Background: Focus on early intervention in Alzheimer's disease (AD) has increased the importance of characterising its preclinical stages and identifying healthy individuals at risk of developing cognitive impairment. Whilst grey matter (GM) atrophy is a well-known biomarker in AD, evidence suggests that white matter (WM) deterioration can also predict conversion to AD from mild cognitive impairment (MCI), possibly even precede GM atrophy in AD pathophysiology. Using magnetic resonance imaging (MRI) data from the Vallecas project (a 5-year longitudinal study of healthy elderly individuals), we investigate if differences in WM density (WMD) are present in cognitively normal individuals before conversion to MCI.

Methods: From a baseline cohort of 813 cognitively normal 70-85 year olds, 23 had converted to MCI by one year later. The MCI converters were matched with 23 non-converters using a novel statistical matching algorithm: each converter was matched exactly for gender and APOE genotype, then the closest match selected based on a composite score of age, years of education and MMSE at baseline. Baseline T1-weighted MRI scans of both groups were analysed using voxel-based morphometry (VBM) with SPM12 software. Segmented WM images were normalised, smoothed and entered into a two-sample t-test comparing converters and non-converters. A second analysis was conducted using the same methodology, but comparing the converters with all 790 non-converters, with matching criteria as covariates.

Results: In both comparisons, converters had lower WMD than non-converters in the body of the fornix ($p<0.01$, uncorrected). The effect was stronger in the matched group comparison ($p<0.001$, uncorrected) than the unmatched, however, neither result was robust enough to survive multiple comparisons.

Conclusions: Our preliminary findings suggest that WMD in the fornix may be lower in elderly individuals destined to develop MCI, prior to symptom onset. These results are consistent with other studies where WM deterioration in the fornix predicts conversion from MCI to AD. Although careful sample matching improved the result, the effects observed did not survive statistical correction, possibly as a result of early disease state or sample size. Further investigation with diffusion imaging and larger samples from the ongoing Vallecas project may provide more robust results.