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Review Article

Diffusion tensor imaging and aging – a review

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ABSTRACT: Diffusion-tensor imaging (DTI) non-invasively provides maps of microscopic structural information of oriented tissue *in vivo*, which is finding utility in studies of the aging population. In contrast to the white matter maturation process, investigators have observed significant declines in the white matter ordering in normal as well as in abnormal aging. These studies suggest that water proton non-random, anisotropic diffusion measured by DTI is highly sensitive to otherwise subtle disease processes not normally seen with conventional MRI tissue contrast mechanisms. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: diffusion tensor imaging; DTI; diffusion-weighted imaging; DWI; MRI

INTRODUCTION

Diffusion-tensor imaging (DTI) is rapidly becoming an established technique that non-invasively maps microscopic structural information of oriented tissue *in vivo*. To do this, DTI maps water proton molecular diffusion; this is exquisitely sensitive to the surrounding tissue configuration, making this particularly useful in monitoring brain abnormalities. While DTI is being widely used to demonstrate subtle abnormalities in a variety of diseases, including multiple sclerosis and schizophrenia, the extent of information offered by a routine DTI exam extends beyond mean diffusivity measures, such as the magnitude of the apparent diffusion coefficient, which is often a measure of overall water content, and anisotropy indices, which reflect axonal restrictions and myelin content. Diffusion tensor imaging measures the amount of non-randomness (anisotropy) of water diffusion within tissues, which is function of the degree to which directionally ordered tissues are either maturing or losing their normal integrity. Much of the early excitement in the use of DTI came from the focus of several papers on the focal increases in the diffusion anisotropy in white matter that occur during the myelination process,[1,2] making DTI an essential assessment of brain maturation in children. Pronounced, age-related increases in white matter continue during childhood and adolescence; white matter increases its overall volume and becomes more myelinated in a region-specific fashion. We expect that future studies will focus on the concurrent use of experimental behavioral test-batteries, with structural MR imaging, to study developmental changes in structure–function relationships.

In contrast to the maturation studies, the use of DTI in the aging population has observed significant declines in the white matter ordering in normal as well as in abnormal aging. Several papers have now appeared on the topic of DTI and aging,[3–5] suggesting that DTI can significantly add to our knowledge of the aging brain. The importance of a full characterization of the patterns of white matter microstructure deterioration that occur in normal aging would lead to an understanding of the pathophysiology of normal cognitive decline and would be a proper background for interpreting observed changes in neurodegenerative diseases of the aged beyond those of normal aging.

MRI AND AGING

The ability to perform working memory tasks together with rapid processing becomes increasingly difficult with increases in age.[6,7] However, identification of the neural components involved in age-related functional decreases has yet to be performed. Even though significant

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Abbreviations used: AC-PC, anterior and posterior commissures line; AD, Alzheimer's dementia; ADC, apparent diffusion coefficient; CSF, cerebrospinal fluid; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; EPI, echo planar imaging; FA, fractional anisotropy; FLAIR, fluid attenuation inversion recovery (an MRI sequence); FOV, field of view; FSE, fast spin-echo (an MRI sequence); IQ, intelligence quotient; MRI, magnetic resonance imaging; RA, relative anisotropy; WM, white matter.

shrinkage in cortical gray matter volume occurs through adulthood,[8] primarily occurring in frontal regions,[9] MR spectroscopy and spectroscopic imaging suggest that gray matter remains viable and relatively resistant to aging, and that concentrations of gray matter metabolites (such as n-acetylaspartate) are stable with increasing age.[10] This is supported by reports that, while gray matter atrophy is readily detectable in the frontal and temporal lobes, there is no change in the total neuron population.[11]

White matter, in contrast to gray, shows little age-related volume alteration, as seen from high-resolution conventional MR imaging studies.[8] Neuropathology has observed substantial age-related decreases or disturbances in the microstructure of white matter evidenced as demyelination, deterioration and axonal loss.[12] Other studies have found non-specific MR imaging hyperintensities in deep white matter that are predictive of psychomotor disturbances and performance declines occurring in aged populations.[13] It appears then that, while the cortical connections of the network may be intact, the overall integrity of the brain's infrastructure (the white matter tracts) appears to deteriorate over time. White matter atrophy is most likely due to a decrease in the number (and perhaps density) of myelinated fibers, which is accompanied by an increase in extracellular space.[14] It is thought that it is the focal white matter losses of myelinated axons and gliosis that give rise to the patchy hyperintensities that are identifiable on conventional MR images.[13] In typical findings in the aged, conventional MRI studies show volume losses, enlargement of the lateral ventricles, patchy areas of abnormal signal intensity within the white matter[15] and basal ganglia, and progressive hypointensity correlating with iron deposition in the globus pallidus and putamen.[16] The volume decreases are typically accounted for by a decline in gray matter rather than white matter volumes, which change very little up to about 70 years, but then decline at about 2% per decade.[17,18]

It is noteworthy that measured WM volumes determined from conventional MRI most likely reflect only the macrostructure within the millimeter-sized voxels from T_2- or proton density-weighted images and may not be sensitive to age-related degradation of the microstructure of white matter which is typically documented from postmortem histopathological slices and stains. However, much of the discrepancy between *in vivo* MRI and postmortem WM histological studies in aging could be due to fixation artifacts and the differences in microscopic tissue vs MR-sensitive tissue water environments.

