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DTI Analyses and Clinical Applications in Alzheimer's Disease

Kenichi Oishi^{a,*}, Michelle M. Mielke^b, Marilyn Albert^c, Constantine G. Lyketsos^b, and Susumu Mori^{a,d}

^aThe Russell H. Morgan Department of Radiology and Radiological Science, School of Medicine, The Johns Hopkins University Baltimore, MD, USA

^bDepartment of Psychiatry and Behavioral Sciences, School of Medicine, The Johns Hopkins University, Baltimore, MD, USA

^cDepartment of Neurology, School of Medicine, The Johns Hopkins University, Baltimore, MD, USA

^dF.M. Kirby Research Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, MD, USA

Abstract

DTI is one of the most effective MR tools for the investigation of the brain anatomy. In addition to the gray matter, histopathological studies indicate that white matter is also a good target for both the early diagnosis of AD and for monitoring disease progression, which motivates us to use DTI to study AD patients *in vivo*. There are already a large amount of studies reporting significant differences between AD patients and controls, as well as to predict progression of disease in symptomatic non-demented individuals. Application of these findings in clinical practice remains to be demonstrated.

Keywords

Alzheimer's disease; mild cognitive impairment; white matter; diffusion tensor imaging; clinical application

INTRODUCTION: WHAT IS DTI?

Diffusion Tensor Imaging (DTI) is one of the MRI techniques that can measure the thermal motion of water molecules. Water molecules move randomly in all directions if there is no structure that prevents their free motion; this probability distribution is isotropic. In the brain, there are many structures that restrict the free motion of water molecules, such as tightly packed axons [1, 2], that alter the magnitude and shape of the probability distribution. For example, water molecules in white matter tend to diffuse more easily along axonal bundles, leading to anisotropic diffusion. On the other hand, the gray matter often does not have a clear structural alignment, leading to a more isotropic diffusion. We can use this water diffusion property as a probe to infer the brain anatomy. In DTI, we quantify the diffusion property by fitting the measured water diffusion to a simple tensor model with a 3×3 symmetric matrix. In this way, we can quantitatively describe the diffusion properties

using eigenvalues (λ_1 , λ_2 , and λ_3 , describing the extent of anisotropy) and eigenvectors, (v_1 , v_2 , and v_3 , describing the orientation of anisotropy).

Once a tensor is calculated in each pixel, several contrasts can be generated. For example, we can measure the mean diffusivity (MD), which is the average of three eigenvalues: $(\lambda_1 + \lambda_2 + \lambda_3)/3$, indicating the magnitude of overall water diffusion in each pixel (Fig. 1C). We can also measure the degree of diffusion anisotropy. One of the most widely used metrics of diffusion anisotropy is “fractional anisotropy (FA),” which is [3, 4] (Fig. 1D):

$$FA = \sqrt{\frac{1}{2} \frac{\sqrt{((\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2)}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}}$$

This is a convenient index because it is scaled from 0 (isotropic) – 1 (anisotropic). If diffusion is isotropic ($\lambda_1 = \lambda_2 = \lambda_3$), this measure becomes 0. An FA close to 1 indicates high diffusion anisotropy. In addition to these scalar measures, we can also visualize orientation information. A color-coded orientation map of the first eigenvector (v_1) [5, 6] is one method to visualize orientation information, in which red (R), green (G), and blue (B) colors are assigned to right-left, anterior-posterior, and superior-inferior orientations, respectively. In Fig. 1, images created from DTI measurements are compared with conventional MR images. In conventional MRI (Fig. 1A and B), the white matter area looks homogeneous. However, the color-coded orientation map in Fig. 1E contains various colors in the white matter area, which represent the orientation of aligned structures.

