The role of structural disconnection secondary to regional grey matter loss in the progression of Alzheimer's disease

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Background and Objective. Amnesic Mild Cognitive Impairment (a-MCI) (1) is considered as a frequent prodromal state of Alzheimer's disease (AD). The annual incidence of conversion from a-MCI to AD is 10-15 %. From a neuropsychological perspective, patients with a-MCI show a relative preservation in most of the cognitive domains (1). Nevertheless, a relevant percentage of them is likely to develop a multi-domain cognitive impairment in a short time, and to eventually convert to fully developed dementia. Whole-brain voxel-based MRI investigations of AD have shown that medial and temporal areas are the sites of earliest atrophy (2), while positron emission tomography (PET) studies of early AD have pointed at the posterior cingulate-precuneus area as a region characterised by early metabolic alterations (3). These findings are also supported by recent resting-state fMRI studies (4). It is also known that AD involves both white and grey matter, and that abnormalities of both tissues correlate with measures of cognitive decline (5). This study aims at investigating the role of the white matter bundle connecting the anterior and posterior cingulate cortices, namely the cingulum, during the pathological process leading to the development of AD.

Subjects and Methods. The study, which is still ongoing, is designed to compare subjects with a-MCI with two different control groups: a group of patients with probable AD (6) and a group of elderly healthy subjects. So far, we studied 5 patients with a-MCI, 7 patients with AD, and 8 healthy subjects. Subject inclusion criteria were the following: right handed subjects; absence of any alternative diagnosis (neurological/psychiatric disorders or major medical illness) that might account for the observed cognitive impairment; absence of any macroscopic brain abnormalities on conventional MRI scans suggestive of an alternative or concomitant diagnosis (cerebrovascular disease), and no history of recent assumption of psychoactive drugs. According to a diagnosis of a-MCI, patients obtained pathological scores exclusively in memory tests. All subjects underwent an MRI scan (Siemens Allegra 3 Tesla head-only scanner) including the following sequences: dual-echo turbo spin echo [TSE] (TR = 6190 ms, TE = 12/109 ms); fast-FLAIR (TR = 8170 ms, TE = 96 ms); 3D MDEFT (TR = 1338 ms, TE = 2,4 ms, Matrix = 256 x 224, n. slices = 176, thick. 1 mm); Diffusion weighted SE EPI (TR= 7 s, TE=85 ms, 61 diffusion directions, maximum b factor=1000 smm^{-2}, isotropic resolution $2.3mm^3$). FLAIR and TSE scans were reviewed to exclude the presence of any macroscopic brain abnormality. Voxel-based morphometry (VBM) was used to assess the presence of reduced GM volume in AD and MCI patients with respect to healthy controls. Diffusion tensor (DT) MRI data were analyzed using CAMINO (7). After tensor fitting, the data were affine-registered to standard space using the preservation of principal direction (PPD) algorithm (8). Probabilistic tractography (9) was used to reconstruct the cingulum, bilaterally. Seed-points were positioned according to published guidelines (10). The resultant connectivity maps were thresholded to include only voxels with a probability of connection > 20%. The thresholded connectivity maps were binarised to obtain a mask on the cingulum for every subject. These masks were used to extract each subject's mean FA of the cingulum, bilaterally. These data were correlated with GM and cognitive measures.

Results. AD patients showed widespread areas of reduced GM volume in the temporal, frontal and parietal lobes (fig 1). Two clusters of reduced GM were found in the precuneus-posterior cingulate cortex (PCC) and in the anterior cingulate cortex (ACC) ($p<0.1$, FWE corrected). These clusters were used as masks to extract the mean GM volume of each subject in both regions. One-way ANOVAs showed that GM volume of both clusters was statistically different among the 3 groups ($p<0.05$). When comparing FA values, a significant effect of both group ($p=0.02$, MCI<controls) and side ($p=0.006$, right<left hemisphere) were observable. Moreover, FA of the left cingulum was correlated with both ACC and PCC GM volume, while FA of the right cingulum was correlated with PCC volume only. Across the whole group, GM volume of both PCC and ACC was significantly associated with performance at tests assessing various cognitive domains (long and short-term memory, executive functions, language, and praxis). FA of the cingulum bundles was only modestly associated with some short term memory tests.

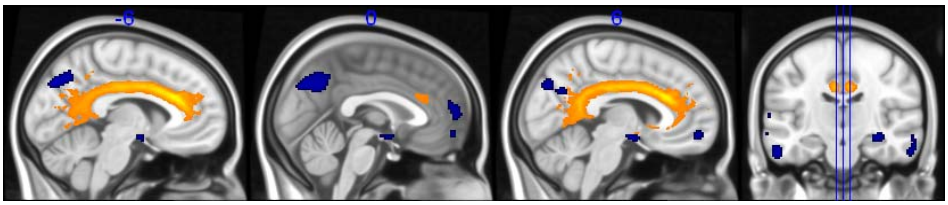

Fig 1. Areas of reduced GM volume in AD patients (blue), and mean cingulum bundles reconstructed by DT MRI tractography (orange).

Conclusions. These data suggest that the cingulum bundle is not spared by the pathological processes occurring in AD. Moreover, the reduced FA observed in the cingulum is associated with a progressive GM loss in the ACC and PCC. As the cingulum connects these two GM areas, these results could be interpreted as a structural WM disconnection probably due to Wallerian degeneration. Despite this WM damage does not appear to be directly associated with cognitive performance, we hypothesise it plays a carrier role in the process of neurodegeneration in AD. This study highlights the potential strategic role of brain disconnection together with regional GM atrophy in determining the progressive accumulation of cognitive disability during AD evolution. Consistently with resting-state fMRI studies, disconnection is likely to be particularly relevant when involving regions of the so called default mode network.

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