DTI AND AGING

The advent of *in vivo* diffusion tensor imaging allows direct measurement of several unique aspects of the bulk tissue microstructure by virtue of mapping water proton motions within the tissue microenvironment. DTI yields a series of quantitative measures that reflects the integrity of white matter fiber tracts. While the bulk translational motion of an ensemble of water molecules in biological systems is characterized by Brownian motion, DTI measures the magnitude of this motion (the ADC) along any number of fixed and definable directions, making the ADC sensitive to the pathways of water translation. Thus, when the water molecules are unconstrained, the direction of motion is random and is described over time as an isotropic Gaussian distribution of pathlengths. In contrast to random (isotopic) proton motions in CSF, brain tissue (especially white matter) has microstructure forming physical boundaries or barriers that restrict or hinder the normally random Brownian motion of water protons. The resulting water diffusion is then constrained with differing diffusion rates along and across these series of barriers resulting in nonrandom (anisotropic) diffusion. Because white matter tracts are highly organized as macrostructured fiber bundles, microscopically ordered axons and microtubules, voxels containing white matter show a graded hindering the random diffusion of water and an orientation-dependent ADC which depends on the direction of the specific fiber tracts observed.

We now know that the degree to which white matter is ordered will have a direct and significant impact on the measured ADC values along the various axes. Within the constraints of in-plane resolution, some regions of white matter normally should have very high FA, while others should have considerably lower fractional anisotropy (FA) even though they are fully volumed, and this probably represents architectural differences in fiber tract organization at the intravoxel level, i.e. intact fibers crossing within a voxel. As these first studies in aging demonstrate, the normally homogeneously ordered corpus callosum has a high measured FA, but the crossing white matter tracts leading to the frontal lobes exhibit lower FA than the corpus callosum. These studies also make compelling arguments that neurodegenerative processes that cause changes at the microstructural level, such as the rate of myelination or demyelination, degradation of microtubules, or loss of axonal structure are likely to cause a significant measurable decrease in FA.

Early clinical studies using DTI concentrated on the early and rapid increases in fractional anisotropy seen in neonatal and young childhood development.[1,2] Neonates typically show significantly higher ADC values with lower FA numbers compared with adults; these values becomes more adult-like within about 6 months after birth, after which there is a marked decrease in the rate of FA increases in most cerebral white matter tissues.[19] In a very early adult study, Peled *et al.*[20] used line-scan diffusion imaging (acquiring slices in three orthogonal diffusion planes) to measure the three orthogonal diffusion ADC values in 24 men and women, varying

in ages from 18 to 44. Although not a strict tensor study in that only three orthogonal axes were measured, the investigators found greater orientation alignment in the anterior limb of the internal capsule on the right than on the left hemisphere. More recently, Klingberg *et al.*[21] found lower fractional anisotropy (FA) in the frontal white matter in seven children (mean age, 10 years) than in five young adults (mean age, 27 years), and the right frontal area had higher values than the left. These studies add to the conviction that the measured diffusion anisotropy is directly related to the development of myelination.

Instrumentation issues continue to complicate any study comparing DTI exams across several groups or populations of patients or volunteers. While the use of echo planar imaging (EPI) for DTI has proven to be practical for clinical applications because it allows acquisition of multislice data in minutes, it suffers from inherent geometric distortions from magnetic field inhomogeneities due to the rapid sampling of the gradient echo train. While this distortion is tolerable for many clinical applications, it is a serious problem for multiple quantitative studies that are required to map brain diffusion characteristics based on structurally identified, specific anatomic regions of interest, identified from other less-susceptibility prone sequences such as FSE. In particular, in order to determine the FA of a given white matter structure, it is preferable to identify the structure on nondistorted images with high gray–white tissue conspicuity (such as fast spin echo, FSE, or inversion-recovery spin-echo sequences) and co-register these locations on FA images. This usually involves the co-registration of rapidly acquired but low resolution EPI exams with highly-detailed conventional MRI images. The issue of geometric distortion now becomes very important when co-registration is required. The Pfefferbaum paper[3] implements an approach in which regions of interest defined on dual-echo high-resolution FSE images were co-registered with EPI-based FA maps after the set of EPI images which are obtained without diffusion weighting ($b = 0$) are then spatially warped to the long-echo T_2-weighted FSE images after which this warping function is applied to the FA images.[3]

Another complicating factor is that intravoxel fiber incoherence (such as fiber crossing or fiber tangles) diminishes the measured FA number within a given voxel. The conventional six gradient direction scheme models proton diffusion as a symmetrical ellipsoid with three principal axes and cannot adequately handle more complicated patterns of diffusion resulting from fiber paths crossing within a voxel. For this, recent studies have begun analysis of the optimal choice of multiple gradient direction schemes in order to minimize any intravoxel coherence effects.[22,23]

