be of special interest, given the present findings and its critical involvement in episodic memory function [59].

One important caveat to these studies is the fact that there is no “gold standard” cutoff score for defining abnormal levels of CSF A β ₄₂ or tau, leading the criteria for pathological levels to vary across laboratories, and sometimes across age groups. There may also be critical information lost by dichotomizing CSF variables; therefore, the next section summarizes information to be gleaned by using both CSF and DTI markers as continuous variables, and directly examining the relationship between them.

Relationships between DTI and CSF biomarkers

In our review of the literature, nine studies directly examined the relationship between DTI metrics and various CSF biomarkers. By treating the biomarkers as continuous variables, these studies were able to get a better sense of how AD pathology, as measured by CSF markers, may be associated with DTI measures. If significant relationships emerge between the two, it would suggest that DTI metrics may carry meaningful information with respect to detectable changes in the human connectome. Across these studies, in cohorts ranging from asymptomatic participants to patients with MCI or AD dementia, widespread significant relationships were revealed throughout the brain. A general overview of the findings is presented in Table 1.

With respect to A β ₄₂, these studies have consistently found that lower levels of A β ₄₂ are associated with lower FA values but higher MD, DA, and RD values. These patterns emerge across both whole brain and region of interest (ROI) based approaches. Correlations have been observed in cohorts consisting of cognitively normal older adults [45], individuals with family history of AD [60], and patients with subjective cognitive impairment (SCI), MCI, or AD dementia [61, 62]. Correlations with A β ₄₂ were most commonly localized to the temporal lobe structures, including the fornix, cingulum, parahippocampal cortex, and inferior temporal gyrus [45, 61, 62]. Relationships were also found in the frontal [60],

parietal, and occipital lobes [61], as well as in the corpus callosum and cerebrospinal tract [62].

Many findings have also emerged linking t -tau with DTI measures, and evidence across studies suggests that higher levels of t -tau are linked to lower levels of FA, but higher diffusivity values (i.e., MD, DA, and RD). Overall, there were fewer significant associations reported with FA; it was more common to see relationships emerge between the tau markers and measures of diffusivity. Across studies, a widespread distribution of relationships emerged across brain regions (see Table 1 for details) in cognitively normal participants [60, 63, 64], as well as cohorts comprised of SCI, MCI, and AD dementia patients [48, 61].

Fewer correlations have been reported with respect to p -tau; however, the directionality is once again consistent across studies. Generally, higher p -tau is associated with lower FA, but higher MD. Relationships were reported in cognitively normal participants [63, 64] and MCI patients [65]. Salient regions include the cingulum [65], frontal lobe, thalamus [63], and corpus callosum [64].

Relationships have also been discovered when constructing ratio measures of the traditional CSF biomarkers (e.g., p -tau/ $A\beta_{42}$, t -tau/ $A\beta_{42}$). These findings arise from four studies in cognitively normal cohorts [45, 60, 64, 66]. Ratio values indicating abnormalities on both $A\beta_{42}$ and p -tau or t -tau measures (e.g., a high p -tau/ $A\beta_{42}$ ratio, which indicates high p -tau coupled with low $A\beta_{42}$) were typically associated with a reduction in FA, but heightened diffusivity values (MD, DA, and RD). Once again, these correlations were widespread across brain regions (see Table 1).

