REGIONAL DEMYELINATION OF SUBCORTICAL WHITE MATTER IN EARLY ALZHEIMER'S DISEASE: A MAGNETIZATION TRANSFER IMAGING STUDY.

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BACKGROUND
Alzheimer's disease (AD) is a neurodegenerative disorder manifested by progressive cognitive deterioration. Since higher cognitive functions are based on distributed neural networks, the AD-associated cognitive impairment is expected to result from the compromised cortical connectivity. Recently, the breakdown of myelination was suggested as an essential factor in AD development (Bartzokis 2004). The aim of this study is to assess the regional state of myelination of the subcortical white matter in the newly diagnosed AD patients.

METHODS
Fifteen AD patients (mean age 68.8 yrs, CDR 0.5-1, FAST 3-4) and 15 age-matched controls were successfully scanned on a 3 Tesla Philips scanner. The protocol included a sagittal T1-weighted 3D gradient-echo sequence (MPRAGE, 160 slices, 1 mm^3 isotropic voxels) and a gradient-echo MTI (FA 30, TE 15, matrix size 256*256, pixel size 1*1 mm, 36 slices (thickness 3mm), MT pulse duration 7.68 ms, FA 500, frequency offset 1.5 kHz). MT images were coregistered to the T1 acquisition. The MTR for every intracranial voxel was calculated as follows: $MTR = (M_0 - M_S)/M_0 * 100\%$, where M_S represents the intensity of voxels with saturation and M_0, without saturation. Subsequently, the T1 images were segmented to produce probability maps for the grey matter (GM), white matter (WM), and CSF for each subject in its native space. A WM mask was defined from the WM probability map by thresholding it at p>0.95. This WM mask was submitted to an iterative erosion process of 3 mm in depth. Then we selected subcortical WM by subtracting the eroded volume from the original WM mask (Fig.1 red contours). The subcortical WM mask was applied to the MTR coregistered images. Only voxels with MTR>5% were included in the analysis. We chose mean regional MTR values as an estimator of myelination. For parcellation of the entire brain, the MNI template and Brodmann Atlas were used. Each ROI was denormalized according to the subject's morphology (see Fig. 1 as an example) and applied separately to the individual MTR maps. For each ROI we calculated the average of MTR values across voxels. Differences between MTR mean values of patients and controls were tested with Two-sample T-test.

RESULTS
When comparing AD patients and controls we found a significant bilateral decrease (p<0.05) in regional MTR values in the temporal, frontal (excluding motor and premotor areas), parietal and occipital lobes. Each of these ROIs was more affected in the left hemisphere. There was no ROI showing an opposite trend. We tested separately motor and premotor areas but failed to reveal any changes in the AD patients compared to the control group.
To investigate more precisely the structural damage of the WM associated with AD, we tested more specific ROI's according to Brodmann areas(9, 10, 22, 44-45, 46, 39, and 40 BA44-45, BA46, BA22, Fig. 2). These areas, analyzed previously, show a characteristic decrease of GM density in AD (Bozzali et al., 2006). In accordance to these findings, we also found a significant decrease in myelination of the subcortical WM in both hemispheres although more salient in the left one (Fig. 2, Table 1).

CONCLUSION
The greatest promise of MT-MRI as a stand-alone method lies in its ability to accurately localize and quantify the degree of brain demyelination. Indeed, the data confirm that the MT-MRI protocol is sufficiently sensitive both at meso- and at fine-scale to quantify regional demyelination even for a small sample of AD patients. Our results point to a diffused degenerative process affecting the subcortical WM early in AD. Regional mapping of myelin loss in AD patients is an accurate tool providing anatomical information that can explain clinical manifestations of the disease, and its early pathogenesis.
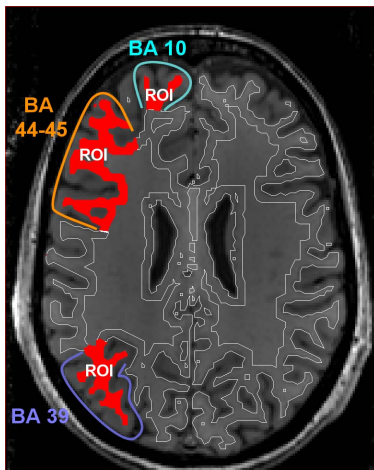

Fig.1. Example of ROI selection. White contours show the subcortical WM mask (3 mm thick). The ROIs for MTR calculation include the subcortical WM (red) below respective cortical BAs.
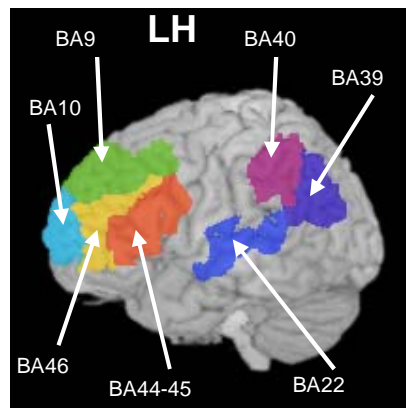

Fig. 2. Fine parcellation for selected BAs. The same regions were tested in both hemispheres.

T-test MTR controls > patients		
	P value	
	LH	RH
BA9	**0.015**	**0.048**
BA10	**0.013**	**0.011**
BA46	**0.012**	**0.036**
BA44-45	**0.012**	0.051
BA22	**0.006**	**0.018**
BA39	**0.019**	**0.027**
BA40	**0.014**	0.071

Table 1. Two-sample T-test of differences between regional MTR values in controls and patients for selected BA regions. Significant P-values are shown in bold

References:
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Bozzali M, Filippi M, Magnani G, Cercignani M, Franceschi M, Schiatti E, Castiglioni S, Mossini R, Falautano M, Scotti G, Comi G, Falini A. The contribution of voxel-based morphometry in staging patients with mild cognitive impairment. Neurology. 2006 Aug 8;67(3):453-60.