White matter damage in MCI converters and non converters to AD: a longitudinal study using probabilistic tractography

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URPOSE. Patients with amnestic mild cognitive impairment (aMCI) have higher probability to convert to AD (1) than elderly controls. The detection of subtle changes in brain structure associated with disease progression and the development of tools to identify patients at high risk for dementia in short time is considered the crucial prerequisite for the management of tailored therapies. Recent studies have described early white matter (WM) changes in Fractional anisotropy (FA) and Mean Diffusivity (MD) in MCI converters using Tract Based Special Statistics (TBSS) (2). Here, we used probabilistic WM tractography to explore microstructural alterations within the main association, limbic and commissural pathways in aMCI patients at baseline and follow-up. In order to capture the full extent of WM changes in aMCI and AD, a number of diffusion tensor imaging (DTI) indices have been considered, including FA, MD, Axial (ADif) and Radial diffusivity (RDif).

MATERIAL AND METHODS. We enrolled 60 AD patients, 26 healthy subjects (HS) and 27 subjects with aMCI at baseline. In the latter group, 1 year later, 13/27 patients remained stable (MCI-stable) while 14/27 converted to probable AD (MCI-converters). 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). DTI data acquisition: 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, RD, and AD 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 (Fig.1) 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). The following tracts were reconstructed: Unicinate Fasciculus- UF; Inferior Longitudinal Fasciculus- ILF; Cingulum; Superior-sCi, and Inferior parahipocampal-iCi;Corpus Callosum; CC) The MRI acquisitions were performed at baseline (T1) and at a second time point (T2) which could be 6,12 or 18 months after T1. A between-subject ANOVA was performed for the 3 groups of patients and HS at T0, introducing age and education as variable of no interest. Second, a repeated measures ANOVA with two groups (MCI converters and non-converters) and two conditions (baseline-T1- and follow-up-T2) was performed, introducing the follow-up as a variable of no interest, in order to assess the patterns of WM microstructural damage evolution.

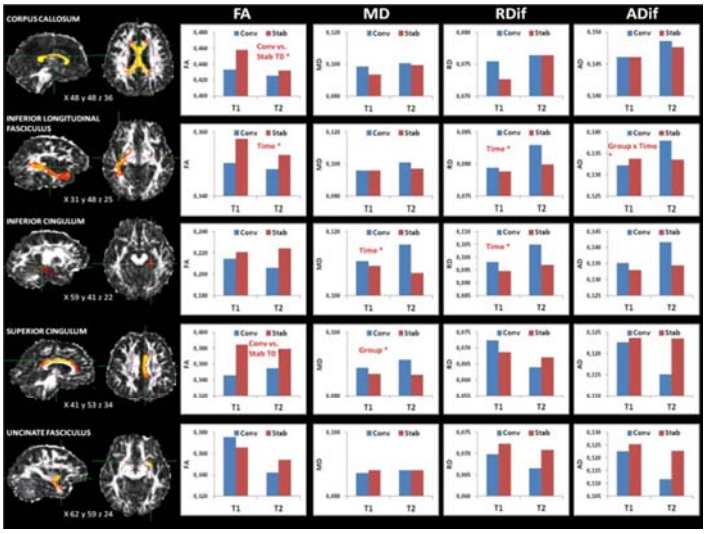

Fig.1. FA, MD, ADif and RD modifications in the Group (MCI converters, stable) x Time (T0, T2) experimental design, for the principal WM fibers.

RESULTS. Cross-sectional analysis at T0: When considering FA, planned contrasts revealed a difference between MCI-converters and MCI-stable in the CC and sCi bilaterally ($p< 0.05$), whereas no difference emerged when comparing the two groups against HS in any of the considered tracts. A difference in MD emerged only when contrasting the two sub-groups of MCI against AD patients, whereas no difference emerged between the two MCI groups contrasted each other or against HS. Interestingly, both ADif and RD were sensitive in detecting MCI-converters and MCI-stable in comparison to HS in the following tracts: CC, iCi, ILF bilaterally, and UF right. When considering RD only, MCI-converters (but not MCI-stable) were more damaged than HS in the following tracts: iCi right, CC and sCi bilaterally. **Within-subject analysis**: Overall, a significant group by time interaction emerged only when evaluating ADif in ILF, showing a more prominent damage over time in MCI-converters vs. MCI-stable. A significant effect of time was evident when considering FA in the CC and ILF; MD in the iCi; RD in ILF and iCi. Conversely, a significant effect of Group was evident when considering FA and MD in the sCi.

DISCUSSION

This study suggests that use of multiple indices is particularly important in the differentiation of the two possible mechanisms underlying changes in WM indexes: primary myelin breakdown vs. axonal loss, probably due to Wallerian degeneration (4). Overall, the pattern of our data suggest the possible coexistence in MCI of both mechanisms, which relate to both WM changes over time and among the two sub-groups of MCI converters and non converters. Notably, when comparing MCI to HS, RD (generally associated to myelin breakdown) was particularly sensitive, thus indicating an earlier myelin damage in MCI converters.

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