Overall, the literature exploring correlations between CSF markers and DTI metrics provides evidence that there are many significant relationships between CSF biomarkers and white matter microstructure throughout the brain. Furthermore, relationships appeared across cohorts of cognitively normal individuals, as well as MCI and AD dementia patients, supporting the potential use of DTI measures as AD-related biomarkers. However, one main caveat remains when interpreting these data. It is important to note that some of the reported findings are subtle and are reported at lower thresholds of correction or in the absence of any multiple comparison adjustment. To get a more complete picture of the literature, we chose to include the subtle effects in our discussion. Many of the studies used cognitively normal participants; a possible explanation for some of the subtle effects. The more robust findings are those correlations that appear across multiple DTI measures, providing consistent evidence of a DTI/CSF relationship. For instance, as can be seen in Table 1, converging correlational evidence across DTI indices has been found in a number of regions within the temporal lobe. Given the critical role the medial temporal lobe is thought to play in memory and aging, it is encouraging to see strong evidence across these regions. Additionally, correlations that appear across analysis approaches are also more robust and compelling findings. For example, Gold et al. [45] demonstrated a significant association between fornix microstructure and the $A\beta_{42}/p$ -tau ratio both in an ROI-based approach and in a voxel-wise whole brain analysis. This strengthens the claims that can be made about the importance of this association. Other types of associations may also bolster the claims that can be made

regarding the importance of DTI metrics. One such association is the potential relationship between DTI markers and behavior.

Relationships between DTI measures and behavior

Only a handful of the reviewed studies have investigated potential DTI-behavior relationships. The main findings of these studies are summarized in Table 2. In one study of SCI and MCI patients with non-pathological levels of τ -tau [67], higher FA and lower RD in the genu of the corpus callosum were significantly associated with better verbal learning performance on the Rey Auditory Verbal Learning Task (RAVLT), indexed by combined performance on all learning lists, as well as better RAVLT overall memory performance (combined performance on immediate and delayed recall tests). Furthermore, in a hierarchical regression analysis predicting verbal learning performance, adding corpus callosum and fornix FA as predictors significantly increased the predictive value of the model when compared to hippocampal volume alone (which was not a significant predictor in either model). However, only corpus callosum FA accounted for a significant amount of unique variance explained.

Although the fornix was not a unique predictor in the hierarchical regression, there were significant bivariate correlations between fornix FA and RD with RAVLT learning score [67]. Similarly, another study [45] reported that higher FA and lower RD were both associated with higher performance on the digit symbol task in cognitively normal participants. The digit symbol task can be thought of as a form of associative learning; therefore, together these findings point to an important relationship between fornix microstructure and enhanced performance on learning tasks.

Examining larger scale brain networks, worse delayed recall performance on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) in asymptomatic participants was significantly related to lower global efficiency in a graph theory analysis of DTI data, which reflects poorer integration of connections within the network [50]. This finding was only present in the asymptomatic participants that were positive for both abnormal levels of $A\beta_{42}$ and markers of neurodegeneration, perhaps indicating that more global connectivity changes begin to manifest when multiple biomarkers indicate abnormalities. Similarly, higher scores on a cognitive reserve questionnaire were related to significantly higher global DA, but only in asymptomatic individuals who exhibited abnormal levels of $A\beta_{42}$ [46]. While this was technically a whole brain analysis, it should be noted that this correlation was specifically calculated for voxels that showed a significant group difference between $A\beta_{42}+$ and $A\beta_{42}$ -participants, which could explain the null finding in the group with more normal $A\beta_{42}$ levels. In general, this compilation of results suggests that behavior, particularly pertaining to episodic memory, has been repeatedly related to alterations in microstructure in both cognitively normal risk samples, as well as patients with SCI or MCI. Therefore, alterations in white matter could serve as meaningful predictors of changes in memory related to AD progression.

Longitudinal studies

It is important to determine whether microstructural alterations are stable over time or whether the rate of change may differ across patient groups. Similarly, it is important to explore whether baseline measurements of DTI microstructure may be related to longitudinal changes in cognitive decline or memory performance. A summary of the longitudinal studies reviewed can be found in Table 2. Of the studies included in the present review, three examined changes in white matter microstructure over time. The findings revealed increased rates of change in RD over time in MCI patients compared to controls; this effect was not present in FA [68]. In a subgroup of MCI patients with pathological levels of t -tau, the strongest RD by time interaction effects (compared to controls) were in the posterior cingulum, inferior longitudinal fasciculus, and superior longitudinal fasciculus. However, the caveat once again is that this effect was tested in voxels that demonstrated significant group differences at the 2–3 year follow up scan.

