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

Elena Makovac1, Barbara Spanò1, Laura Serra1, Giovanni Giulietti1, Mario Torsö1, Mara Cercignani1,2, Carlo Caltagirone1,4, and Marco Bozzali1

1Neuroimaging Laboratory, IRCCS Santa Lucia Foundation, Rome, Italy; 2Clinical Imaging Sciences Centre, Brighton and Sussex Medical School, United Kingdom; 3Department of Neuroscience, University of Rome “Tor Vergata”; Rome, Italy; 4Department of Clinical and Behavioural Neurology, IRCCS Santa Lucia Foundation, Rome, Italy

PURPOSE: Amnestic mild cognitive impairment (aMCI) is considered as a frequent prodromal stage of Alzheimer’s disease (AD). Two main clinical subtypes of aMCI can be observed: (a) aMCI single-domain (SDmci, characterized by isolated episodic memory deficit) and (b) aMCI multiple-domain (MDmci, 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 to WM damage in the disease course, paralleling 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 to WM damage in the disease course, paralleling clinical evolution. Therefore, this study examined the CC by applying DTI-based tractography in order to delineate the specific WM damage in SDmci and MDmci when compared to both healthy subjects (HS) and AD patients.

MATERIAL AND METHODS: We enrolled 54 patients with AD, 42 with aMCI (23 SDmci and 19 MDmci 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]= 6,190 msec, 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 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 (RD) and Axial diffusivity (AD) 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 diffusion coefficient (PDC) 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 tissue included in the tracts. 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, family-wise error corrected (FWE) at cluster level.

RESULTS: Compared to HS, SDmci reported signs of damage in the Splenium of the CC when considering FA and RD, and in the body when considering AD (Fig.1 1b,c, d yellow areas). Conversely, no significant differences were obtained using MD. MDmci showed significantly greater damage to the Genu of the CC when compared to both HS and SDmci, in all considered matrices (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 SDmci and MDmci in all diffusivity measures.

DISCUSSION: This study indicates a specific pattern of WM damage in the CC in MDmci and SDmci 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.