The role of the uncinate fasciculus in the development of dementia: a DTI-tractography study

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Background and Objective.
Several studies have proposed the disconnection hypothesis as an explanation for brain dysfunction in Alzheimer's disease (AD) (1). Cognitive impairment in AD can result not only from the local damage of specialized brain regions (e.g., hippocampus and parahippocampal gyrus), but also from disconnection of areas belonging to complex neuronal networks. This might explain why the accumulation of cognitive disabilites over time may exceed the corresponding increases of GM atrophy (2). The uncinate fasciculus (UF), the largest of the fronto-temporal connections, is a ventral limbic pathway that originates rostrally in the temporal lobe and terminates in the ventral, medial and orbital parts of the frontal cortex. It connects cortical regions involved in memory (entorhinal, perirhinal and parahippocampal cortices) with frontal areas implicated in executive functions. Despite a better understanding of its anatomy, its role in AD pathophisiology remains controversial, some studies revealed a damage of UF in patients with mild cognitive impairment (MCI) and early AD (3-4), postulating its possible implication in the memory decline observed in patients with AD pathology. The main aims of the present study were to assess, using diffusion tensor (DT) MRI and tractography, the potential role of UF damage in the progression from amnesic (a-MCI) to completely developed AD; and whether a selective involvement of UF could distinguish between the two main forms of dementia: AD and dementia with Lewy Body (DLB).
Subjects and Methods. A large cohort of patients were enrolled in this study, including 17 patients with a-MCI (5), 31 patients with probable AD (6); 14 patients with probable DLB (7). Thirteen healthy subjects (HS) were also recruited and served as controls. All subjects had to be right handed. The absence of any alternative neurological/psychiatric diagnosis was excluded in each patient. Moreover, major medical illnesses and the presence of macroscopic brain abnormalities on conventional MRI were carefully excluded in all subjects. All subjects underwent an extensive neuropsychological assessment. All subjects had an MRI examination at 3 Tesla, by collecting the following scans: (i) dual-echo turbo spin echo [TSE] (TR=6190 ms, TE=12/109 ms); (ii) fast-FLAIR (TR=8170 ms, TE=96ms); (iii) Diffusion weighted SE EPI (TR= 7 s, TE=85 ms, 61 diffusion directions, maximum b factor=1000 smm^{-2}, isotropic resolution 2.3mm^3). Diffusion tensor (DT) MRI data were analyzed using CAMINO (8). After tensor fitting, the data were affine-registered to standard space using the preservation of principal direction (PPD) algorithm (9). Probabilistic tractography was performed using PICo (10) to reconstruct the UF, bilaterally. Seed-points were positioned according to published guidelines (11). The resultant connectivity maps were thresholded to include only voxels with a probability of connection > 10%. The thresholded connectivity maps were binarised to obtain a mask on the uncinate for every subject. These masks were used to extract each subject's mean FA on the UF, bilaterally. These data were compared across groups (mANOVA to assess the effects of group and hemisphere) and correlated with cognitive measures.
Results. The UF was successfully reconstructed in all subjects (see Fig 1). Comparing the FA of the UF between groups, a significant effect of group ($p=0.01$;AD<a-MCI;AD<HS; AD=DLB; DLB< a-MCI; a-MCI=HS) and side ($p<0.001$, L<R) were observable (See Fig 2). Moreover, FA of UF bilaterally (but more significantly in the right hemisphere) were associated with cognitive measures assessing memory and phonological verbal fluency ($p<0.05$, r ranging from 0.4 to 0.5) when considering all patients grouped together. When removing patients with a-MCI, FA of the UF was bilaterally associated with phonological verbal fluency only ($p<0.05$, $r=0.7$).

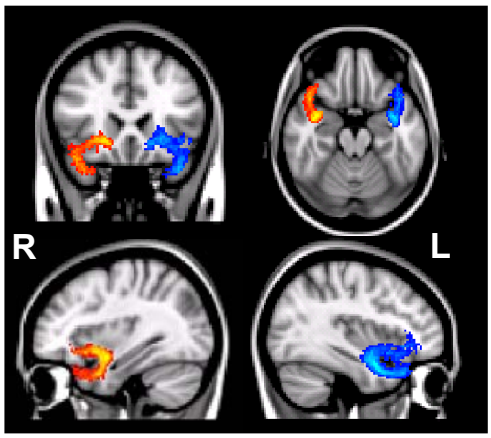

Fig. 1. Mean left (blue) and right (red) uncinate fasciculus reconstructed in healthy controls, overlaid onto a T1-weighted template.

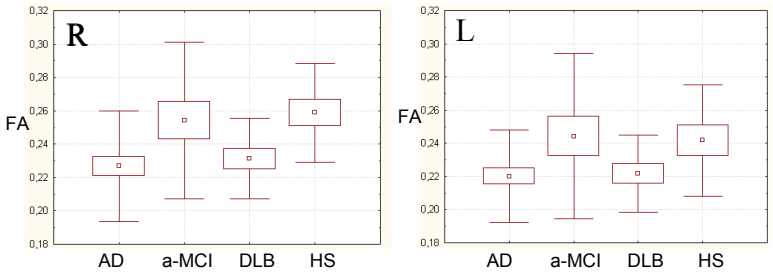

Fig 2. Box-plots of mean (SD) of right and left FA of the uncinate fasciculus across groups.

Conclusions. This study revealed that the FA of the UF was reduced in patients with dementia (regardless of the type), compared to HS and patients with a-MCI. This suggests that this WM bundle plays an important role in the development of some of the symptoms of dementia, but the damage of UF did not permit to distinguish between AD and DLB patients. Consistently, FA of the UF was associated with memory and frontal functions observed in all patients (including those with a-MCI). This fits well with the clinical features of the different types of dementia.
References
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