Association of White Matter Hyperintensities with White Matter Changes in Alzheimer's Disease as Studied by DTI

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Introduction White matter hyperintensities (WMH) observed on MRI provide an important expression of small vessel diseases, which can produce a clinical syndrome of mild to moderate or severe cognitive impairment and recurrent falling due to gait and balance disturbances. WMH also have an additive effect on cognitive decline in dementia and is considered as a risk factor of Alzheimer's disease (AD). The main objective of this study was to gain insight into the heterogeneity of WMH-related diffusion changes in AD by analyzing the diffusion measures in AD patients with different grade of WMH [1]. Since interpreting diffusion tensor imaging (DTI) measurements of WMH related white matter changes, ie, fractional anisotropy (FA) and mean diffusivity or axial (DX) and radial diffusivity (DR) in (AD) with white matter hyperintensities, can be ambiguous [2-6]. We investigated: (1) which DTI indices, such as fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (DR) and axial diffusivity (DX) values, were more sensitive to differentiate AD from normal control (NC) in order to infer underlying pathological mechanisms between AD and WMH; (2) how different levels of WMH may contribute to AD in a specific areas of the white matter.

Methods and Subjects Elderly subjects with normal cognition (NC) (n=27; 12 men, 15 female; age 70.1±7.7 years), AD (n=27; 17 men, 10 female; age 71.4±7.7 years), which included 5 AD with severe WMH (diameter > 3 mm, number of lesion > 2), 15 AD with moderate WMH (diameter < 3 mm, number of lesion < 2) **[Fig 1]**, and 7 AD without WMH. DTI and structural MRI were performed on a Siemens 3T Trio scanner (Siemens Medical System). DT images were recorded in the axial direction with 60 slices and 2-mm thickness without gap and field of view (FOV) of 224 mm with a matrix of 128 x 128 reconstructed to 256 x 256. Directional sensitized diffusion-weighting single-shot spin-echo echo-planar imaging sequence with 12 gradient directions was used with imaging parameters: TR, 9800 ms; TE, 74 ms, b-values of 0 or 1000 s/mm^2.. The same FOV and section locations used in the T_2-weighted fast spin-echo imaging (TR, 4900 ms; TE, 110 ms). For post-processing of DTI data, the maps of FA, MD and tensor eigenvalues (λ_1, λ_2 and λ_3) were generated using the FSL program (University of Oxford, Oxford, UK) with b=0 images as references. Images of radial diffusivity (DR) and axial diffusivity (DX) were calculated on a voxel-by-voxel basis by first ranking the size of eigenvalues ($\lambda_1 > \lambda_2 > \lambda_3$) and then computing DX = λ_1 and DR = (λ_2 + λ_3)/2. FA, MD, DX and DR measurements in each subject were obtained from regions-of-interest (ROIs) selected from areas based on the skeletal maps obtained from Tract based spatial statistical (TBSS) analysis. ROIs **[Fig 1]** were typically a square of 5 x 5 pixels (1 cm^3) with continuous 5 slices and were selected in frontal, middle temporal (MT), superior temporal (ST), occipital, parietal, anterior and posterior internal capsule (AIC and PIC) bilaterally, genu and splenium of corpus callosum (GC and SC). Statistical Package (SPSS 15.0) was performed to compare the mean differences of FA, MD, DR and DX values in ROIs of different groups. Nonparametric statistics receiver operator characteristic (ROC) was used to evaluate which DTI indices are more powerful to differentiate AD from NC using area under the curve (AUC). Multiple comparison procedure with Tukey HSD test ($p < 0.05$) was then carried out to discriminate the groups with different grade of MWH.

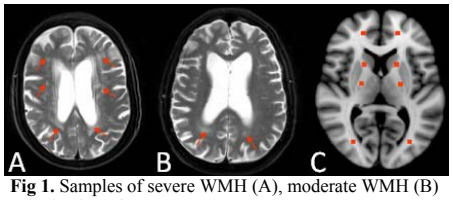


Fig 1. Samples of severe WMH (A), moderate WMH (B) and selection of ROIs (C).