DTI is a powerful method by which to identify specific fiber bundles that are affected by diseases. Various pathological conditions alter DTI-derived parameters and we can three-dimensionally map the area(s) that show such alterations. The other important feature of DTI is the ability to parcellate white matter structures. Using the images shown in Fig. 1E, we can identify and study the degeneration of specific white matter structures, such as the cingulum (Fig. 1F). It should be emphasized that, in imaging studies, we can investigate the anatomy of a specific structure only when it is discretely identifiable. Because of the capability to provide detailed anatomical information about the white matter, DTI could be one of the most effective MR tools for the investigation of the white matter anatomy. Although the use of DTI is not restricted to studies of the white matter, the majority of DTI studies are related to the normal or diseased anatomy of the white matter. However, directional information derived from DTI is less useful for investigating gray matter structures, except for several fiber-rich gray matter structures [7–12] and the fetal cortex, with the columnar structures showing clear directionality [13]. For the gray matter analysis, MD is often used to quantify the effects of various diseases.

Although DTI meets the requirements of many basic and clinical research purposes, the two main limitations should be noted. First, water diffusion is an INDIRECT indicator of the underlying neuroanatomy, and there are numerous microscopic structures that may affect the diffusion. Therefore, different histopathological conditions may result in similar alterations of DTI-derived parameters. Second, the diffusion process (1–10 μ m during the 20–100 ms of diffusion time) is averaged over a large voxel volume, with typically 2–3 mm resolution. This leads to the sensitivity of DTI to macroscopic configuration of fiber bundles, such as the mixture of multiple fiber populations with different fiber orientations in a voxel or partial volume effects. Therefore, we cannot immediately conclude whether the source of changes in diffusion lies in cellular level structures or is due to the macroscopic reorganization of fiber structures. There have been several attempts to ameliorate the latter limitation (thus reducing the impact of the macroscopic averaging effect). For example, we can increase the total number of voxels within the brain (= increased image resolution). We

can also extract more parameters from each voxel(= increased intra-voxel information) by using sophisticated non-tensor diffusion analysis methods rather than using a simple tensor approach [14–21]. The application of these new approaches to AD studies could be an important future research endeavor.

Recent technological advancements in both hardware (machine) and software (scan sequence) have greatly facilitated the use of DTI, and broadened the applications much more than was previously possible. The typical scan time required to gather whole brain DTI data using a 3 T scanner is only approximately 5 min, with 30 gradient axes and 2–3 mm cubic resolution. The short scanning time is very important because AD patients have difficulty remembering and following instructions during the scan, and thus, scanning in as short a time as possible is optimal. MRI scanners, equipped with devices for parallel imaging techniques, which are required to gather less-distorted DTI, are now widely available. In addition, modern clinical MRI scanners are equipped with DTI calculation tools, and the calculated images can be visualized in a filmless image-reading system. Thus, it may be possible for the clinician to utilize DTI-derived images as part of the diagnostic evaluation.

WHAT IS THE POTENTIAL OF DTI TO EVALUATE THE AD BRAIN?

Researchers have long been focused on the cortical pathology of Alzheimer's disease (AD), and have primarily used conventional MRI to characterize that pathology. Indeed, the most important pathologic features of AD are the senile plaques and the neurofibrillary tangles found in the cortex, as well as the cortical neuron loss. For instance, the loss of layer III and layer V large pyramidal neurons is seen in cortical association areas [22] and the loss of layer II pyramidal neurons is seen in the entorhinal cortex [23]. Loss of neurons in these areas results in GM atrophy that can be measured on conventional MR images [24, 25]. DTI has also identified altered water diffusivity in the GM. Increased MD was consistently found in the areas with the neurofibrillary pathology of AD [10, 26–30], such as the hippocampus, the entorhinal cortex, the parahippocampal gyrus, the temporo-parietal association cortex, and the posterior cingulate gyrus. Although the exact cause of these changes in DTI measurements are difficult to identify, the fact that the degree of MD increase is more evident in the areas with GM atrophy [26] suggest that neuronal loss [31] is one of the reasons. In addition, several studies indicate that the addition of MD measurements to GM morphometry in the hippocampus and parahippocampal gyrus improved the ability to distinguish an AD group from a control group [26, 28], which suggests the possibility of the existence of additional pathologies sensitively detected by DTI over conventional MRI.

