Regional Degradation of White Matter Ultrastructure in Mild Cognitive Impairment and Alzheimer's Disease by Diffusion Tensor Imaging

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Introduction:

Structural MRI studies consistently found prominent loss of brain tissue in the entorhinal cortex and hippocampus in Alzheimer's disease (AD) and mild cognitive impairment (MCI), a condition with considerable risk for developing AD [1]. In contrast to structural MRI, functional studies of brain metabolism and blood flow using PET or SPECT found the most prominent abnormalities in the posterior cingulate in AD and MCI [2]. While the topological dissociation between MRI and PET/SPECT findings seems at first puzzling, it may be related to degradation of cingulum fibers, which link the medial temporal and the posterior cingulate regions [3]. Several studies using diffusion tensor imaging (DTI) found reduced fractional anisotropy (FA) and increased mean diffusivity (D) in various white matter regions, including posterior cingulate fibers in AD and MCI [4,5,6,7]. However, previous DTI studies did not completely evaluate the fiber links between posterior cingulate and the hippocampal regions. In addition, the value of DTI for detection of AD and MCI as compared to MRI measured hippocampal atrophy, which is currently considered the best imaging marker for AD, has not been investigated. The major goals of this study were: 1) to determine FA and D abnormalities in cingulum fibers, including parahippocampal and posterior cingulate regions, in MCI and AD; 2) to relate FA and D abnormalities of the cingulum fibers with those of the cortical fibers converging in genu and splenium of corpus callosum; 3) to determine the extent to which DTI improves separation of AD and MCI from healthy aging over the separation achieved with MRI measurements of hippocampal volume loss.

Methods:

Seventeen AD patients (mean age 77.1±8.8 yrs), 17 MCI (73.1±7.4 yrs), and 12 cognitive normal (CN) subjects (69.9±8.3 yrs) were studied at a 1.5 Tesla scanner. DTI was acquired using a double refocused single shot EPI sequence [8] (TR/TE/TI=6000/100/2000 ms; 2.34 x 2.34 mm^2 in-plane resolution, 20 slices, 5mm thick, no gap, 6 directions b=0, b=1000 s/mm^2). FA, D and color-coded images were calculated from raw data using offline software DTIstudio. Region of interesting (ROIs) were drawn on the color-coded images and subsequently overlaid on the FA and D images to obtain regional FA and D values. A radiologist blinded to the clinical information placed the ROIs (as depicted in Figure1) on the main fiber tracts, which including: 1) cingulum tracts: bilateral parahippocampus and posterior cingulate; 2) cortical tracts: genu and splenium of the corpus callosum; and as reference 3) sensorimotor tracts: posterior limb of the internal capsule. In addition to DTI, 3D T1-weighted MP-RAGE was acquired to measure hippocampal volumes using semi-automated software (Surgical Navigation Technology) [9].

Results:

Results of FA and D are summarized in Table1. Statistical analyses of FA as a function of diagnosis, using age, sex, and brain size as covariates, showed AD was associated with significantly lower FA values than CN in cingulum fibers, including bilateral parahippocampal fibers (left, p=0.002; right, p=0.02), and posterior cingulate fibers (left, p<0.0001; right, p=0.003), as well as cortical fibers in the splenium of the corpus callosum (p=0.003). Compare to CN, MCI patients had FA reductions predominantly in cingulum fibers, which were: bilateral parahippocampal (left, p=0.007; right, p=0.01), and left posterior cingulate regions (p=0.003). In contrast to AD, however, MCI had no significant alterations of FA in the corpus callosum. Also shown in Table1 are the results from hippocampal volume measurements. Consistent with previous MRI studies, AD was associated with substantial hippocampal volume loss, while in MCI the volume losses did not reach significant levels. Lastly, classification of the groups based on MRI and DTI is summarized in Table2. This shows that MCI and CN could not reliably be separated (58% overall) based on hippocampal volume alone, but when DTI was added, the separation markedly improved to 70% accuracy. As expected, using hippocampal volumes reliably separated AD and CN with 82% accuracy. Including DTI information further improved the separation to 94% accuracy.

Discussion and Conclusions:

The DTI findings indicate that degradation of the cingulum fibers is already detectable in MCI and becomes more regionally widespread in AD. Furthermore, degradation of the cingulum fibers may also hold a key in explaining the relationship between PET/SPECT-based findings of posterior cingulate dysfunction and MRI-based findings of hippocampal atrophy in MCI and AD. Our results also suggest that assessment of cingulum fibers using DTI is more powerful than assessment of hippocampal atrophy for early changes in MCI and therefore may be a sensitive marker for AD pathology.

References:

1. Du AT, J. Neurol Neurosurg Psychiatry, 71 (2001) 441-447
2. Minoshima S, J Nucl Med, 36 (1995) 1238-1248
3. Wakana S, Radiology, 230 (2004) 77-87
4. Fellgiebel A, Dement Geriatr Cogn Disord, 18 (2004) 101-108
5. Takahashi S, Neurosci Lett, 332 (2002) 45-48
6. Fellgiebel A, Neurobil Aging, 26 (2005) 1193-1198
7. Rose SE, J Neurol Neurosurg Psychiatry, 69 (2000) 528-530
8. Reese TG, Magn Reson Med, 49 (2003) 177-182
9. Hsu YY, J Magn Reson Imaging, 16 (2002) 305-310

Figure1. Illustration of the ROI selection on color-coded map.

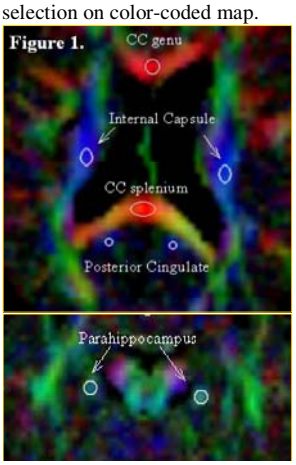

Table1. Group comparison of regional mean FA, D and hippocampal volume (/TIV ‰) – ANOVA results after accounting for age, sex and total brain size.

	ROIs	CN	MCI	AD
FA	l.PH	0.42	**0.37***	**0.36***
	r.PH	0.4	**0.37†**	**0.36†**
	l.PC	0.42	**0.38***	**0.34****
	r.PC	0.41	0.4	**0.36***
	s.CC	0.79	0.77	**0.71***
	g.CC	0.74	0.7	0.71
D	l.PH	0.85	0.85	0.87
	r.PH	0.83	0.87	**0.91***
	l.PC	0.77	**0.8†**	**0.82***
	r.PC	0.77	0.77	**0.82†**
	s.CC	0.85	0.84	0.89
	g.CC	0.85	0.85	0.92
Hippo Volume	l.Hip	1.6	1.41	**1.99****
	r.Hip	1.61	1.39	**1.25***

PH: parahippocampus, PC: posterior cingulate, sCC: splenium, gCC: genu, Hip: hippocampus
† $p < 0.05$, * $p < 0.01$, ** $p < 0.001$

Table2. Results for univariate (left hippocampal volume) and multivariate (left hippocampal volume + left posterior cingulate) analysis based on logistic regression in classifying MCI and CN, AD and CN.

Classification	Measurement	Sensitivity	Specificity	Accuracy	Under curve Area
MCI & CN	l.Hip	65 %	50 %	58 %	67 %
	l.Hip + l.PC-FA	71 %	69 %	70 %	80 %
AD & CN	l.Hip	77 %	88 %	82 %	87 %
	l.Hip + l.PC-FA	94 %	94 %	94 %	98 %