Any model can, however, examine the degree to which the diffusion in adjacent voxels has a common principal orientation. This 'intervoxel coherence' can be mapped using the orientation of the largest eigenvector of the tensor. This is useful in that it represents a measure of fiber coherence at the voxel level beyond that of the intravoxel measurement. The calculation of intervoxel coherence is based on a determination of the similarity of orientation of adjacent voxels. In other words, if the proton diffusion vector within a given voxel has the same orientation as corresponding vectors from the nearest neighboring voxels, that voxel has a high intervoxel coherence. Because of this property, we anticipate that these measures of intervoxel coherence will become important as work in 'fiber-tracking' evolves. In the Pfefferbaum paper,[3] the investigators implemented a measure of intervoxel coherence, using information from the eigenvector corresponding to the largest eigenvalue (λ_1) from the tensor computations similar to maps of the degree of 'alignment' between two neighboring vectors.[3] While not completely independent of FA, images of intervoxel coherence could conceivably highlight structures, since the coherence should be higher in white matter than in gray matter.

In the first full paper using DTI to study the specific effects of aging on measured anisotropy values, Pfefferbaum *et al.* used measured intravoxel FA values as well as intervoxel coherence values, to provide a qualitative assessment of age-related changes in white matter microstructure.[3] In particular, this study sought to measure the different degrees of anisotropy, dependent on the homogeneity of the fiber structures known from histological exams. They hypothesized that, even in regions of fully volumed white matter, FA would decline with age in normal, healthy individuals. In contrast to FA, it was unknown whether the intervoxel coherence would show an age-related decline in neurologically healthy individuals. The age range is this group of 31 normal, healthy men was 23–76 years. Following a series of MRI scout images to determine the anterior and posterior commissures (AC-PC) line, and a fast spin-echo (FSE) sequence for high-resolution anatomy, DTI was performed using a single shot spin-echo EPI technique acquiring eighteen 5/0 mm thick slices, $TR/TE = 6000/106$ ms, matrices of 128×128 over a 24 cm FOV. The slice locations were chosen from the FSE exam. The amplitude of the diffusion-sensitizing gradients was 1.4 Gauss cm^{-1} with 32 ms duration and 34 ms separation. This resulted in a total b-value of 860 s mm^{-2}. In this particular DTI study, ADC was measured along six non-collinear directions: $(x, y, z) = [(1, 1, 0), (0, 1, 1), (1, 0, 1), (-1, 1, 0), (0, -1, 1), (1, 0, -1)]$. For each gradient direction, four images were acquired and averaged. Two images with no diffusion weighting ($b = 0$ s mm^{-2}) were acquired with and without a FLAIR inversion recovery pulse to better delineate brain surfaces. The DTI acquisition time was less than 3 min.

The study compared FA and intervoxel coherence across five ROIs: genu, splenium, centrum semiovale, left + right frontal pericallosal regions, and left + right

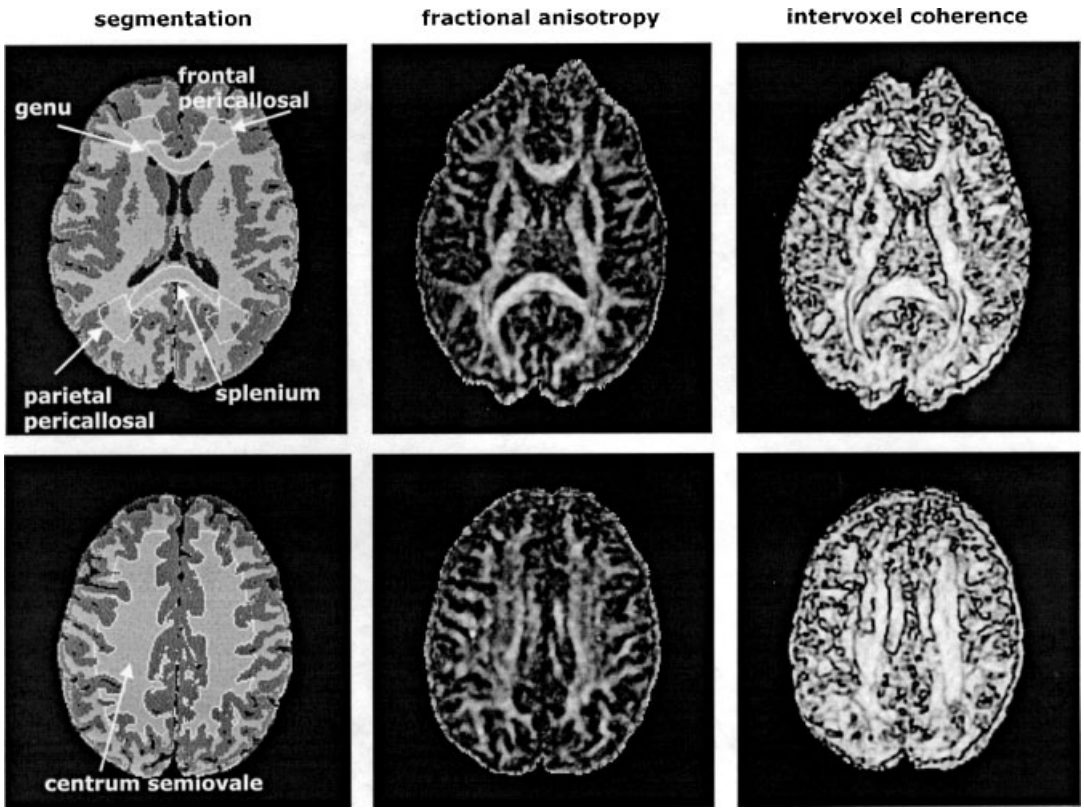

Figure 1. Segmented axial images with geometric identification of regions of interest: genu and splenium of corpus callosum and centrum semiovale. Each region was measured on three contiguous slices. (Figure printed with permission from Sullivan *et al.*[4])

