Multivariate Analysis of Diffusion Tensor Metrics in Mild Cognitive Impairment and Healthy Aging

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Introduction

Diffusion tensor imaging (DTI) is generally considered a sensitive tool (1) for the detection of white matter (WM) microstructural alterations in mild cognitive impairment (MCI), a potential precursor of Alzheimer's disease. Previous DTI studies in MCI have used univariate tests of either fractional anisotropy (FA) or radial diffusivity (DR) (2,3) that may not provide maximum sensitivity to detect WM alterations in MCI. The goal of this study was to compare the sensitivity of univariate and multivariate tests in detecting white matter microstructural alterations in MCI. We predicted that multivariate tests of the three eigenvalues of the diffusion tensor would be more sensitive than univariate tests using FA or DR.

Methods

Subjects and data acquisition: 66 healthy elderly controls (age: 67.2±10; MMSE: 29.4±1.0) and 54 MCI subjects (age: 73.3±8.7; MMSE: 27.6±2.0) participated this study. All subjects had high-resolution MPRAGE and DTI (TR/TE = 6000/77ms; 2 ×2 ×3mm^3 with 40 continuous slices, 6 diffusion sensitizing directions, b = 800 s/mm^2, 4 averages, and 2-fold acceleration by parallel imaging) scans on a 4 Tesla (Bruker /Siemens) MRI system. Individual DTI images were corrected for eddy-currents, susceptibility distortions and aligned to the T1-weighted images.

WM parcellations: A white matter atlas package in 'JHU ICBM-DTI-81' (cmrm.med.jhmi.edu/) with 50 labeled deep WM ROIs was imported in SPM8. DARTEL algorism (4) was applied to transform FA image and WM parcellations from ICBM space onto individual FA space to obtain mean DTI metrics in each ROI. To reduce noise bias, regional DTI values were included only in voxels with FA>0.2. ROIs with visual misregistration or white matter lesions were excluded. As demonstrated in Figure, three commissural ROIs, 15 limbic ROIs and 8 association ROIs were measured.

Statistics: The regional DTI data was first corrected for age and gender by cross-covariance and then the effect of diagnosis was tested on the corrected data sets using linear models. For univariate analyses, t-tests were used to determine the effect of diagnosis on the distributions of FA or DR, while for multivariate analyses, MANOVA was used to test the effect of diagnosis on the mixed distribution of the three eigenvalues l1, l2 and l3. All reported p-values are two-sided and significance is adjusted at p≤0.03, based on the concept of a false discovery rate (FDR).

Figure: The ICBM-DTI-81 WM atlas and ROIs.

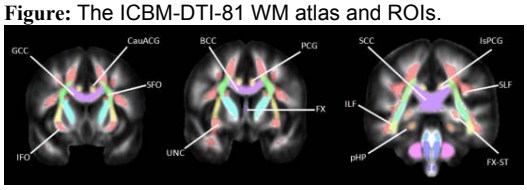

Table: Group comparisons between MCI and control for regions using univariate analysis (UV) of either FA or DR, and multivariate analysis (MV) of all three eigenvalues. GCC, BCC and SCC = genu, body and splenium of corpus calosum; RosACG, CauACG, PCG, IsPCG = rostral, caudal anterior cingulum, posterior cingulum and isthmus posterior cingulum; pHP = parahippocampal cingulum; FX = fornix body; FX-ST = fornix (cres) / stria terminalis; UNC = Uncinate fasciculus.

ROI group	ROIs	*p* - values		
		UV(FA)	UV(DR)	MV
Commissural Fibers (3 ROIs)	GCC	n.s.	n.s.	n.s.
	BCC	n.s.	n.s.	**.02**
	SCC	**.004**	**.002**	**.005**
Limbic Fibers (15 ROIs)	L RosACG	n.s.	n.s.	n.s.
	R RosACG	n.s.	n.s.	n.s.
	L CauACG	n.s.	n.s.	n.s.
	R CauACG	n.s.	n.s.	n.s.
	L PCG	n.s.	n.s.	n.s.
	R PCG	n.s.	n.s.	n.s.
	L IsPCG	**.008**	**.02**	**.03**
	R IsPCG	n.s.	n.s.	n.s.
	L pHP	n.s.	n.s.	n.s.
	R pHP	n.s.	n.s.	n.s.
	FX	**.03**	n.s.	**.03**
	L FX-ST	n.s.	n.s.	n.s.
	R FX-ST	n.s.	n.s.	n.s.
	L UNC	n.s.	**.01**	**.003**
	R UNC	n.s.	**.0005**	**.03**

Results

The table lists p-values from uni- and multivariate tests of group differences for ROI in limbic and commissural fibers, which are usually impacted by MCI. Both univariate and multivariate tests showed group differences in some regions of the limbic and commissural fiber regions. However, the univariate tests of FA and DR were not entirely consistent: Specifically, univariate analyses between MCI and controls showed significant FA reduction in splenium, left isthmus posterior cingulum and fornix regions, whereas significant DR effects were found in the splenium, left isthmus posterior cingulum and bilateral uncinate fasciculi regions. In contrast to the univariate tests, the multivariate analyses of the diffusion eigenvalues captured all regions that appeared significant in FA or DR.

Conclusion and Discussion

We used multivariate analyses of all three diffusion eigenvalues to capture microstructural WM alterations in mild cognitive impairment subjects. Our results show that a multivariate analysis of the diffusion eigenvalues detects regions of white matter alterations more consistently than a univariate analysis. This method has potential to identify early cognitive impairment.

Reference:

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