White Matter Tract Integrity, Amyloid burden and Structural atrophy in normal aging and Mild Cognitive Impairment: a PET-MRI study.

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Target audience: Clinicians and imaging scientists interested in detecting the transition from normal aging to amnestic Mild Cognitive Impairment (aMCI).

Purpose: Along with cortical abnormalities, white matter (WM) microstructural changes are involved in the pathogenesis of Alzheimer's Disease (AD)[1]. These changes can be characterized with diffusion kurtosis imaging (DKI) and its derived WM Tract Integrity (WMTI) model[2], which previously differentiated normal controls (NC), subjects with aMCI and AD[3,4]. We report here WMTI metrics in normal aging and aMCI, now with correlations to cortical amyloid burden and hippocampal atrophy, in an effort to determine the temporal and spatial sequence of pathological pathways in aMCI and early AD.

Methods: Participants (**NC**: N=8, 4 males, 71.8 ± 3.6 y/o ; **aMCI**: N=5, 4 males, 70.4 ± 3.2 y/o ; **AD**: N=1, male, 74 y/o) underwent examination on a 3T integrated MR-PET scanner (Siemens Biograph mMR, VB20). **PET**: ^{18}F-Florbetapir (9 mCi) (Eli Lilly) was injected intravenously and a 20-minute PET image was reconstructed starting at 40 min post-injection using a UTE-based attenuation map. **MRI**: MRI acquisition was simultaneous with the PET. A 1-mm isotropic anatomical MP-RAGE was acquired for cortical and sub-cortical segmentation using Freesurfer. For DKI, a total of 140 diffusion-weighted images were acquired over 6 *b*-values (range 0 —2.5 ms/μm^2). **Processing**: The standardized uptake values (SUV) in cortical regions known for pathological uptake of Florbetapir (anterior and posterior cingulate, medial orbito-frontal, precuneus, parietal and temporal) were extracted, normalized to the cerebellum, and averaged to yield mean cortical relative SUV (SUVr)[5]. Hippocampal volume was normalized to the estimated total intra-cranial volume (eTIV). Diffusion postprocessing[6] provided parametric maps of DTI, DKI and WMTI metrics. Each FA map was registered to the Johns Hopkins University FA template using non-rigid registration and eight WM ROIs known to be involved by AD pathology or processing speed were automatically segmented[7-9] [Fornix (Fx) Body and Crus, Cingulum (CGGyrus and CGHippocampus), Uncinate Fasciculus (UF) and Corpus Callosum (CC G: Genu, B: Body), Superior Corona Radiata (SCR)]. For DTI/DKI metrics, the entire ROIs were considered in the analysis; for WMTI, an additional FA threshold of 0.4 was applied on the template to ensure selection of voxels with highly unidirectional fiber orientation. This threshold also minimized the partial volume of CSF in tracts adjacent to the ventricles. In this preliminary study, data from NC, aMCI and AD subjects were pooled to look at relationships between atrophy, amyloid load and diffusion metrics using Pearson correlations.

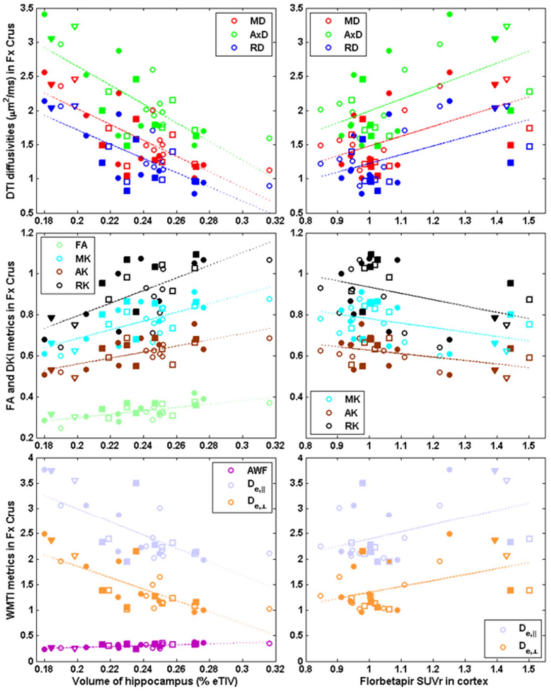

Figure 1. Significant correlations of diffusion metrics in the Fx Crus, with hippocampal volume (left) and amyloid burden (right). *Right/Left hemisphere: Open/Solid symbols. NC: circles; MCI: squares; AD: triangles. Lines: linear correlations.*

