Regional Pattern of Age-Related Water Diffusion Changes in Human Brain by Concordance and Dissociation Analysis of High-Field DTI

Y. Zhang[1], A-T. Du[1], G-H. Jahng[1], S. Mueller[1], J. Hlavin[2], L. Stables[1], M. W. Weiner[1], and N. Schuff[1]

[1]VA Medical Center and UC San Francisco, San Francisco, California, United States, [2]UC San Francisco, San Francisco, California, United States

Background: Diffusion tensor imaging (DTI) studies have reported age-related reduction of fractional anisotropy (FA) in frontal white matter regions [1,2], implying normal aging is associated with progressive white matter degradation. However, an alteration of FA alone is difficult to interpret, because it can indicate a variety of pathological changes, including demyelination and axonal loss as well as inflammation and ischemia. It has been suggested that demyelination and axonal loss may be primarily associated with increased radial diffusivity (Dra) and decreased axial diffusivity (Dax) [3,4], while inflammation and ischemia are generally associated with increased mean diffusivity (MD). This implies that a conjunction or comparison between Dra and Dax changes could indicate one or the other group of pathological condition. For example, concordant FA and MD changes could reflect any of the above alternations; while a greater Dra increase than Dax change is expected for myelin or/and axonal damage rather than inflammation or ischemia**.** In this study, we used recently developed non-parametric statistics for multimodal imaging to co-analyze FA, MD, Dra and Dax changes in normal aging.

Objectives: To determine the age-related regional patterns of: 1) reduced FA and increased MD; 2) the conjunction and dissociation between FA and MD changes; and 3) the comparisons of Dra and Dax changes.

Methods: Fifty-one cognitively normal (determined by a battery of neuropsychologic tests) subjects (29 male, 22 female; Age range 22-76 yrs) had structural MRI and DTI scans using a 4 Tesla (Bruker /Siemens) MRI system. EPI scans with a factor 2 parallel imaging acceleration were used for DTI (TR/TE = 6000/77ms, b = 800 s/mm2, 6 directions, 2 x 2 mm^2 in-plane resolution, 40 slices each 3 mm thickness). Maps of FA, MD, Dra, Dax were generated using DTIstudio[5] and dTV Volume-one[6] software. For voxelwise analyze, these maps were first registered to the EPI reference image (B=0) of each subject, then normalized to an EPI brain template and finally smoothed using an $8mm^3$ FWHM kernel. A threshold mask of FA > 0.2 was used to limit analysis to regions containing primarily white matter. Linear correlations between DTI maps and age were tested using SPM2, including covariance for sex and adjustments for multiple comparisons with $p < 0.05$ as threshold for family wise error. Co-analysis used a statistical non-parametric (SnPM) [7] package for the comparisons of bi-modal imaging data, i.e. FA versus MD or Dra versus Dax maps, including permutation tests for non-parametric statistics.

Results:

Age-related FA and MD alterations: The regional patterns of age-related FA reduction and MD increase are shown in Figure 1. Reduction of FA (cold color) was primarily found in frontal white matter, the genu of the corpus callosum, and the pericallosal regions, while increase of MD (hot color) involved all major lobes, pericallosal regions, anterior corpus callosum, cingulum, and thalamus.

Figure 1. Age-related FA reduction (cold color) and MD increase (hot color)