parietal pericallosal regions. The measured FA values were found to have a significant regional variation where differences between each regional pairing was significant and progressed from largest to smallest FA as follows: splenium, genu, parietal pericallosal regions, centrum semiovale, and frontal pericallosal regions. For all seven ROIs, median FA was negatively correlated with age. These correlations were significant in the genu, centrum semiovale, and left and right frontal and parietal pericallosal areas but were not significant in the splenium. Further, there was no evidence of asymmetry in pericallosal FA. In contrast to FA (intravoxel coherence), the intervoxel coherence was not significantly correlated with age in six of the seven regions examined. The exception was the genu, in which coherence unexpectedly increased with age. Further, none of the regions showed significant correlations between median FA and coherence.

They observed significant age-related declines in median FA in anatomically determined volumes of densely packed white matter fibers. In particular, the structures showing the greatest FA declines were the genu of the corpus callosum and the centrum semiovale. In addition to regions of the corpus callosum, the frontal and parietal pericallosal white matter also showed considerable declines in anisotropy with age and again with no evidence of hemispheric asymmetry. In addition to this decline in the median FA in most regions, there was also some evidence for within-region increased FA in homogeneity with age in the centrum semiovale and posterior pericallosal white matter.

As anticipated, they found that the highest FA was present in the regions with the most homogeneously oriented fibers systems, namely, the genu and splenium of the corpus callosum. By contrast, the centrum semiovale and the pericallosal regions are characterized by crossing fiber systems, traversing all three axes, and consequently have considerably lower FA and intervoxel coherence than did the callosal tracts. These differences in intravoxel and intervoxel coherence, observed in normal, healthy individuals, indicate that lower indices of fiber coherence are not necessarily representative of abnormality or degeneration, but rather can be characteristic of fundamental differences in normal white matter microstructure.

The Pfefferbaum paper concluded that FA, as a measure of intravoxel coherence, reflects the integrity of microstructure, such as myelination, microtubule and microfiber condition and integrity. The opposite effect, that is a decrease in FA, with aging may be indicative of mild demyelination and loss of myelinated axons observed in postmortem MRI as well as in histological

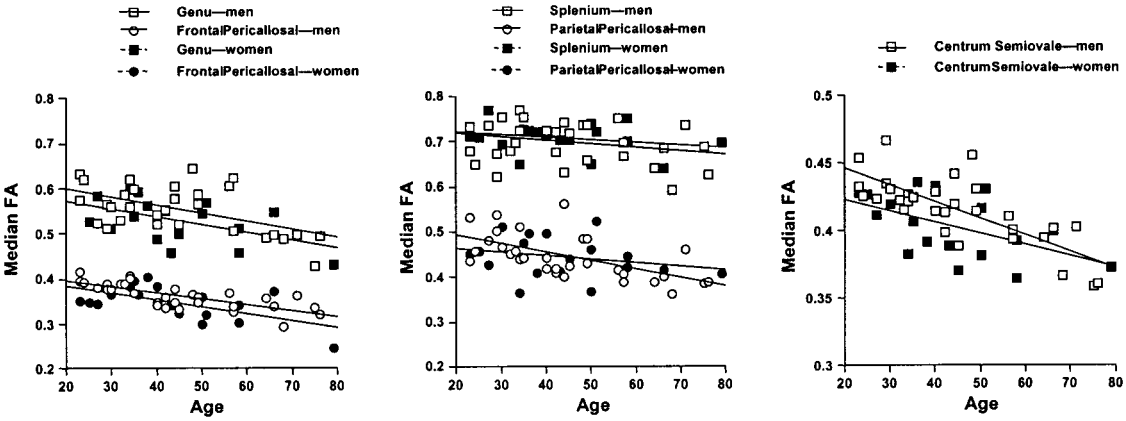

Figure 2. Correlations between DTI regional measures of FA and age in men and women separately. (Figure printed with permission from Sullivan *et al.*[4])

studies of normal aging.[24] The declines observed in intravoxel coherence with age may reflect tissue status that could result in normal age-related functional decreases. This would be in contrast to fiber disconnection, which could be reflected in disruption of intervoxel coherence and could result in more severe, discrete functional abnormalities.