Using a more targeted ROI approach, Racine and colleagues [66] examined how baseline CSF levels in cognitively normal participants were associated with longitudinal changes in cingulum MD. Here, the authors found a correlation between p -tau/ $A\beta_{42}$ and MD at baseline; however, longitudinal changes in MD did not differ based on baseline levels of p -tau/ $A\beta_{42}$. In other words, abnormal baseline levels of p -tau and $A\beta_{42}$ did not confer increased rates of change in cingulum MD. By contrast, in the posterior cingulum, the neuroinflammatory marker YKL-40, which indicates activation of microglia resulting from neuroinflammation, did not exhibit a significant correlation with MD at baseline, but higher baseline levels of YKL-40 were associated with a higher rate of increasing MD over time. With a small number of findings and mixed results, it is difficult to interpret these effects, but the existence of potentially important longitudinal microstructural changes certainly warrants further investigation.

Baseline measures of DTI microstructure can also be used to predict longitudinal changes. These baseline measures have been linked to longitudinal changes in medial temporal lobe macrostructure [69], cognitive decline [69, 70], and behavioral performance [46, 71]. First, across SCI, MCI, and control participants, whole brain mean FA, MD, and RD all significantly predicted future medial temporal lobe atrophy (measured as thickness for cortical regions or volume for the hippocampus) in the hippocampus, entorhinal cortex, and parahippocampal gyrus [69]. In the same participants, marked cognitive decline (assessed through clinical interview and neuropsychological testing) over a 2 to 3 year period was associated with higher global mean MD and RD, and lower mean FA at baseline [69]. No such relationship was found in participants who exhibited cognitive improvement at follow up. Within specific ROIs, similar patterns of results were found for MD and RD within the entorhinal cortex, parahippocampal cortex, retrosplenial cortex, posterior cingulate, precuneus, and supramarginal gyrus. In line with these findings, Egli et al. [70] demonstrated that longitudinal changes in MCI patients' Mini-Mental State Examination (MMSE) scores were significantly predicted by baseline levels of fornix FA, as well as a primacy measure (i.e., memory for early list items relative to other items) from the California Verbal Learning Test (CVLT). These results suggest that microstructural abnormalities at baseline can be used to predict future cognitive decline.

Specific to memory performance, in a study where a subset of the cognitively normal participants returned for a 2-year follow up, participants with higher DA at baseline exhibited higher levels of memory deterioration, as indexed by the memory alteration test, on the follow up assessment [46]. Additionally, in an analysis of a subset of participants from the ADNI dataset, a large-scale publicly available longitudinal database of cognitively normal participants, MCI patients, and AD dementia patients, Scott and colleagues [71] found that at baseline, there was no relationship between memory performance and whole brain global MD; however, longitudinal changes in memory were predicted by baseline levels of MD. Here, a composite memory score was derived from scores on the RAVLT, ADAS-Cog recall and recognition, MMSE to-be-remembered words, and Wechsler Memory Scale immediate and delayed logical memory tests. Changes in composite memory score assessed at four time-points over a 3-year period were significantly related to baseline MD, with higher MD predicting larger declines in memory performance. It is important to note, however, that many models were constructed in this study, and the only model to yield a significant interaction between MD and memory changes was one that also modeled hippocampal volume and PET measures of general activation; furthermore, the effect was specific to patients classified as early MCI. Despite the limitations, these findings seem to suggest that white matter microstructure assessed at baseline can be used to predict future memory decline, at least in early stages of AD progression.

In the same study [71], baseline scores on a composite measure of executive function were related to baseline MD in the overall cohort including cognitively normal individuals, early MCI patients, late MCI patients, and AD dementia patients. At baseline, higher executive function performance was predicted by lower levels of MD. However, longitudinal changes in executive function were not predicted by MD (i.e., no MD by time interaction). The same pattern of results emerged in separate analyses of late MCI and AD dementia patients. Therefore, findings may depend on the particular outcome measure of interest, since different effects were observed in the memory and executive function domains. The longitudinal effects may also differ by patient group, but given the limited number of studies, further research is needed.