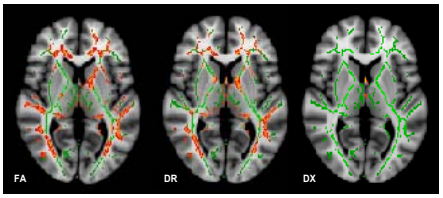


Fig 2. TBSS showed both of FA and DR were much more sensitive than DX and pronounced in the left

Results No statistical significant differences in age, gender, and educational levels were found between the AD and NC groups. Compared to controls, 27 AD patients had decreased FA and increased DR values in most regions. It is found that the increase in DR was much more significant than the decrease in DX in the affected area. Furthermore, both decreased FA and increased DR were more pronounced in the left hemisphere **[Fig 2]**. A greater decrease in FA was found in the right middle temporal (P = 0.011) and AIC (P = 0.001) in the AD group, however, no significant difference between AD and NC was observed in DR in these regions. ROC showed that both decreased FA and increased DR were powerful enough to differentiate AD from NC, especially using measurements in the left temporal and AIC. **Table 1** summarizes areas exhibiting statistical significant differences in DR and DX between AD and NC groups. When comparing AD patients with and without WMH, AD patients with WMH exhibit white matter changes in different and more spread region when compared to AD without WMH. For example, AD with moderate WMH had a decreased FA in the bilateral ST and AIC, right MT and PIC, left occipital and GC, which were not observed in AD without WMH **[Table 2]**. There were statistically significant decreased FA in the left superior temporal (P < 0.001), in the GC (P = 0.014) and in the bilateral AIC (left P = 0.042; right P = 0.027) when comparing AD with severe WMH to AD without WMH. However, increased DR was not observed in all ROIs from this group. Multiple comparisons were preformed in AD with different grade of WMH. White matter changes were found in different regions and extent in AD patients with severe and moderate WMH. There were significant increased DRs in the right frontal (P = 0.01; P = 0.003) and left PIC (P = 0.031; P = 0.014) when comparing AD with severe WMH to AD-with moderated WMH or AD without WMH, but increased DR only observed ,in bilateral AIC (LP = 0.018; RP = 0.049) when comparing AD with severe WMH to AD without WMH **[Fig 3]**. It is found that increased DX was not as much as increased DR in most regions**.**

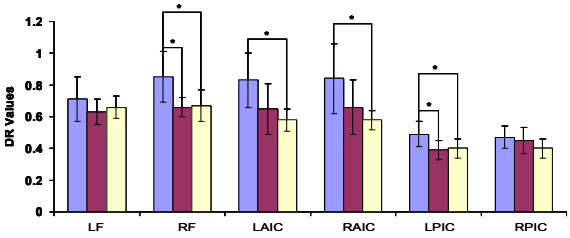
Discussion WMH pathology caused by vascular comorbilities often presentsin AD patients [7]. Current study demonstrated the association between AD and WMH that may be important to understanding the AD development and diagnosis of AD. It suggested that WMH may contribute to the development of AD and was more preponderance in those specific regions investigated such as posterior internal capsule. Our results revealed that decreased FA was coupled with increased DR in the most regions, but not coupled with DX when comparing all of AD with normal controls. It is suggested that increased DR is more closely associated with demyelination and is indicative of the underlying pathological mechanisms of AD that cause demyelination, but not axonal damage [8]. Such alterations were more predominated in the left hemisphere, which is consistent with our previous paper [9].

Conclusion White matter hyperintensities caused from small vessel diseases may associate to in the development of AD. FA and DR were helpful to discriminate AD with different grade of WMH, as well as differentiate AD from NC. Different WMH contributed AD in different regions and extent. The alteration of increased DR indicated demyelination of AD in pathology.

Tab 1. Comparison of the Area Under Curve (AUC) using different DTI Indices and ROIs

	LMT	RMT	LST	RST	LAIC	RAIC
FA	0.85	0.65	0.78	0.69	0.86	0.81
DR	0.83	0.67	0.85	0.61	0.76	0.74
MD	0.82	0.63	0.83	0.61	0.65	0.67
DX	0.75	0.55	0.75	0.57	0.47	0.50

Fig 3. Changes of DR Values in AD with different Grade WMH



Tab 2. FA Values of Selected ROIs in AD with different Level of WMH and NC

Group	RMT	LST	RST	LO	LAIC	RAIC	RPIC	GC
AD-SWMH	0.23*	0.24*	0.25*	0.36*	0.38*	0.41*	0.62*	0.50*
AD-SWMH	0.24*	0.28*	0.27*	0.35*	0.43*	0.46*	0.63	0.60
AD w/o WMH	0.26	0.31	0.30	0.36	0.47	0.50	0.65	0.61

References [1] DeBoy, C.A., et al. *Brain*, 2007. [2] Huang, J, et al, *AJNR Am J Neuroradiol*, 2007. [3] Gao, W, et al, *AJNR,* 2009. [4] Wheeler-Kingshott, C.A., et al. 2009. [5] Bennett, I.J., et al, *Hum Brain Mapp,* 2009. [6] Gold, et al., *Stroke*, 2005. [7] Riekse, R.G., et al. *JAGS,* 2004. [8] Sheng-Kwei Song, et al, *NeuroImage*, 2002. [9] Wang, L, et al, *AJNR,* 2009.