In a related study using similar MRI and DTI techniques, Sullivan, *et al.*[4] measured FA between a group of 31 neuropsychologically normal men vs a group of 18 women. Within five similar regions of interest, they found no significant gender or regional differences in the adult age ranges of 23–79 years (Figures 1 and 2). However, they did find small but statistically significant FA differences between every pair of the identified regions, with men and women showing similar patterns of FA magnitudes. In correlations between white matter coherence and age, they found negative correlations between FA with age in both men and women, where FA declined with age, as expected. Both men and women exhibited similar patterns of regional FA differences in white matter intravoxel and intervoxel coherence. The greatest coherence was measured in the corpus callosum where fibers have one primary orientation, less coherence was measured in the centrum semiovale where fibers cross from different angles, and the lowest coherence was found in the pericallosal tissues were fibers weave and interstitial fluids commonly pool. Again, the fractional anisotropy in the genu of the corpus callosum showed a deeper decline over age than did the splenium. The investigators reasoned that, with increasing age, myelinated fibers, particularly those greater than 1 mm in diameter, decline in number in the corpus callosum.

This study also made a significant contribution to the future potential of DTI by correlating white matter intravoxel coherence measured from FA with neuromotor performance exams using tests of gait and balance in these groups. Surprisingly, scores from a finger tapping test correlated with FA in the splenium and in the parietal pericallosal regions. For both of these regions, FA correlated better with task performance than did age. This paper is significant in that it provides one of the first glimpses of *in vivo* evidence for age-related microstructural deterioration measured by FA of regional white matter coherence in both adult men and women in addition to the idea that measured FA values could correlate with motor tasks. This study is the first to report significant brain FA relationships with behavior in normal aging, in subjects not marked with discrete observable lesions. They go on to conclude that the integrity of the normal aging brain may be slowly eroded by deterioration of the required conductivity to form routine tasks. This study lays the foundation for further correlations between regional white matter microstructure and specific cognitive and motor functions with the long-term goal that DTI may provide unique critical outcome measures for evaluating therapy strategies aimed at improving these age-related functional decreases.

In a study published early in 2001, Nusbaum *et al.*[5] sought to investigate microstructural changes of cerebral white matter during normal aging using DTI to analyze alterations in white matter structure. Regional changes in white matter relative anisotropy (RA) with normal aging were measured and analyzed by using whole-brain apparent diffusion coefficient (ADC) histograms. Their original hypothesis was that the relative anisotropy would show regional changes and that quantitative ADC histograms might serve as a method to document global cerebral parenchymal changes in normal aging. Twenty volunteers (seven women and 13 men, 20–91 years old) were studied with a DTI exam similar to the Pfefferbaum study above. The Nusbaum study defined their measurable RA as the magnitude of the anisotropic part of the ADC divided by the magnitude of the isotropic part of ADC.[5] Areas with significant RA declines with age were identified in the frontal white matter, genu and splenium of the corpus callosum, and in the parietal and occipital

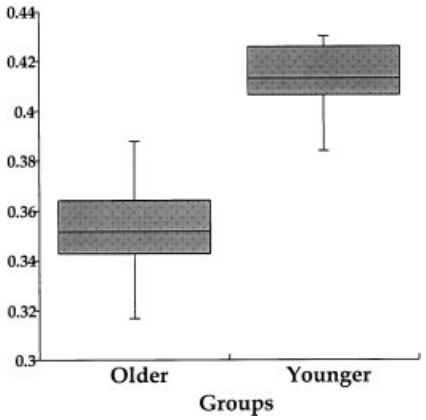

Figure 3. Mean values of FA (vertical axis) as a function of older and younger age groups. There was a significant decrease in whole brain, atrophy corrected, fractional anisotropy in the aged group with basically no overlap between young and old. Figure reproduced by permission of Stebbins *et al.*

periventricular white matter. However, surprisingly, statistically significant increases in RA were also seen in the internal capsules bilaterally and diffusely at the periphery of the brain, notably at brain–CSF interfaces, although they caution that these observed increases with age require more study. The average brain ADC was significantly correlated to subject's age ($r = 0.735$; $P = 0.0002$) using linear regression analyses, with the older subjects as a group (those older than 55) showing a higher average brain ADC relative to younger subjects (less than 55). The investigators also reported that the peak height of the ADC histograms was inversely correlated to subject's age ($r = -0.656$; $P = 0.0017$) with peak heights of ADC histograms was significantly lower for the older group than for the younger group. They observed that this study found both regional and global changes in brain diffusion accompanying normal aging that were present despite the absence of white matter T_2-weighted hyperintensities.

They conclude that while a highly significant and selective decline in the total volume of white matter is seen at autopsy and by MR imaging in aging humans, observed white matter hyperintensities on MR images[24] do not clearly correspond with decreases of white matter volume with age.[25,26] Cortical cholinergic nerve fibers showing age-related changes[27] have been found in the cerebral cortex, suggesting that atrophy of the white matter may be due to a decrease in the number of nerve fibers. Nusbaum *et al.* suggest that there is data to indicate that a more diffuse process in white matter may be taking place that is not necessarily confined to regions of abnormal signal intensity on conventional MR images. Correlation of the observed regional decreases in diffusion anisotropy in the genu and splenium of the corpus callosum with published findings in a histological