In addition to the GM pathology, increasing evidence shows that neuronal degeneration begins in the neuronal periphery, such as in the axons and dendrites [32–35]. White matter atrophy also could be an indirect indicator of nerve cell loss, since the volume of the cell body is much smaller than its myelinated fiber [36]. Consistently, pathological studies have revealed various types of white matter alterations in AD, such as altered myelin and oligodendrocytes, axonal degeneration, and vascular pathologies [37–39]. Therefore, white matter seems to be a good target for both the early diagnosis of AD and for monitoring disease progression, which motivates us to use DTI to study AD patients *in vivo*. Indeed, DTI has identified WM alterations in many WM tracts and superficially located WM areas. A meta-analysis of 41 DTI studies, published from 2002 to 2010 [40], indicates that the white matter abnormality of AD is widespread through the entire WM area. The limbic fibers, in particular, which have a direct connection to the medial temporal lobe, were repeatedly reported as the vulnerable WM structures [29, 41–49]. WM damage quantified by DTI has been correlated with atrophy in the anatomically connected GM areas in AD patients, but the correlation was not clear in patients with amnesic MCI in most of the WM tracts [50]. These findings suggest that primary WM damage that precedes GM atrophy may

possibly exists in the pre-diagnostic phase of AD, but the WM damage seen in clinically diagnosed AD patients may reflect secondary degenerative processes after neuronal loss. An attempt to identify the earliest DTI-detectable WM abnormality using an AD mouse model identified a reduced first eigenvalue (λ_1 , parallel diffusion) in the WM, suggesting that the earliest anatomical change is axonal damage [51]. However, in contrast to this finding, an increased first eigenvalue, as well as increased MD, is often found in *in vivo* DTI scans of human AD patients [48, 52, 53]. Again, we would like to emphasize that, because of the oversimplification of the anatomical information during the multiple steps of DTI acquisition and calculation, interpretation of the DTI-derived parameters is not straightforward. DTI is useful for localizing and quantifying the anatomical abnormalities, but apparently not adequate to investigate the histopathological background of the diseases.

STRATEGIES TO INVESTIGATE THE PATHOLOGICAL FEATURES OF AD USING DTI

There are many important questions we want to answer through DTI analysis of AD. For example, what are the AD-specific features that can be observed with DTI? Can these features be observed in persons with mild cognitive impairment, thought to be the earliest symptomatic stage of AD, or even in the presymptomatic phase? How does DTI reflect or predict the progression of AD? Are there correlations between DTI and cognitive functions? To answer these questions, the quantification of DTI parameters is the first important step.

Several issues arise when we quantify DTI results. First, regions of interest (ROI) should be defined to measure DTI-derived parameters, such as FA or MD. The smallest ROI we can define is a single voxel, and the maximum ROI is the whole brain. The localization information is maximized when the smallest ROI (single voxel) is adopted, but the statistical power is lost because of the low signal-to-noise ratio and the difficulty of identifying the corresponding voxel across subjects. The statistical power is maximized when the size and shape of the ROI exactly follow pathological locations. If we have an *a priori* hypothesis about the locations of the pathologic tissues, we could pre-define the size and shape of ROIs according to the hypothesis. If we hypothesize that the pathology is seen in specific fiber tracts, we can use tractography to draw ROIs (tract-specific analysis, see, eg. [54, 55]). ROI-based DTI analyses have been widely used for AD studies and have successfully identified reduced FA or increased MD, or both, within the splenium of the corpus callosum [47, 56–59], the cingulum bundle [11, 27, 42, 60–62], and the fornix [43, 44]. However, this approach is hypothesis-dependent, and the majority of the brain area remains unexamined, which makes it difficult to evaluate the localization specificity.