Results and discussion: Table 1 provides correlation coefficients of diffusion metrics in WM ROIs relative to hippocampal volume and cortical SUVr (columns 1 and 2 respectively). Only WM tracts where at least two metrics correlated significantly are shown. Both hippocampal volume and mean cortical SUVr of Florbetapir show strongest correlations with diffusion metrics in the Fx Crus (Fig.1). Mean cortical SUVr also correlated significantly with hippocampal volume (coeff.: -0.59 / p<0.001). All other WM ROIs investigated show strong correlations with hippocampal volume. This is consistent with the Fx, CG and UF connecting the hippocampus and other adjacent temporal lobe regions to cortical areas. The correlations with SCR and CC also suggest that markers for cognitive reserve should be factored into the dynamic model of AD WM and cortical pathology progression. Among WMTI metrics, the best correlations are found for $D_{e,\perp}$ and AWF indicating potential chronic degeneration (demyelination and/or axonal damage) in early AD pathology.

		Correlation coefficients with hippocampal volume…								…and with SUVr	
		Fx Crus	Fx Body	CGG	CGH	UF	CC G	CC B	SCR	FxCrus	SCR
DTI	FA	0.68***	0.68**	-0.13	0.36	0.16	0.66**	0.68**	0.01	-0.40*	-0.13
	MD	-0.75***	-0.68**	-0.11	-0.40*	-0.41*	-0.69**	-0.55*	-0.72***	-0.33	0.43*
	AxD	-0.75***	-0.42	-0.30	-0.29	-0.42*	-0.62*	-0.32	-0.77***	0.55**	0.24
	RD	-0.75***	-0.76**	-0.01	-0.44*	-0.39*	-0.72**	-0.62*	-0.66***	0.56**	0.37
DKI	MK	0.71***	0.85***	0.60***	0.19	0.28	0.67**	0.54*	0.64***	0.54**	0.13
	AK	0.69***	0.82***	0.28	-0.20	0.08	0.26	-0.56*	0.59**	-0.43*	-0.21
	RK	0.68***	0.82***	0.52**	0.26	0.38*	0.70**	0.60*	0.53**	-0.45*	-0.16
WMTI	AWF	0.69***	0.81***	0.43*	-	0.40*	0.66**	0.64*	0.67***	-0.34	-0.14
	D_a	-0.37	-0.52	0.23	-	-0.19	0.36	0.71**	-0.30	0.36	0.54**
	$D_{e,\parallel}$	-0.69***	-0.47	-0.48*	-	-0.42*	-0.35	0.03	-0.76***	0.44*	0.50**
	$D_{e,\perp}$	-0.76***	-0.74**	-0.20	-	-0.44*	-0.57*	-0.53*	-0.60***	0.46*	0.20

Table 1. Correlation coefficients of diffusion metrics with hippocampal volume and/or Florbetapir SUVr. Due to strong lateralization in AD, left and right hemispheres were treated independently, where applicable. **: p<0.05 **: p<0.01; ***: p<0.001.* **Abbreviations**: FA: Fractional anisotropy; M/Ax/R-D: Mean/axial/radial diffusivity; M/A/R-K: Mean/axial/radial kurtosis; AWF: Axonal water fraction; D_a: Axonal diffusivity; $D_{e,\parallel}/D_{e,\perp}$: Extracellular axial/radial diffusivity.

Conclusion and future work: In a pooled comparison of elderly subjects with different clinical status, DKI/ WMTI metrics demonstrate changes consistent with demyelination and axonal loss in WM ROIs spatially connected to the hippocampus and cortex, and these changes correlate significantly with measurements of gray matter AD pathology, including hippocampal atrophy and amyloid burden. As our study progresses, a larger accumulated population of subjects will enable comparisons between clinically-defined groups (NC vs aMCI). These data should help us investigate which specific imaging biomarker(s) can discriminate clinical status first, and whether there is a spatial-temporal progression of AD pathology detectable by structural MRI[10].

References: [1] Brun and Englund, Ann. Neurol., 1986. [2] Fieremans et al., Neuroimage 2011. [3] Fieremans et al., AJNR 2013. [4] Benitez et al., Neuroimage Clin., 2013. [5] Clark et al., JAMA 2011. [6] Veraart et al., Neuroimage 2013. [7] Mielke et al., Dement., 2012. [8] Teipel et al., Neuroimage, 2007. [9] Birdsill et al., Neurobiol. Aging 2014. [10] Seeley et al., Neuron 2009.