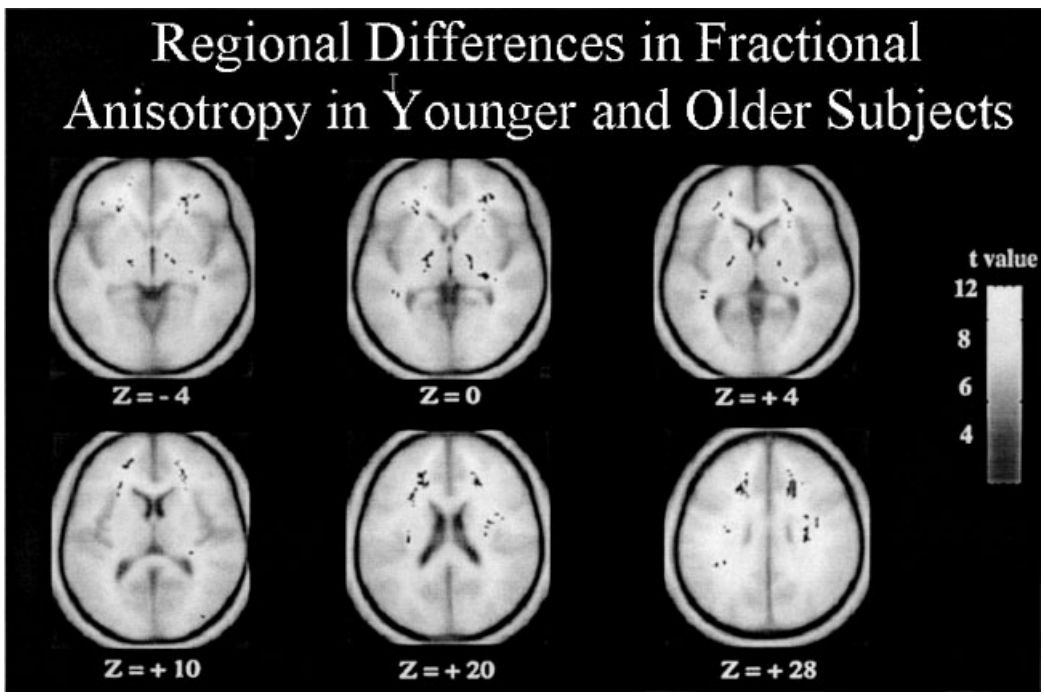

Figure 4. Highlighted regions where FA was significantly reduced in healthy aging. These areas were significantly different on a voxel by voxel basis at the $p < 0.001$ level corrected for multiple comparisons at the cluster level. Decreased FA was evident in the superior longitudinal fasiculus, but mostly in the frontal white matter fields, and the posterior limb of the internal capsule. There were no regions in which the younger group evidenced decreased anisotropy in comparison to the older group. Figure reproduced by permission of Stebbins, *et al.*

study[28] found a loss of total nerve fiber area accompanied by an increased extracellular space with increasing age in the corpus callosum. Also noted was an interesting paper by Tang *et al.*[29] reporting age-correlated declines in the total volume of white matter, total volume of myelinated fibers, and total length of myelinated fibers.

In a series of studies comparing DTI-observed changes in normal aging compared to the changes seen in suspected cases of AD, Stebbins *et al.*[30–32] examined frontal-lobe FA in selected regions-of-interest (corrected for atrophic differences) in 10 younger (mean age 29 years) and 10 older (mean age 80 years) right-handed healthy participants (Figures 3 and 4). Participants were group-matched for education and pre-morbid IQ. Both groups were highly and equivalently educated, of intact mental status as indicated by the Mini Mental Status scores and of equivalent estimated intelligence. The groups differed significantly on measures of reaction time, processing speed as measured by the Symbol Digit Modalities Test, and reasoning performance as measured by the Raven's Progressive Matrices Test with older persons scoring worse than the younger. Both processing speed and reasoning abilities appear to be important components to executive and working memory processes—processes adversely affected by aging.

DTI was performed using a diffusion weighted single-shot spin-echo echo-planar sequence using the anatomical slice prescription from a high resolution FSE series. The DTI data were processed to provide fractional anisotropy (FA) with the group DTI data analyses performed using SPM'99. Immediately before scanning, each subject's reasoning performance was measured. The investigators found that the frontal FA and other regions was significantly reduced in older compared to younger participants ($p < 0.0001$; Figs 3 and 4). The authors suggested that the less organized diffusion in the aged group's WM and greater organization of the diffusion in the younger group's WM, providing a proxy measure for WM integrity.

When the investigators then correlated the measured FA with cognitive skills, the processing speed and reasoning performance were significantly correlated with frontal FA (both $p < 0.0001$) while other cognitive parameters such as mental status, education and pre-morbid IQ did not significantly correlate with frontal FA.

In a separate but related study,[31] Urresta *et al.* from the same group examined alterations in FA in Alzheimer's disease (AD). Participants consisted of 10 healthy older right-handed subjects and 10 patients with a diagnosis of probable AD. In those patients with suspected AD, the measured FA was significantly decreased ($p < 0.05$) in white matter areas corresponding bilaterally to the frontal lobes, the superior longitudinal fasciculus and the temporal stem. Compared with the effects of normal aging on white matter integrity, these results show a further disease-induced deterioration in the microstructure of frontal and temporal lobe white matter, but not in the subcortical white matter tracts.

The investigators concluded that decreases in frontal white matter microstructural integrity measured by DTI FA values occur in older participants independent of atrophic changes. The correlation with reasoning performance supports a role for frontal white matter integrity in this ability.

