White matter loss in the healthy elderly brain indicative of impending cognitive decline.

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Introduction

- Focus on early intervention in Alzheimer's disease (AD) has increased the importance of characterising its preclinical stages.
- Grey matter (GM) atrophy has been found to precede cognitive symptoms before conversion to mild cognitive impairment (MCI) and AD.
- White matter (WM) deterioration can predict conversion from MCI to AD, but whether it occurs earlier is uncertain.
- Determining whether WM deterioration is present in MCI patients prior to symptom onset can provide further insight on AD pathophysiology, and may be used as a biomarker for identifying individuals at risk of developing cognitive impairment.

- **Using MRI data from the Vallecas project, we investigate if differences in WM integrity are present in cognitively normal individuals before conversion to MCI.**

Methods

- The Vallecas project is a 5-year longitudinal study of healthy elderly individuals in Madrid, Spain.
- MRI and cognitive assessments are carried out at yearly follow-ups.
- From a baseline cohort of 813 cognitively normal elders, 32 had converted to MCI by the second year.
- A group of 32 non-converter controls to match the converter group was selected by:
    1) Finding an exact match for gender and APOE genotype
    2) Selecting the closest match based on a composite score of age, years of education, and MMSE at baseline assessment.

Methods (cont.)

- T1 and diffusion MRI images were analysed using voxel-based morphometry (VBM) with SPM12, and FSL, respectively.
- Scans from the baseline assessment were used for controls, whilst scans from the assessment 1 year before MCI diagnosis were used for converters.
- For VBM analysis, smoothed, normalised, and modulated white matter maps were created; fractional anisotropy (FA) maps were calculated for diffusion analysis.
- Both sets of images were entered into separate two-sample t-tests, comparing whole-brain differences between converters and controls, with age, gender, years of education, MMSE and total intracranial volume as covariates.

Results

Table 1. Subject demographics

	Mean ± SD, Range	
	Controls	**MCI Converters (1 year before conversion)**
n (female/male)	32 (18/14)	32 (18/14)
Age	76.3 ± 3.43, 70.4-83.4	76.3 ± 4.34, 69.8-85.4
Years of Education	7.7 ± 4.31, 0-19	9.0 ± 5.00, 0-24
MMSE	28.4 ± 1.13, 27-30	28.4 ± 1.10, 27-30
CDR-SB	0.3 ± 0.25, 0-0.5	0.3 ± 0.25, 0-0.5
GDS	1.7 ± 1.89, 0-9	2.1 ± 2.79, 0-11

MMSE = Mini Mental State Exam; CDR-SB = Clinical Dementia Rating – Sum of Boxes score; GDS = Geriatric Depression Scale

- VBM analyses showed lower white matter density in the head of the fornix and in bilateral posterior periventricular white matter tracts in converters than in controls (Fig. 1A, B).
- Similarly, converters had lower FA values than controls in the same regions (Fig. 1C, D).
- However, these findings did not survive correction for multiple comparisons.
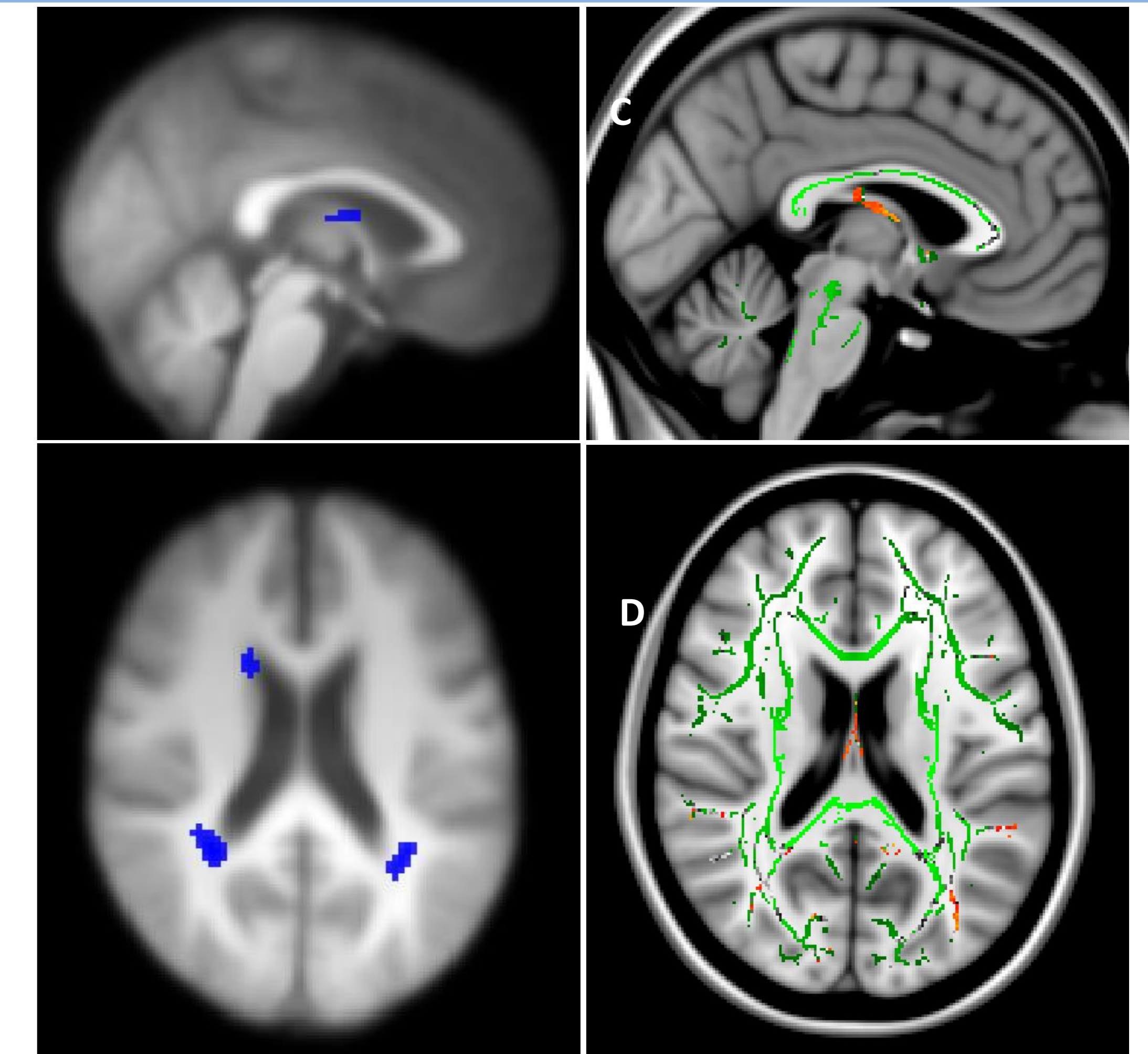
Results (cont.)

Fig. 1 – A) B) Results from VBM analyses, blue clusters indicate regions where converters have lower white matter density than controls. C) D) Results from diffusion analyses, red clusters indicate regions where converters have lower FA values than controls. p<0.01, uncorrected.

Conclusions

- Our findings suggest that WM integrity, as measured by WM density and FA, is lower in those who will develop MCI, before the onset of cognitive symptoms.
- The regions of WM deterioration are consistent with previous studies that predicted conversion from MCI to AD.
- Lack of significance after statistical correction may be due to early disease state or sample size.
- Future work will include those who convert to MCI in the third and fourth year assessments to increase sample size and improve robustness.