Second, we need to decide whether we should explore the whole brain or limited areas of the brain. Whole brain analysis is ideal for evaluating the regional specificity of the findings. However, drawing a number of ROIs manually that would cover the whole brain is a tremendous effort. Thus, automated method, such as those based on image normalization (transformation), are typically used. After transforming images to a common template space (atlas), we can even quantify the image at the voxel level (voxel-based analysis). Although image normalization has been widely used to analyze conventional MRI contrasts, the transformation of DTI poses a unique challenge. DTI data consists of tensor fields (as opposed to scalar fields for conventional MRI), and white matter tracts revealed by the tensor field must be registered after normalization [63, 64]. To avoid false-positive and false-negative findings, the accuracy of the registration is a crucial requirement. Accuracy is especially critical when dealing with small structures, string-like structures, and sheet-like structures, which are often found in the white matter. In these structures, only a few pixel gaps between the subject and template image will cause significant misregistration.

Various non-linear transformation methods have been proposed for DTI analyses, such as tensor-to-tensor matching [65–69], scalar measures matching [69, 70], or other DTI-derived information, as well as some combination of these methods [71–75]. Transformation methods based on non-DTI contrasts have also been applied to transform DTI, with high registration accuracy [64, 76].

To perform whole brain analysis with no *a priori* hypothesis, voxel-based analysis is one of the most widely used approaches [29, 52, 77–79]. Fig. 2A is an example of such an analysis, designed to find brain areas with AD-specific white matter alterations. This analysis indicates significant FA reduction in the fornix, the splenium of the corpus callosum, as well as several small areas in the superficial white matter in the frontal lobe. Although this result seems to be consistent with previous ROI-based investigations, we must interpret the results with great caution, since this approach tends to miss the widely distributed regions that show only small changes in the parameters [80]. One of the attempts to overcome such limitations is to apply multivariate models [81], such principal component analysis (PCA) [78] or canonical correlation analysis (CCA) [82], which have already been applied to DTI analysis of AD. Other methods include voxel grouping. For example, if we hypothesize that the white matter pathology of AD is tract-specific or structure-specific, especially in the early stages, we may apply tract-based voxel grouping, such as Tract-Based Spatial Statistics (TBSS) [83], or structure-based voxel grouping, such as atlas-based analysis (ABA) [84]. Indeed, TBSS has already revealed important findings, such as deteriorations in the limbic fibers, the fronto-occipital fasciculi, the inferior longitudinal fasciculi, and the forceps major, even in the early-symptomatic patients or in participants at high risk for developing AD [45, 53, 85–90]. ABA is a method that uses a set of pre-defined ROIs, called a parcellation map (Fig. 3), which covers the entire brain, in the atlas space. The parcellation map can be overlaid on the images normalized to the atlas space to measure DTI-derived parameters (eg., FA or MD) in each ROI (parcel), or can be transformed to each image to measure DTI-derived parameters as well as the volumes of each ROI. One additional feature that sets the ABA apart from TBSS is that ABA provides morphometric (volume) information about brain atrophy in the volume of each parcel. Our initial results from ABA (Fig. 2B) indicate a higher sensitivity for ABA in detecting changes in FA, especially in the areas with widely distributed small FA reductions, compared to the voxel-based analysis. The drawback of this approach is that if the region is limited in the small portion of the structure (parcel), the effect is diluted and sensitivity is decreased.

APPLICATION OF DTI TO AD RESEARCH AND CLINICAL PRACTICE

In the previous section, we discussed the detection of AD-specific pathology using DTI. There are already a large amount of studies reporting structure-specific brain abnormalities even in the very early stages of AD. In this section, we would like to discuss the application of DTI to studies of AD from the following two points of views.