The issue of white matter integrity in AD has also been examined by Rose *et al.*[33] DTI was used to compare the integrity of several white matter fiber tracts in patients with probable Alzheimer's disease. Relative to normal controls, patients with probable Alzheimer's disease showed a highly significant reduction in the integrity of tracts such as the splenium of the corpus callosum, superior longitudinal fasciculus, and cingulum relative to the unchanged pyramidal tracts. This important finding is consistent with a global cognitive decline in Alzheimer's disease and argues for continued research into DTI techniques such as fiber tracking.[34]

CONCLUSION

The few published studies focusing on normal aging and the observed changes in diffusion-weighted MRI find significant changes in regional and fractional anisotropy occurring in the corpus callosum, internal capsules and frontal, parietal and occipital white matter with normal aging, despite a normal appearance on conventional T_1-, T_2- or proton-density-weighted MR images. As one would expect from examination of these tissues, the highest measured FA was present in the regions with the most homogeneously oriented fibers systems, namely, the genu and splenium of the corpus callosum. Sullivan *et al.*[4] adds evidence that the deterioration of regional white matter coherence occurs in both men and women, with evidence for steeper decline in frontal than parietal regions, a finding supported by Pfefferbaum *et al.*[3]

The declines in these measured anisotropic values (FA, RA, etc.) are most likely a reflection of the underlying microstructural changes found in normal aging, which include a loss of myelin and axonal fibers and an increase in extracellular space, suggested explanations corroborated by histological studies. Regardless of precise microstructural correlates, these studies suggest that the orientational dependence of water proton diffusion measured by DTI is highly sensitive to otherwise subtle disease processes not normally seen with conventional MRI tissue contrast mechanisms. They also imply that it is the changes in organization of white matter pathways that occur with normal aging that are being observed with DTI. The use of DTI, in combination with quantitative structural imaging to determine atrophy may provide a better understanding of not only normal brain aging processes but eventually brain-behavior relations *in vivo* in degenerative diseases.