Building predictive models

Based on the literature discussed thus far, it seems clear that DTI microstructure does provide meaningful information with respect to early alterations that may be related to progression through the AD continuum. Yet, our discussion has not addressed whether one of these measures, DTI or CSF, may be a better marker for predicting AD progression. It is also possible that combining the two markers could actually provide enhanced predictability over either marker alone. This approach could be tested by building a model to predict some outcome related to disease progression that includes both DTI metrics and CSF measures in the same model. Unfortunately, only a few studies to date have conducted such analyses, and their findings are mixed (see Table 2). Perhaps surprisingly, only two of the presently reviewed studies used DTI and CSF markers to predict time to conversion from MCI to AD dementia. When Egli and colleagues [70] examined each marker in isolation, fornix FA, $A\beta_{42}$, $A\beta_{42}/t\text{-tau}$, and primacy score on the CVLT all significantly predicted time to conversion. However, in a model that combined all of the variables, only $A\beta_{42}$ and CVLT

primacy score predicted time to conversion, suggesting that when combined with other markers, fornix FA did not uniquely contribute a significant portion of explained variance to the model. Similarly, when Selnes et al. [69] examined DTI and CSF markers separately, both t -tau and whole brain DTI metrics (FA, MD, and RD) were significantly associated with cognitive decline; yet, when both MD and t -tau were entered into a logistic regression to predict future cognitive decline, only MD was a significant predictor. Furthermore, in separate models that included MD with either $A\beta_{42}$, p -tau, or t -tau, MD was still the only significant predictor across the three models. Therefore, in the first study, $A\beta_{42}$ and memory performance were better predictors of AD conversion than DTI, while in the second study, MD was a better predictor of cognitive decline than CSF markers.

In addition to modeling cognitive decline, Selnes and colleagues [69] also used multiple linear regressions to predict longitudinal changes in gray matter volume of medial temporal lobe regions. In this analysis, both MD and CSF markers ($A\beta_{42}$, t -tau, and p -tau) were found to be significant predictors of future atrophy in the hippocampus and parahippocampus, each explaining a unique amount of the variance. This finding seems to indicate an advantage in using both markers; however, the variables were entered into the model simultaneously rather than in a step-wise hierarchical fashion, so it remains unclear whether predictability of the model was increased by including both measures.

One study did directly assess the predictability obtained by the measures alone compared to combined. Here, Douaud et al. [72] computed classification accuracy to measure the model's ability to distinguish MCI patients who remained stable for at least three years after initial assessment from MCI patients who progressed to dementia at least two years after initial assessment. ROIs consisted of regions that yielded significant differences between MCI and AD dementia patients in a separate analysis. When MD, $A\beta_{42}$, t -tau, and p -tau were assessed in isolation, MD yielded the highest classification accuracy (77%). However, when MD and t -tau/ $A\beta_{42}$ were combined into a single measure which also consisted of volume (of significant ROIs) and mode of anisotropy (a less frequently used DTI metric), classification accuracy increased to 91%. This finding signifies added utility of combined examination of DTI and CSF measures, along with measures of gray matter volume.

Overall, the results of these studies seem to provide somewhat conflicting evidence, and are inconclusive in determining whether one marker is more effective than the other. Given that the studies were predicting different dependent measures, it is certainly possible that the efficacy of each marker may depend on the particular outcome measure the model is attempting to predict. It may also depend on the control variables modeled and the number of overall predictors in the model. Future studies will benefit from a step-wise hierarchical approach which will allow for observation of how each individual biomarker contributes to the predictability of the overall model.

