Reduced regional fractional anisotropy in cognitively normal individuals with biochemical and imaging evidence of cerebral amyloid deposition

J. Mettenburg[1], D. N. Daniels[1], Y. I. Sheline[1,2], B. Ances[3], H. Peng[3], A. Z. Snyder[1], J. C. Morris[3], M. A. Mintun[1], and T. L. Benzinger[4]
[1]Mallinckrodt Institute of Radiology, Washington University in Saint Louis, [2]Psychiatry, Washington University in Saint Louis, [3]Neurology, Washington University in Saint Louis, [4]Mallinckrodt Institute of Radiology, Washington University in Saint Louis, St. Louis, MO, United States

Background: Alzheimer Disease is characterized by cerebral atrophy and dementia, with deposition of amyloid plaques. In addition, white matter injury seen by diffusion imaging is associated with dementia (1). Importantly, in some individuals, amyloid plaque deposition precedes the onset of dementia (2) as evidenced by uptake of Pittsburgh Compound B (PIB), measured by the mean cortical binding potential (MCBP). Furthermore, a decline in amyloid beta$_{42}$ peptide in cerebral spinal fluid (CSF Aβ_{42}) is associated with the cerebral uptake of PIB (3) in cognitively normal individuals (4). Finally, PIB uptake is shown to disrupt functional connectivity prior to dementia (5) and is associated with abnormal BOLD response within the precuneus (6). Taken together, these findings describe underlying functional abnormalities related to amyloid deposition. We hypothesize the presence of associated white matter structural abnormalities, manifested by a reduction of fractional anisotropy (FA), prior to the onset of clinically apparent dementia, related to amyloid biomarkers.

	MCBP			CSF Aβ_{42}		
Region	< 0.18	>0.18	p=	>500	<500	p=
Genu	0.84	0.83	ns	**.86**	**.79**	**.001**
Splenium	0.89	.90	ns	.90	.88	ns
Parietal	0.57	0.53	ns	.57	.56	ns
Precuneus	**0.40**	**0.36**	**0.025**	.40	.38	ns
Temporal	0.50	.47	ns	.50	.50	ns
Prefrontal	0.31	0.29	ns	.32	.30	ns
N=	74	27		58	26	

Table 1. Abnormal white matter integrity in non-demented individuals with amyloid deposition as evidenced by abnormal PIB uptake.

Methods: 101 cognitively normal participants received standard anatomic and diffusion tensor MR imaging (25 direction/multiple B-value echo planar diffusion imaging on a 3.0 Tesla Siemens scanner) and PIB PET imaging according to an IRB approved protocol. 84 of these subjects underwent lumbar puncture and determination of Aβ_{42} levels in the CSF in addition to diffusion and PIB PET imaging. An additional 20 participants with mild dementia of the Alzheimer type (DAT) as defined by Clinical Dementia Rating (CDR) scores of 0.5 or 1 were scanned in a similar manner. Hand-drawn regions of interest were generated for determination of fractional anisotropy (FA) on subject's atlas-registered images following tensor fitting. Analyses were performed by multiple regression/ANOVA between groups of individuals with MCBP > 0.18 or with CSF Abeta$_{42}$ < 500 pg/mL, while controlling for age (Table 1). Age matched one-way ANOVA analyses of FA in groups of individuals classified by mCPB or CSF Aβ_{42} levels were then compared the DAT subjects (Table 2). Linear regression controlling for age, global cerebral atrophy and gender was then used to analyze the relationship of CSF Aβ_{42} and FA within the genu of the corpus callosum.

	Cognitively normal				
	MCBP		CSF Aβ_{42} (pg/ml)		
Region	< 0.18	>0.18	>500	<500	DAT
Genu	0.83	0.83	**.84**	**.75**	.81
Splenium	0.89	.90	.90	.86	0.91
Parietal	0.55	0.51	.56	.52	0.54
Precuneus	**0.39***	**0.35**	.38*	.36	0.33*
Temporal	0.48	.46	.48	.48	0.47
Prefrontal	0.29	0.29	.29	.29	0.26
N=	40	19	58	26	20
CSF Aβ_{42} (pg/ml)	693	409	749	392	453

Table 2. Group age matched comparison of FA. *indicates significant difference compared to very mild DAT, with p < 0.05. Bold indicates significance between cognitively normal individuals by MCBP or CSF Aβ_{42} classification.

Results: There is a significantly lower FA in white matter of the precuneus in individuals with evidence of amyloid deposition by PIB imaging (Table 1); this finding was also confirmed in individuals with MCI (Table 2). Loss of FA was also noted in the genu related to a decline in CSF Aβ_{42} levels (Table 1 & 2) and was significantly correlated (p=0.022) by linear regression analysis, correcting for age, atrophy and gender.

Conclusions: These findings support the hypothesis that regional white matter integrity, as measured by FA, is compromised prior to the onset of dementia, and is significantly correlated with imaging and fluid biomarkers of amyloid deposition.

References
1. Rose SE, et al 2000 J Neurol Neurosurg Psych 69:528-530
2. Fagan AM, et al 2009 Ann Neurol 65:176-183.
3. Fagan AM, et al 2006 Ann Neurol 59:512-519.
4. Mintun MA, et al 2006 Neurology 67:446-52.
5. Sheline YI, et al 2009 Biol Psychiatry epub ahead of print.
6. Sperling RA, et al 2009 Neuron 63:178-188.