

Structural differences can be found between MCI converters and non-converters more than 2 years prior to conversion to AD

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Introduction There is great interest in developing biomarkers that will permit the prediction of the conversion of mild cognitive impairment (MCI) to Alzheimer's disease (AD), and for monitoring the course of the disease as much as its underlying pathophysiology. Voxel-based morphometry provides whole-brain information about the topographic distribution of grey matter volume differences, making no a priori assumptions about the location of possible abnormalities. However, despite a rich VBM literature on AD, only 6 studies investigated the neurostructural predictors of conversion to AD by looking at baseline differences between amnesic MCI patients that remained stable and MCI patients who later converted to AD (Ferreira et al., 2009). Moreover, we are not aware of any study investigating *white matter* predictors using diffusion tensor imaging. Our aim was to investigate whole-brain grey *and* white matter differences between "stable" and "conversion" MCI groups. **We chose to focus on "late conversion", i.e. on patients who converted to probable AD (without a vascular component) at least 2 years after their first visit, in order to increase the clinical value of the predictive information we could find.**

Methods 56 MCI patients took part in this study. MCI subjects were diagnosed according to the criteria by Winblad and colleagues (Winblad et al., 2004). The diagnosis of AD was made when both the DSM-IV criteria (American Psychiatric Association, 1994) and the NINCDS-ADRDA criteria (McKhann et al., 1984) were fulfilled. All patients were clinically followed up once a year for 4 years. For this analysis, we included 9 "late converters", i.e. MCI patients who converted to probable AD *at least 2 years* after their first visit, and compared them with 13 "stable" amnesic MCI patients who had not converted to AD after *at least 3 years*. All patients underwent the same imaging protocol at their first visit, including whole-brain MPRAGE T1-weighted and diffusion-weighted scans using a 3T Allegra MR imager. T1-weighted images were obtained with an MPRAGE sequence (TE/TI/TR = 3.5/1000/2150 ms, 1.1x1.1x1.1 mm³), diffusion images using echo-planar imaging (SE-EPI, TE/TR = 89/7000 ms, 54 axial slices, bandwidth = 2056 Hz/vx, 2.5x2.5x2.5mm³, 30 gradient orientations, b-value 900 s.mm⁻², two repeats). FA maps (n=21 as one diffusion image contained artefacts) were generated with FSL (Smith et al., 2004), and voxel-wise differences in DTI indices were assessed using TBSS (Smith et al., 2006). We also looked at GM volume differences using FSL-VBM (Douaud et al., 2007). We used permutation-based nonparametric inference within the framework of the GLM to look for significant abnormalities across the two diagnosis groups (Nichols et al., 2002). Results were considered significant for P<0.05 corrected for multiple comparisons after initial cluster-forming thresholding at P<0.05 uncorrected.

Results We found significant GM differences between the "stable" and the "late conversion" groups, with a reduced GM volume in the MCI patients who will later convert to AD bilaterally in the caudate, putamen, ventral striatum, temporal pole, as well as in the left hippocampus, amygdala and parahippocampal gyrus (Fig. 1). We also found some significant FA differences, with a bilateral *increase* of FA (dark blue in Fig.2) in the future converters to AD essentially where superior longitudinal fasciculus (SLF from the Jülich atlas, in pink) and corticospinal tract (CST from the Jülich atlas, in blue-violet) are crossing. Remarkably, when using the significant differences between the two groups as regions of interest, we found that FA values in the SLF/CST were *discriminating* very well the two groups (Fig3, right), on the contrary to GM volumes in the striatum and left hippocampus (Fig 3, left).

Discussion and Conclusion Our results obtained in the GM are in good accordance with a recent VBM meta-analysis looking at the neurostructural predictors of AD in 6 studies (Ferreira et al., 2009). They found a single cluster of reduced GM volume in the left hippocampus and parahippocampal gyrus. To the best of our knowledge, this is the first diffusion imaging study looking at differences at baseline in amnesic MCI patients who will later convert to AD compared with patients who remained stable. In a previous diffusion study, we showed that the only difference between healthy elderly and MCI patients was an *increase* of anisotropy (in MCI) explained by a relative sparing of the motor-related fibres (CST) compared with the fronto-parietal association fibres (SLF II) (Douaud et al., in revision). Most interestingly, our results here suggest that these microstructural alterations, detected in crossing-fibre tracts using diffusion imaging, are also more sensitive to predict which MCI patients will convert to AD more than two years prior to their conversion.

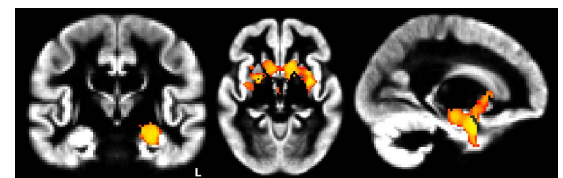


Figure 1: Significant VBM GM results

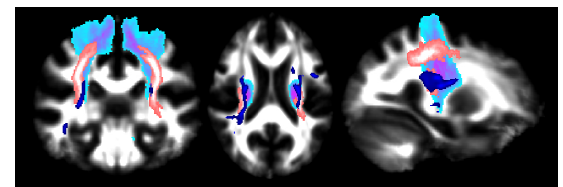


Figure 2: Significant TBSS FA results (dark blue)

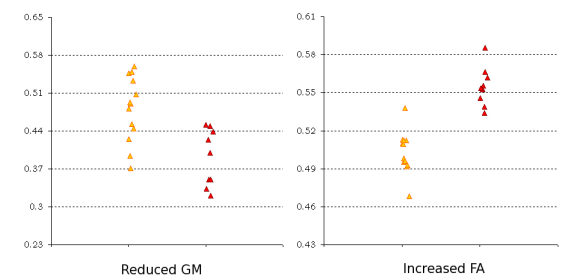


Figure 3: Significant GM results (left) and FA results (right)