LIMITATIONS AND FUTURE DIRECTIONS

The present review has provided a foundation for understanding the relationship between measures of white matter microstructure and CSF, as well as the value added from incorporating DTI metrics into analyses of early AD. Yet, there are some limitations to the

current findings that highlight open questions warranting further investigation. First, it is important to note that DTI measures lack specificity in terms of detecting AD pathology. DTI metrics can detect alterations in the underlying microstructure of the human connectome, but unlike CSF markers which map onto the specific neuropathological features of AD (i.e., amyloid plaques and neurofibrillary tangles), white matter changes may be present across various neurodegenerative disorders. Therefore, DTI measures can likely not be used in isolation as biomarkers of AD, but this does not render them unimportant. For example, in the A/T/N classification system of AD biomarkers [8,35], neurodegeneration markers do not provide AD-specific information, but are still recognized as important biomarkers that can be combined with amyloid and p -tau measures to improve predictability of cognitive decline [8]. Likewise, while white matter alterations do not provide information regarding AD-specific pathology, our review suggests combination with CSF markers may improve utility for predicting longitudinal changes in cognition.

Additionally, the present studies exhibit a relative lack of attempts to link DTI markers with behavioral performance. All of the reviewed studies collected a large amount of behavioral data on their cohorts; however, only a few directly utilized these measures beyond clinical assessment. Memory performance, in particular, is an obvious behavioral measure of interest, given its tight coupling with cognitive decline in aging. In fact, the studies that did directly test brain-behavior relationships provided consistent evidence of an important relationship between episodic memory measures and DTI metrics. Moreover, a memory measure was also one of the only two significant variables in a combined model to predict time to onset of AD dementia [70]. Future studies should place more emphasis on memory measures in their analyses and ideally, these memory measures should go beyond the standardized tests to target more specific research questions.

Another limitation is the small number of studies that directly compared the efficacy of DTI and CSF biomarkers. As discussed, the results were inconsistent, making it difficult to assess whether there is an advantage to using one over the other. Future studies should continue to uncover efficacy differences by constructing hierarchical models as discussed above, or models that include both classes of biomarkers, as well as potential interaction terms, in order to test which combination of variables provides the most advantageous predictability of various outcome measures. In practice, measuring CSF biomarkers may be less costly than acquiring DTI data, but DTI scans are much less invasive than lumbar punctures. In determining efficacy, it is also important to examine the time course of each of these measures. For instance, it is well-known that among the CSF markers, $A\beta_{42}$ is the earliest to exhibit abnormalities; however, it also asymptotes and becomes more stable over time [3]. Therefore, it is most useful in very early stages, while tau measures are more informative after $A\beta_{42}$ asymptotes. It remains unclear where DTI indices fall on this time course. Many studies here report alterations in cognitively normal cohorts, but further investigation is needed to directly compare trajectories across biomarkers, and also to determine whether alterations in one particular DTI metric may emerge earlier than others.

Similarly, neither class of markers has established a gold standard in terms of data analysis. With respect to CSF measures, this results in no standardized cutoff scores, complicating comparison across studies or potential use in prediction at the individual subject level. With

DTI data, there is a lack of consensus on a standardized processing protocol. As can be seen throughout this review, there is still a wide variety of analysis approaches taken, ranging from exploratory whole brain analyses to hypothesis-driven approaches resulting in very restricted ROI analyses. Exploratory whole brain analyses may lack proper adjustments for multiple comparisons, while analyses restricted to small ROIs may be particularly prone to partial volume effects due to CSF signal contamination [73]. Additionally, in this particular body of literature, there appears to be a preference for voxel-based approaches over tractography. In fact, only one of the studies reviewed here [50] utilized tractography. All of these factors lead to studies that vary greatly in terms of power and susceptibility to false positives, which in turn, results in inconsistent effects that are often difficult to compare across studies. This variability in methodology can also lead to a failure to replicate findings, making it challenging to disentangle which DTI effects are genuine and warrant further investigation and which are likely spurious. Future studies may begin to resolve some of these discrepancies by utilizing advancements in DTI acquisition methods, such as multi-shell acquisition, which allows for higher order modeling of diffusion-weighted imaging data [74].

