Regional White Matter disruption within the Corpus Callosum in patients with Mild Cognitive Impairment Single and Multiple domain

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PURPOSE: Amnestic mild cognitive impairment (aMCI) is considered as a frequent prodromal stage of Alzheimer's disease (AD). Two main clinical subtypes of aMCI vcan be observed: (a) aMCI single-domain (SD_amci, characterized by isolated episodic memory deficit) and (b) aMCI multiple-domain (MD_amci, characterized by episodic memory impairments and additional deficits other cognitive domains), with the former group having a higher risk of converting to AD (1) and more severe gray matter (GM) atrophy (2). The investigation of the microstructural abnormalities of white matter (WM) among different subtypes of aMCI and their relationships with cognitive performances can help to understand the variability among aMCI patients, and to construct potential imaging based biomarkers to predict individual clinical evolution. There were only a few investigations of WM disruption in aMCI subgroups adopting prevalently the tract-based spatial statistic methodology (3). The largest white matter tract, the corpus callosum (CC), has been shown to be particularly vulnerable; however, little work has been done so far to investigate the regional specificity of tract abnormalities within the CC in different aMCI subtypes. Thus, this study examined the CC by applying DTI-based tractography in order to delineate the specific WM damage in SD_amci and MD_amci when compared to both healthy subjects (HS) and AD patients.

MATERIAL AND METHODS: We enrolled 54 patients with AD, 42 with aMCI (23 SD_amci and 19 MD_amci characterized by executive function disorders) and 25 matched HS. All subjects underwent extensive neuropsychological assessments and MR scanning 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 mm^2, slice thickness=1 mm). 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:*** Fractional anisotropy (FA), mean diffusivity (MD), Radial (RDif) and Axial diffusivity (ADif) were computed from the diffusion tensor (DT) fitted with weighted linear least-square with Camino after correction for head movements and eddy currents based on non-linear registration to the first b0 volume with FSL (ref). ***Tractography:*** The Corpus Callosum was 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). In order to obtain a binary map of the "average tract", every subject's reconstructed CC map was thresholded at a value chosen to minimize the amount of tract volume variation with PICo threshold. The images were then warped into standard space using the FA to ICBM152 MNI space transformation previously calculated, and averaged. The resulting maps were thresholded to retain only those voxels that were common to at least 50% of subjects. Age and gender were set as nuisance variables and T-contrasts evaluated with voxel significance set at $p < 0.05$, and family-wise error corrected (FWE) at cluster level .

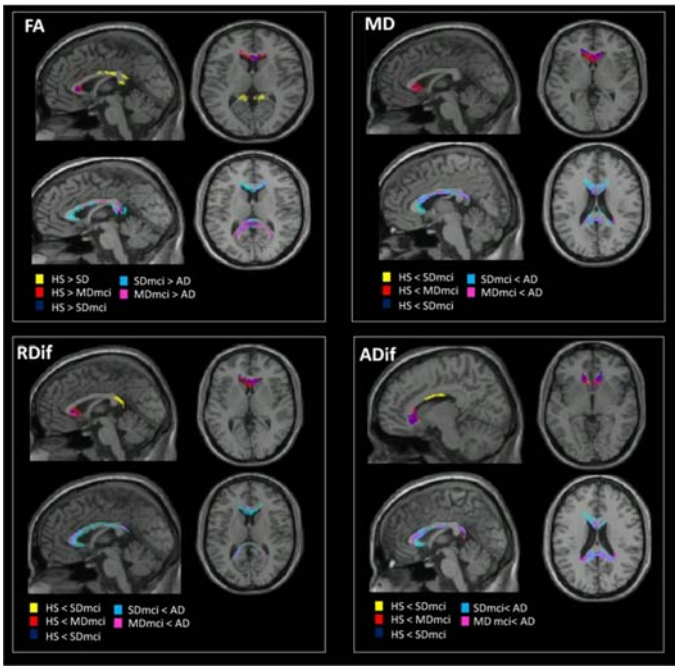

Figure 1. Main differences between HS, SDamci, MDamci and AD, considering the four diffusivity measures: Fracional anisotropy (FA), Mean diffusivity (MD), Radial (RD) and Axial diffusivity (AD). MD = mean diffusivity; FA= Fractional anisotropy; ADif= Axial; RD = Radial diffusivity.

RESULTS: Compared to HS, SD_amci reported signs of damage in the Splenium of the CC when considering FA and RD, and in the body when considering ADif (Fig.1 1,b,c, d yellow areas). Conversely, no signitificant differences were obtained using MD. MD_amci showed significantly greater damage to the Genu of the CC when compared to both HS and SD_amci, in all considered matrixes (Fig.1 a, b, c, d, upper panel). Conversely, AD patients showed an overall damage in the Splenium, body and Genu of the CC when compared to both SD_amci and MD_amci in all diffusivity measures.

DISCUSSION: This study indicates a specific pattern of WM damage in the CC in MD_amci and SD_amci that precedes the conversion to AD. Our results are consistent with the evidence that aMCI is a heterogeneous condition, including patients at different clinical stages between normal aging and dementia.More importantly, this study delineates a precise direction of WM damage that, in MCI patients, parallels the accumulation of cognitive disability and the increased risk for conversion to AD.

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