Functional correlation

One of the important questions after the identification and quantification of structure-specific brain abnormalities is whether the degree of abnormalities correlates with cognitive functions. For example, even if we find reduced FA in a specific brain area, if the observed FA reduction does not correlate with the cognitive decline, the finding is not valuable as a marker to visualize the disease progression or to see the effects of therapeutic interventions. Research has identified the disruption of global WM [56], the frontal WM [91], or specific WM tracts, including the fornix, the cingulum, the cingulate WM, the genu and splenium of the corpus callosum, and the perforant pathway, which are related to global cognitive decline [44, 47, 92, 93]. Less is known about the tract or structure-specific contribution of cognitive domains, although several researchers have discovered a contribution by the

temporal lobe WM [94, 95] and the posterior cingulate WM [10] to delayed recall, the frontal WM to executive function [95], and the posterior part of the corpus callosum to verbal fluency and figural memory [96]. However, the localization specificity of these findings has not been established, since these studies are based on a limited number of ROIs selected by an *a priori* hypothesis. Unfortunately, the anatomical background of the behavioral and psychiatric symptoms of AD, which are the most challenging and distressing effects of the disease, has not been fully explored.

Clinical application

AD studies typically adopt cognitively normal participants as a control group to identify AD-specific features. However, in the clinical situation, identification of AD-specific DTI markers would be of great value to differentiate it from other neurodegenerative dementias, such as frontotemporal dementia (FTD) and dementia with Lewy bodies (DLB). There are studies reporting more prominent DTI-detectable WM damage, especially in the frontal WM and the genu of the corpus callosum, in FTD than in AD [52, 82]. Although DTI findings about the DLB are controversial [26, 28, 97, 98], elevated MD without atrophy in the amygdala was proposed as a potential marker to differentiate DLB from AD [26]. However, the sensitivity and the specificity of the DTI-based indices to differentiate AD from these neurodegenerative dementias is still not established.

In summary, many of the scientific findings, to date, are not readily transferrable to clinical practice, even though the findings are important for understanding of the pathology of AD. A multi-center research project, seeking imaging biomarkers for AD, the Alzheimer's Disease Neuroimaging Initiative (ADNI, ADNI-GO) [99], and the upcoming ADNI-2, did not adopt DTI as a core protocol because of the uncertain long-term test-retest precision, questionable relevance to clinical trials, and absence of an established calibration method [100], all of which should be thoroughly investigated before clinical application.

CONCLUSIONS

DTI measures have been used to demonstrate significant differences between AD patients and controls, as well as to predict progression of disease in symptomatic non-demented individuals. Application of these findings in clinical practice remains to be demonstrated.

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Fig. 1.

Comparison of conventional T1- (A) and T2- (B) weighted images, and DTI-derived mean diffusivity (MD) (C), fractional anisotropy (FA) (D), and color-coded orientation (E) maps of cognitively normal 72-year-old woman (upper row) and 70-year-old woman with Alzheimer's disease. The areas surrounded by yellow rectangles in (E) are magnified and shown in (F) [left (F-1): from the cognitively normal woman; right (F-2): the Alzheimer's disease patient]. The yellow arrows indicate the cingulum hippocampal part.

Fig. 2. Statistical group comparison of FA after image normalization. Nineteen patients with Alzheimer's disease and 22 age-matched cognitively normal participants were compared, and the areas with significance (t -test, $p < 0.05$ after correction for multiple comparisons using a false discovery rate) were shown with color scaling overlaid on the averaged FA map (A): Results from voxel-based analysis. (B): Results from atlas-based analysis. See Fig. 3. for the parcellation map used in this atlas-based analysis. CC, corpus callosum; SS, sagittal stratum; WM, white matter.

Fig. 3.

Atlas-based analysis. The original FA map from a patient with Alzheimer's disease (A) was normalized to the atlas space (B). The atlas used as the template is shown in (C). After image normalization, pre-defined three-dimensional ROIs (color-contours, called a parcellation map) in the atlas space enables researchers to measure the FA value of each parcel. This parcellation map can be inversely transformed to the original space to measure the volume of each parcel, as well as to measure the FA value of each parcel without normalization-related artifacts (eg., effects of interpolation after normalization).