There is also still debate about which of the DTI measures is the best in terms of capturing the underlying properties of white matter. Early studies relied very heavily on FA, leading to the pitfall that many studies still only report this value. Based on the findings outlined in this review, it seems clear that FA should certainly not be the only value reported. Many studies yielded null effects in terms of FA, but significant findings across other DTI indices. In fact, as evidenced by the overview in Table 1, diffusivity measures such as MD and RD tended to yield significant effects more frequently than FA. Therefore, a reduced focus on FA and inclusion of “absolute diffusivities” (MD, DA, and RD) is warranted, since they tend to be more sensitive, specific measures of the underlying microstructure [19,28]. Moreover, these absolute diffusivities have been implicated in AD-related white matter changes, especially in early disease stages [19]. Despite these issues, having a range of available methodologies and indices to select from is still advantageous, since different research questions may be better answered using different techniques. Therefore, an important step for future investigations requires researchers to be very vigilant and deliberate in their choice of methods. The research question of interest should ideally influence the choice of method, but may also be supplemented with more exploratory measures. The most compelling studies will be those that are designed in such a way that the effects are robust enough to replicate across techniques and measures. Such findings will require large sample sizes, high resolution data, and careful, consistent multiple comparison adjustments.

Future studies could also benefit from the incorporation of CSF measures beyond the traditional $A\beta_{42}$ and tau markers. For instance, neurofilament light chain protein is a CSF marker that has been used to detect neurodegeneration and has previously been shown to correlate with white matter microstructure in cognitively normal participants [60, 63]. There are also CSF markers related to neuroinflammation, which have been shown to exhibit associations with microstructure in asymptomatic participants [64], as well as MCI and AD dementia patients [75]. Additionally, one study [63] suggested that neuroinflammatory biomarkers interact with the traditional AD pathology CSF markers, such that when

aberrations were present in both, correlations emerged with white matter; thus, further research is needed on the potential interactions between different classes of biomarkers.

CONCLUSIONS

The present body of literature appears to advocate for a multimodal approach incorporating both CSF and DTI metrics in studies of early AD to facilitate detection of early AD-related brain changes. Differences in white matter microstructure do seem to be related to variation in CSF markers, whether assessed categorically or as continuous variables, alterations in white matter can be further related to behavioral variability, DTI indices can be used to track longitudinal changes in cognitive ability, and regression models can be used to evaluate potential benefits of examining DTI and CSF in tandem versus alone. However, further investigations are needed to determine which methodological approaches are best suited for the DTI measures, and to evaluate situations in which one type of measure may be more advantageous than another.

ACKNOWLEDGMENTS

We thank Drs. Marilyn Albert and George Rebok for helpful commentary on early versions of this manuscript. This work was supported by the National Institute on Aging (T32-AG027668).

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Table 1

Overview of brain regions exhibiting significant correlations between DTI measures and traditional CSF biomarkers across reviewed studies

	$A\beta_{42}$	p -tau	t -tau	p -tau/ $A\beta_{42}$	t -tau/ $A\beta_{42}$
Frontal lobe					
Med. FG	FA		MD, RD		MD, DA, RD
Mid. FG			MD, DA, RD		MD, RD
SFG					DA
IFG		MD	MD		
OFC			MD		
Orbital gyrus					MD
Precentral gyrus				MD	MD, DA, RD
Temporal lobe					
Mid. TG			MD, DA, RD		MD, DA, RD
STG			MD, DA, RD		MD, DA, RD
ITG	MD		MD	MD	MD
Fornix	FA			FA ($A\beta_{42}/p$ -tau)	
PHC	MD		MD		RD
ERC			MD		
Cingulum	FA, MD, DA, RD	FA	FA, RD	MD	
Fusiform gyrus			MD, DA, RD		
Uncus			DA, RD		MD, RD
Insula					MD, RD
Parietal lobe					
Precuneus	MD		MD, DA, RD		DA
IPL			MD, RD		
Supramarg.					MD
Operculum					MD
Occipital lobe					
Mid. OG			RD		

