Quantitative magnetization transfer characteristics of white matter tracts correlates with DTI indices in predicting the conversion from mild cognitive impairment to Alzheimer's disease

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PURPOSE. Patients with amnestic mild cognitive impairment (aMCI) have higher probability to convert to AD[1] than elderly controls. The development of tools to identify patients at high risk for dementia is crucial for the management of tailored therapies. Here, we used probabilistic WM tractography to explore microstructural alterations within WM tracts in aMCI patients who converted to AD at follow-up (MCIconverters) and those who remained stable (MCIstable). Both DTI and quantitative magnetization transfer (qMT) parameters have been assessed for a full pathophisiological characterization of the WM damage. Our data suggest that DTI and magnetization transfer imaging might be sensitive to micro-structural and metabolic changes of both white and grey matter, and therefore they might provide more accurate prognostic information than atrophy assessment on its own.

MATERIAL AND METHODS. 43 AD patients, 34 patients with aMCI and 21 healthy controls (HC) were enrolled for this study. Patients were reviewed after 1 year to assess whether they had converted to AD or remained stable. All subjects underwent extensive neuropsychological assessments and an MR scan at 3T (Magnetom Allegra, Siemens), including the following acquisitions: Dual-echo turbo spin echo (TSE) (repetition time [TR]= 6,190msec, echo time [TE]= 12/109 msec); (2) fast-FLAIR (TR= 8,170 msec, TE= 96 msec, TI= 2,100 msec); (3) 3D Modified-Driven-Equilibrium-Fourier-Transform (MDEFT) scan (TR=1338 ms, TE=2.4 ms, Matrix=256x224x176, in–plane FOV=250x250 mm2, slice thickness=1 mm); (4) a series of 12 MT-weighted 3D fast low-angle shot (FLASH) sequences (TR=35 ms, TE=7.4, flip angle=7; matrix=128x96x28; FOV= 230x172.5x140mm3), with various combinations of on-resonance equivalent flip angle and offset frequency (f) of the Gaussian MT pulse (pulse duration= 15ms), optimized as described elsewhere[2]. DTI data were obtained along 61 non-collinear directions, with b values of 0 and 1000 s.mm^{-2},resulting in 45 contiguous slices volumes with a 2.3 mm isotropic reconstructed voxel size. ***DTI processing:*** FA, MD, radial diffusivity (RDif), and axial diffusivity (ADif) were computed from the diffusion tensor (DT) fitted with weighted linear least-square with Camino[3], after correction for head movements and eddy currents based on non-linear registration to the first b0 volume with FSL. ***Tractography:*** The WM tracts were reconstructed with multi-fiber probabilistic tractography carried out using 10000 iterations of the probabilistic index of connectivity (PICo) algorithm[4] applied to fiber orientation distribution functions estimated with PAS-MRI[5]. We reconstructed the Uncinate Fasciculus- UF; Inferior Longitudinal Fasciculus- ILF; Cingulum; Superior-sCi, and Inferior parahippocampal-iCi). ***Extraction of Tract-specific Indices:*** For every subject, the spatial transformation matching the DTI scan to the MT-weighted scans was then computed by affine followed by nonlinear registration. The non-linear step was added to compensate for EPI geometric distortions. The transformations were then applied to the maps defining the WM tracts which were used to compute the mean macromolecular pool ratio (F) and forward exchange rate (RM^B_0). A between-subject ANOVA was performed for the 3 groups of patients and HC, adjusting for age and years of education.

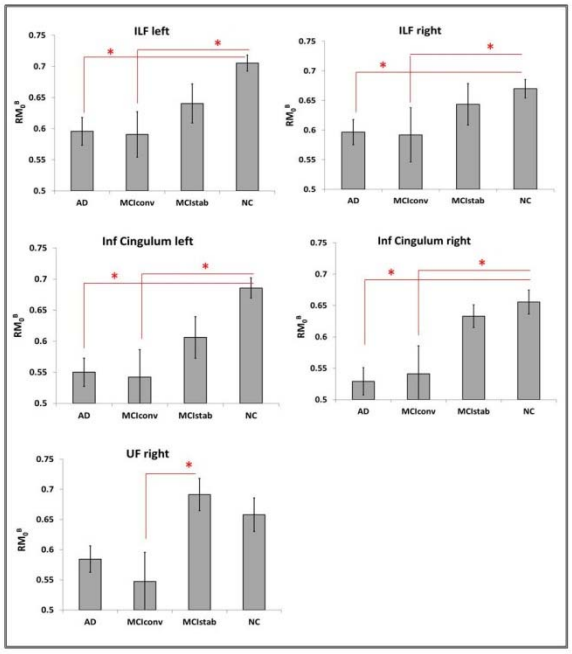

Fig 1. Significant differences in RM^B_0 estimated in WM tracts, between the three groups of patients and HC. RM^B_0 in UF differentiated $MCI_{converters}$ from MCI_{stable} already at baseline.

RESULTS. After 1 year, 17 aMCI remained stable (MCIstable) and 17 converted to probable AD (MCIconverters). **DTI results:** Planned contrasts revealed a difference between MCIconverters and MCIstable in the sCi bilaterally when considering FA ($p< 0.05$). ADif and RDif were sensitive in detecting MCIconverters and MCIstable in comparison to HC in the iCi, ILF bilaterally, and UF right. **qMT results**: Compared to HC, AD patients reported lower RM^B_0 in left ILF, bilateral iCi and left sCi, whereas MCIconverters reported lower levels of RM^B_0 in left ILF, bilateral infCi and right UF. A difference between MCIstable and AD patients emerged in right iCi. When directly comparing MCIconverters to MCIstable, their RM^B_0 different in the right UF. No significant differences were obtained when considering F value among the three groups of patients and HC (Fig 1).

Correlation between qMT and DTI: RDif and MD correlated negatively with RM^B_0 values in almost all tracts (except ILF and UF left). MD negatively correlated also with F values in sCi left and UF left. A negative correlation was evident between RDif and F in left UF. As regards ADif, a negative correlation was evident with RM^B_0 values of the bilateral iCi, whereas no correlation was evident with F values. Finally, a positive correlation was observed between FA and RM^B_0 values in bilateral ILF and F values in left.

DISCUSSION: This is the first study that estimates qMT parameters in WM tracts reconstructed with probabilistic tractography in AD patients and individuals with aMCI. We report that both qMT and DTI parameters from WM tracts can differentiate aMCI patients who converted to AD from those who remained stable in time. Among qMT parameters, we confirm that RM^B_0 is the most sensitive to AD WM pathology, consistent with a previous study[6]. RM^B_0 values correlated with of RDif of in almost all tracts (but ILF right), suggesting that the two parameters might reflect similar –or highly linked - features of WM integrity.

REFERENCES: [1] Risacher S.L et al. (2009) Current Alzheimer Research, 2009, 6, 347-361; **[2]** Cercignani M, Basile B, Spano` B, et al. NMR Biomed 2009; 22: 646–653.; **[3]** Cook, PA. et al., (2005) An automated approach to connectivity-based partitioning of brain structures. In: *Proc. MICCAI*. **[4]** Parker et al. (2003), *J Magn Reson Imaging*. **[5]** Jansons KM, Alexander DC (2003) *Inf Process Med Imaging*;18:672-83 **[6]** Giulietti G, et al,. Neuroimage. 2012 Jan 16;59(2):1114-22.