Converging microstructural evidence in prodromal and early Alzheimer's disease: alteration of commissural and association pathways, sparing of motor pathways

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Introduction There is a crucial need for developing biomarkers that will permit to accurately diagnose MCI and AD and to monitor the course of the disease and its underlying pathophysiology. However, despite a rich literature on diffusion tensor imaging in MCI and AD, *whole-brain* voxel-wise studies, where no *a priori* knowledge of the location of abnormalities is required, are rare. Particularly, there is a striking scarcity of whole-brain diffusion imaging publications examining healthy elderly, MCI and AD populations together (only two to our knowledge: Medina et al., 2006; Serra et al., 2009). Our aim was to investigate whole-brain diffusion abnormalities in the largest study to date including these three populations. For this purpose, we used the tract-based spatial statistics (TBSS) (Smith et al., 2006) and also investigated the 'mode' (MO) of anisotropy, which specifies the *type* of anisotropy, ranging from -1 for planar anisotropy (e.g. in the case of crossing or "kissing" fibres) to 1 for linear shape (e.g., if there is one dominant fibre population) (Ennis and Kindlmann, 2006). Finally, we present results showing a regional *increase* of MO and FA that is atypical for a degenerative disorder (Douaud et al., 2009). We used *direct* and *quantitative* tests based on crossing-fibre probabilistic tractography to demonstrate that the local FA increase arose from the fact that the motor-related pathways were neuropathologically spared compared with the superior longitudinal fasciculus.

Methods 170 participants took part in this study (61 normal controls, 56 MCI patients and 53 probable AD patients without a vascular component). They underwent the same imaging protocol including a whole-brain diffusion-weighted scan using a 3T Allegra MR imager. Diffusion images were obtained using echo-planar imaging (SE-EPI, TE/TR = 89/7000 ms, 54 axial slices, bandwidth = 2056 Hz/vx, 2.5×2.5×2.5mm^3, 30 gradient orientations, b-value 900 s.mm^{-2}, two repeats). FA, MD and MO maps were generated using DTIFit within the FMRIB Diffusion Toolbox, and voxel-wise differences in DTI indices were assessed using TBSS. We also looked at smoothed voxel-wise (as opposed to skeletonised) MO and FA values in a region of crossing fibres that the TBSS skeleton does not investigate. We used permutation-based nonparametric inference within the framework of the GLM to look for significant abnormalities across the three diagnosis groups using an *F*-test and between each pair of groups using *t*-tests. Results were considered significant for P<0.05 corrected for multiple comparisons using the threshold-free cluster enhancement (TFCE, Smith et al., 2009). Finally, using crossing-fibre probabilistic tractography (Behrens et al., 2007), we investigated a singular *increase* of MO and FA that we interpreted as possibly reflecting the relative sparing of the motor-related pathways compared with intra-hemispheric association fibres.

Results We found converging results for FA, MD and MO differences across the three groups. The results were located mainly bilaterally in the corpus callosum (from genu to splenium), in the anterior commissure, in the external/extreme capsule/temporal stem (probably in the uncinate fasciculus), in the cingulum bundle (dorsal and left posterior part) and in the superior longitudinal fasciculus (**Figure 1:** FA results at the top, MD in the middle, MO at the bottom). We also found what seemed, at first, to be a surprising increase of MO in the centrum semiovale and a co-localised increase of FA when looking further at voxel-wise (as opposed to skeletonised) results in this region of crossing fibres (**Figure 2:** voxel-wise increase of FA in white with blue edges). By using this region of significant increase of FA as seed for tractography, we were able to show that these increases of MO and FA were actually related to the relative sparing of the motor-related pathways in this region: we showed a highly significant decrease of particles "belonging" to the cognitive-related association fibres (AF) in the AD patients (P=0.0002), no significant difference for the motor-related projection fibres (PF) (P=0.217) and a significant increase of the ratio of particles PF/AF (P=0.002) (**Figure 2:** the association fibres on the left, projection fibres in the middle and the ratio of projection over association fibres on the right).

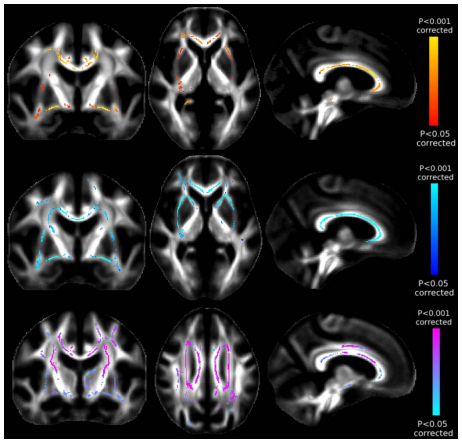

Figure 1: Significant TBSS FA, MD and MO results

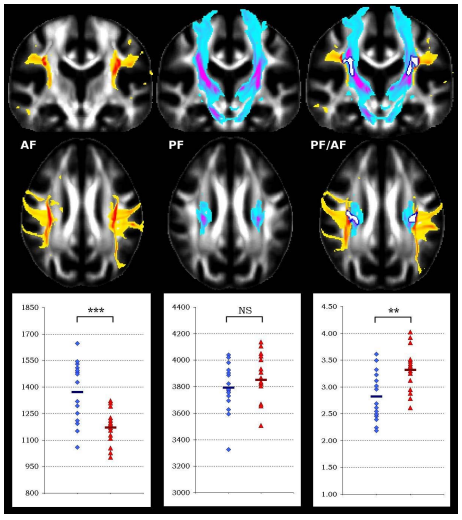

Figure 2: Crossing-fibre tractography results

Discussion and Conclusion All indices converged to show that the uncinate fasciculus, the cingulum bundle, the corpus callosum, the anterior commissure and the superior longitudinal fasciculus were affected in Alzheimer's disease. For all indices, MCI patients represented an intermediate state between controls and AD patients – though closer to the healthy control group – with significant differences between MCI and AD being almost confined entirely to the corpus callosum (data not shown). For the first time in such studies, we introduced an application of a recently developed diffusion tensor index, the mode of anisotropy (Ennis and Kindlmann, 2006), as well as quantitative crossing-fibre tractoraphy which gave us the ability of not only tracing pathways *through* crossing-fibre region, but also *from* it. The mode of anisotropy provided the only significant difference when looking for *whole-brain* diffusion abnormalities in MCI patients compared with healthy subjects, with an increase of mode in the centrum semiovale (data not shown). In general, with respect to the effects reported here, the mode was more sensitive than FA. We also showed, using quantitative tractography, that increases of FA and mode were related to a relative sparing of the motor-related projection fibres (corticospinal/corticopontine tracts, superior thalamic radiations) compared with the fronto-parietal association fibres (superior longitudinal fasciculus). The lower vulnerability of the white matter motor pathways had been assumed before and these tracts had therefore previously been used as an internal control for ROI-based measures of FA (Rose et al., 2000; Bozzali et al., 2002; Kiuchi et al., 2009). Here, we showed directly and quantitatively the sparing of the motor pathways at an early stage of the disease, which is consistent with the sparing of motor cortex (Karas et al., 2003; Chetelat et al., 2008; Dickerson et al., 2009).