	$A\beta_{42}$	p -tau	t -tau	p -tau/ $A\beta_{42}$	t -tau/ $A\beta_{42}$
SOG					MD
LOC	FA		MD		
Cuneus			MD		
Lingual gyrus			MD		DA
Other					
CC	FA, MD, DA, RD	MD	MD	MD, FA ($A\beta_{42}/p$ -tau)	MD
SLF				FA ($A\beta_{42}/p$ -tau)	
ILF				FA ($A\beta_{42}/p$ -tau)	
IFOF				MD, FA ($A\beta_{42}/p$ -tau)	RD
CST	MD, DA, RD				
Thalamus		FA	FA		
Putamen			MD, DA, RD		MD, RD
Cerebellum					MD, DA, RD

FA, fractional anisotropy; MD, mean diffusivity; DA, axial diffusivity; RD, radial diffusivity; Med. FG, medial frontal gyrus; SFG, superior frontal gyrus; IFG, inferior frontal gyrus; OFC, orbitofrontal cortex; Mid. TG, middle temporal gyrus; STG, superior temporal gyrus; ITG, inferior temporal gyrus; PHC, parahippocampal cortex; ERC, entorhinal cortex; IPL, inferior parietal lobule; Supramarg., supramarginal gyrus; Mid. OG, middle occipital gyrus; SOG, superior occipital gyrus; LOC, lateral occipital cortex; CC, corpus callosum; SLF, superior longitudinal fasciculus; ILF, inferior longitudinal fasciculus; IFOF, inferior fronto-occipital fasciculus; CST, corticospinal tract.

Table 2

Overview of key multimodal studies

Study	Sample	Methods	Main findings
DTI-behavior correlations			
Gold et al. [45]	20 cognitively normal	ROIs in the fornix and cingulum; controlled for age, sex, education, and gray matter volume of ROIs	Positive correlation between fornix FA and digit symbol task; negative correlation between fornix RD and digit symbol task
Molinuevo et al. [46]	38 cognitively normal ($n = 19$ amyloid positive, $n = 19$ amyloid negative)	Whole brain voxel-based analysis; voxels with significant group difference were used for correlations; groups matched for age, sex, and education	Positive correlation between DA and cognitive reserve in the amyloid positive participants
Pereira et al. [50]	357 cognitively normal	Whole brain tractography and graph theory analysis with 82 nodes; controlled for age, sex, and education	Negative correlation between global efficiency and ADAS-Cog delayed recall in participants with abnormal amyloid and neurodegeneration markers ($n = 57$)
Grambaite et al. [67]	35 SCI and MCI patients with non-pathological levels of τ -tau	ROIs in the forceps major and minor, genu and splenium of the CC, posterior cingulum, and fornix	Positive correlations: CC genu FA with RAVLT learning and RAVLT overall memory, fornix FA with RAVLT learning; negative correlations: CC genu RD with RAVLT learning and RAVLT overall memory, fornix RD with RAVLT learning
Longitudinal studies/predictive models			
Molinuevo et al. [46]	38 cognitively normal ($n = 19$ at follow up)	Whole brain voxel-based analysis; voxels with significant group difference were used for correlations; groups matched for age, sex, and education	Higher DA at baseline predicted greater longitudinal memory deterioration on the memory alteration test at follow up
Racine et al. [66]	151 cognitively normal with family history of AD	ROIs in the cingulum; controlled for age, sex, and imaging site	Positive correlation between p -tau/ $A\beta_{42}$ and MD at baseline, but no difference in longitudinal MD changes based on abnormal baseline p -tau/ $A\beta_{42}$; in the posterior cingulum, no baseline correlation between MD and YKL-40 (inflammatory CSF marker), but increased longitudinal rate of MD change for higher baseline YKL-40
Amlien et al. [68]	39 MCI patients ($n = 9$ high τ -tau, $n = 30$ low τ -tau), 16 healthy controls	Whole brain voxel-based analysis; ROIs in the CC, ATR, cingulum, CST, ILF, SLF, IFOF, UF, and forceps major and minor; analyses run on voxels that showed group difference at follow up; controlled for age, sex, and imaging site	Greater rate of longitudinal RD increase in MCI patients compared to controls; in the high tau sub-group, greater rate of RD increase in the posterior cingulum, ILF, and SLF compared to controls
Selnes et al. [69]	15 SCI patients, 51 MCI patients, 28 healthy controls	Whole brain voxel-based analysis; ROIs in the hippocampus, ERC, PHC, RSC, PCC, precuneus, IPL, supramarginal gyrus, and middle temporal cortex; controlled for age, sex, and imaging site	Baseline whole brain FA, MD, and RD predicted future atrophy in the hippocampus and ERC; baseline MD and RD predicted future atrophy in PHC; baseline FA, MD, and RD predicted longitudinal cognitive decline – significant for whole brain, ERC, PHC, RSC, PCC, precuneus, and supramarginal gyrus; baseline $A\beta_{42}$, τ -tau, and p -tau predicted future hippocampal atrophy; baseline τ -tau predicted future ERC atrophy; baseline τ -tau and p -tau predicted future PHC atrophy; baseline τ -tau predicted longitudinal cognitive decline
Egli et al. [70]	36 MCI patients ($n = 13$ converted to probable AD dementia at follow up)	ROI in the fornix	Lower baseline fornix FA and CVLT primacy scores predicted longitudinal decreases in MMSE score; in separate regressions, CVLT primacy, fornix FA, $A\beta_{42}$, and $A\beta_{42}/\tau$ -tau predicted time to AD conversion; in a combined model with all 4 predictors, only CVLT primacy and $A\beta_{42}$ predicted time to conversion