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REFERENCES

1. Neil JJ, Shiran SI, McKinstry RC, Schefft GL, Snyder AZ, Almli CR, Akbudak E, Aronovitz JA, Miller JP, Lee BC, Conturo TE. Normal brain in human newborns: apparent diffusion coefficient and diffusion anisotropy measured by using diffusion tensor MR imaging. *Radiology* 1998; **209**(1): 57–66.
2. Paus T, Collins DL, Evans AC, Leonard G, Pike B, Zijdenbos A. Maturation of white matter in the human brain: a review of magnetic resonance studies. *Brain Res. Bull.* 2001; **54**(3): 255–266.
3. Pfefferbaum A, Sullivan EV, Hedehus M, Lim KO, Adalsteinsson E, Moseley M. Age-related decline in brain white matter anisotropy measured with spatially corrected echo-planar diffusion tensor imaging. *Magn. Reson. Med.* 2000; **44**(2): 259–268.
4. Sullivan EV, Adalsteinsson E, Hedehus M, Ju C, Moseley M, Lim KO, Pfefferbaum A. Equivalent disruption of regional white matter microstructure in ageing healthy men and women. *Neuroreport* 2001; **12**(1): 99–104.
5. Nusbaum AO, Tang CY, Buchsbaum MS, Wei TC, Atlas SW. Regional and global changes in cerebral diffusion with normal aging. *Am. J. Neuroradiol.* 2001; **22**(1): 136–142.
6. Gunning-Dixon FM, Raz N. The cognitive correlates of white matter abnormalities in normal aging: a quantitative review. *Neuropsychology* 2000; **14**(2): 224–232.
7. Raz N. Aging of the brain and its impact on cognitive performance: integration of structual and functional findings. In: *Handbook of Aging and Cognition II*, Craik FIM, Salthouse TA (eds). Erlbaum: Mahwah, NJ, 2000; 1–90.
8. Pfefferbaum A, Mathalon DH, Sullivan EV, Rawles JM, Zipursky RB, Lim KO. A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. *Arch. Neurol.* 1994; **51**(9): 874–887.
9. Pfefferbaum A, Sullivan EV, Rosenbloom MJ, Mathalon DH, Lim KO. A controlled study of cortical gray matter and ventricular changes in alcoholic men over a 5-year interval. *Arch. Gen. Psychiat.* 1998; **55**(10): 905–912.
10. Adalsteinsson E, Sullivan EV, Kleinhans N, Spielman DM, Pfefferbaum A. Longitudinal decline of the neuronal marker N-acetyl aspartate in Alzheimer's disease. *Lancet* 2000; **355**(9216): 1696–1697.
11. Terry RD, DeTeresa R, Hansen LA. Neocortical cell counts in normal human adult aging. *Ann. Neurol.* 1987; **21**: 530–539.
12. Aboitiz F, Rodriguez E, Olivares R, Zaidel E. Age-related changes in fibre composition of the human corpus callosum: sex differences. *Neuroreport* 1996; **7**(11): 1761–1764.
13. Baloh RW, Yue Q, Socotch TM, Jacobson KM. White matter lesions and disequilibrium in older people. I. Case-control comparison. *Arch. Neurol.* 1995; **52**(10): 970–974.
14. Meier-Ruge W, Ulrich J, Bruhlmann M, Meier E. Age-related white matter atrophy in the human brain. *Ann. NY Acad. Sci.* 1992; **673**: 260–269.
15. Zimmerman RD, Fleming CA, Lee BC, Saint-Louis LA, Deck MD. Periventricular hyperintensity as seen by magnetic resonance: prevalence and significance. *Am. J. Roentgenol.* 1986; **146**: 443–450.
16. Drayer BP. Imaging of the aging brain, I: normal findings. *Radiology* 1988; **166**: 785–796.
17. Kemper TL. Neuroanatomical and neuropathological changes during aging and dementia. In: Clinical Neurology of Aging, Albert ML, Knoefel JE (eds). Oxford University Press: New York, 1994.
18. Miller AKH, Alston RL, Corsellis JAN. Variations with age in the volumes of grey and white matter in the cerebral hemispheres of man: measurements with an image analyzer. *Neuropathol. Appl. Neurobiol.* 1980; **6**: 119–132.
19. Nomura Y, Sakuma H, Takeda K, Tagami T, Okuda Y, Nakagawa T. Diffusional anisotropy of the human brain assessed with diffusion-weighted MR: relation with normal brain development and aging. *Am. J. Neuroradiol.* 1994; **15**: 231–238.
20. Peled S, Gudbjartsson H, Westin C-F, Kikinis R, Jolesz FA. Magnetic resonance imaging shows orientation and asymmetry of white matter fiber tracts. *Brain Res.* 1998; **780**: 27–33.
21. Klingberg T, Vaidya CJ, Gabrieli JD, Moseley ME, Hedehus M. Myelination and organization of the frontal white matter in children: a diffusion tensor MRI study. *Neuroreport* 1999; **10**: 2817–2821.
22. Wedeen VJ, Reese TG, Napadow VJ, Gilbert RJ. Demonstration of primary and secondary muscle fiber architecture of the bovine tongue by diffusion tensor magnetic resonance imaging. *Biophys J.* 2001; **80**(2): 1024–1028.
23. Wiegell MR, Larsson HB, Wedeen VJ. Fiber crossing in human brain depicted with diffusion tensor MR imaging. *Radiology* 2000; **217**(3): 897–903.
24. Scheltens P, Barkhof F, Leys D, Wolters EC, Ravid R, Kamphorst W. Histopathologic correlates of white matter changes on MRI in Alzheimer's disease and normal aging. *Neurology* 1995; **45**: 883–888.
25. Christiansen P, Larsson HBW, Thomsen C, Wieslander SB, Henrikson O. Age dependent white matter lesions and brain volume changes in healthy volunteers. *Acta Radiol.* 1994; **35**: 117–122.
26. Guttman CRG, Jolesz FA, Kikinis R *et al.* White matter changes with normal aging. *Neurology* 1998; **50**: 972–978.
27. Geula C, Mesulam MM. Cortical cholinergic fibers in aging and Alzheimer's disease: a morphometric study. *Neuroscience* 1989; **33**: 469–481.
28. Meier-Ruge W, Ulrich J, Bruhlmann M, Meier E. Age-related white matter atrophy in the human brain. *Ann. NY Acad. Sci.* 1992; **673**: 260–269.
29. Tang Y, Nyengaard JR, Pakkenberg B, Gundersen HJG. Age-induced white matter changes in the human brain: a stereological investigation. *Neurobiol. Aging* 1997; **18**: 609–615.
30. Stebbins GT, Carillo MC, Medina D, deToledo-Morrell L, Klingberg T, Poldrack RA, Moseley ME, Karnil O, Wilson RS, Bennett DA, Gabrieli JDE. Frontal white matter integrity in aging and its role in reasoning performance: a diffusion tensor imaging study. *Soc. Neurosci. Abstr.* 2002 (in press).
31. Urresta F, Medina D, deToledo-Morrell F, Gabrieli JDE, Klingberg T, Moseley ME, Wilson RS, Bennett JD, Stebbins G. *In vivo* detection of white matter changes in Alzheimer's disease with diffusion tensor imaging. *Soc. Neurosci. Abstr.* 2002 (in press).
32. Stebbins GT, Poldrack RA, Klingberg T, Carrillo MC, Desmond JE, Moseley ME, Hedehus M, Wilson RS, Karni O, Bennett DA, deToledo-Morrell L, Gabrieli JDE. Aging effects on white matter integrity and processing speed: a diffusion tensor imaging study. *Neurology* 2001; **56** (Suppl. 3): A374.
33. Rose SE, Chen F, Chalk JB, Zelaya FO, Strugnell WE, Benson M, Semple J, Doddrell. Loss of connectivity in Alzheimer's disease: an evaluation of white matter tract integrity with colour-coded MR diffusion tensor imaging. *J. Neurol. Neurosurg. Psychiat.* 2000; **69**(4): 528–530.
34. Melhem ER, Mori S, Mukundanl G, Kraut MA, Pomper MG, van Zijl PCM. Diffusion tensor MR imaging of the brain and white matter tractography. *Am. J. Roentgenol.* 2002; **178**: 3–16.