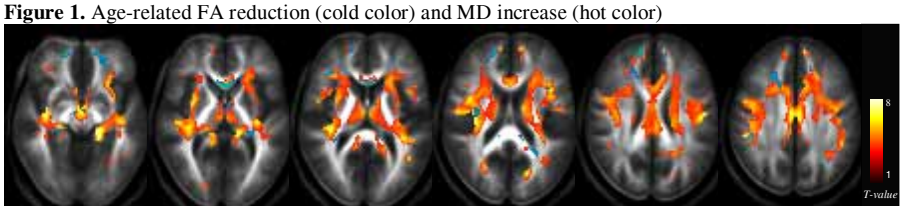
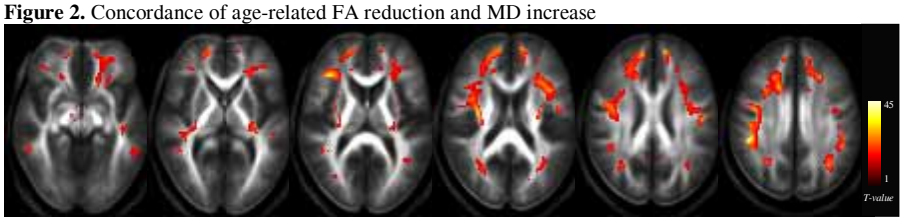
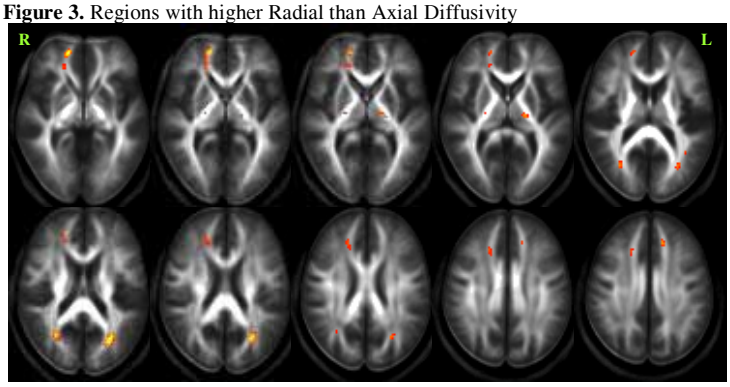


Figure 2. Concordance of age-related FA reduction and MD increase



Concordance and dissociation between FA decrease and MD increase: Regions of significant concordance between FA decrease and MD increase are shown in Figure 2; and predominantly involved frontal, parietal and temporal white matter regions. In the dissociation analysis, most of the major lobes, pericallosal regions, cingulum, and thalamus showed an age-related FA reduction without MD increase; while no region had significant MD increase without FA reduction.

Figure 3. Regions with higher Radial than Axial Diffusivity



Comparsions between Dra and Dax: Both Dra and Dax increased with age. Regions of significantly larger Dra than Dax increases are depicted in Figure 3, involving primarily bilateral frontal white matter fibers, the posterior limb of the internal capsule, and posterior pericallosal (superior temporal) regions. There was no region showing larger Dax than Dra increases.

Discussion: The regional patterns of age-related FA reduction and MD increase are consistent with findings from several previous DTI studies [2,8]. Moreover, we identified regions of significant concordance between decreased FA and increased MD and significant larger radial than axial diffusivity changes. The topography of changes suggest that certain fiber pathways, including frontal, superior temporal and motor fiber bundles, are specifically implicated by processes of aging. Furthermore, the finding of larger radial than axial diffusivity changes along these pathways suggests that demyelination or/and axonal damage rather than inflammation or ischemia is part of the aging process. The results have implications for studies of age-associated causes of mental decline, such as Alzheimer's disease and frontotemporal dementia.

Reference:

1. Head D, et al. Cereb Cortex. 2004 Apr;14(4):410-23.
2. Salat DH, et al. Neurobiol Aging 2005;26(8):1215-1227.
3. Song SK, et al. Neuroimage 2002;17(3):1429-1436.
4. Kim JH, et al. Neurobiol Dis. 2006 Mar;21(3):626-32.
5. Jiang H, et al. Comput Methods Programs Biomed, 2006 Feb;81(2):106-16.
6. Masutani Y, et al. European J. of Radiology, 46:53-66, 2003.
7. Hayasaka S, et al. Neuroimage 2006;30(3):768-779.
8. Barrick TR, et al. ISMRM 2006:772