Study	Sample	Methods	Main findings
Scott et al. [71]	46 cognitively normal, 48 early MCI patients, 29 late MCI patients, 39 AD dementia patients	Whole brain voxel-based analysis; models included age, sex, education, hippocampal volume, global FDG PET activation, intracranial volume, and APOE status	In early MCI patients, no relationship between baseline MD and composite memory score; in early MCI patients, higher baseline MD predicted greater longitudinal decline in memory; in the overall cohort, negative correlation between baseline MD and composite executive function score; in the overall cohort, baseline MD did not predict longitudinal change in executive function
Douaud et al. [72]	56 MCI patients ($n = 13$ progressed to probable AD dementia, $n = 22$ did not progress, $n = 21$ “other” MCI)	Whole brain voxel-based analysis with ROIs derived from group differences between “other” MCI patients and 59 AD dementia patients; linear discriminant analysis to classify MCI progressed versus MCI stable	MD was the best single predictor of conversion (77% classification accuracy); combined predictor of MD, gray matter volume, MO, and tau/A β ₄₂ yielded highest overall classification accuracy (91%) with 85% sensitivity and 96% specificity

ROI, region of interest; FA, fractional anisotropy; MD, mean diffusivity; DA, axial diffusivity; RD, radial diffusivity; MO, mode of anisotropy; SCI, subjective cognitive impairment; MCI, mild cognitive impairment; AD, Alzheimer’s disease; RAVLT, Rey Auditory Verbal Learning Task; CVLT, California Verbal Learning Test; ADAS-Cog, Alzheimer’s Disease Assessment Scale - Cognitive Subscale; MMSE, Mini-Mental State Examination; CC, corpus callosum; ATR, anterior thalamic radiation; CST, corticospinal tract; ILF, inferior longitudinal fasciculus; SLF, superior longitudinal fasciculus; IFOF, inferior fronto-occipital fasciculus; UF, uncinate fasciculus; ERC, entorhinal cortex; PHC, parahippocampal cortex; RSC, retrosplenial cortex; PCC, posterior cingulate cortex; IPL, inferior parietal lobe; FDG PET, fluorodeoxyglucose positron emission tomography; APOE, apolipoprotein E.