Comparing *APOE* subgroups in Alzheimer's disease using structural and diffusion MRI

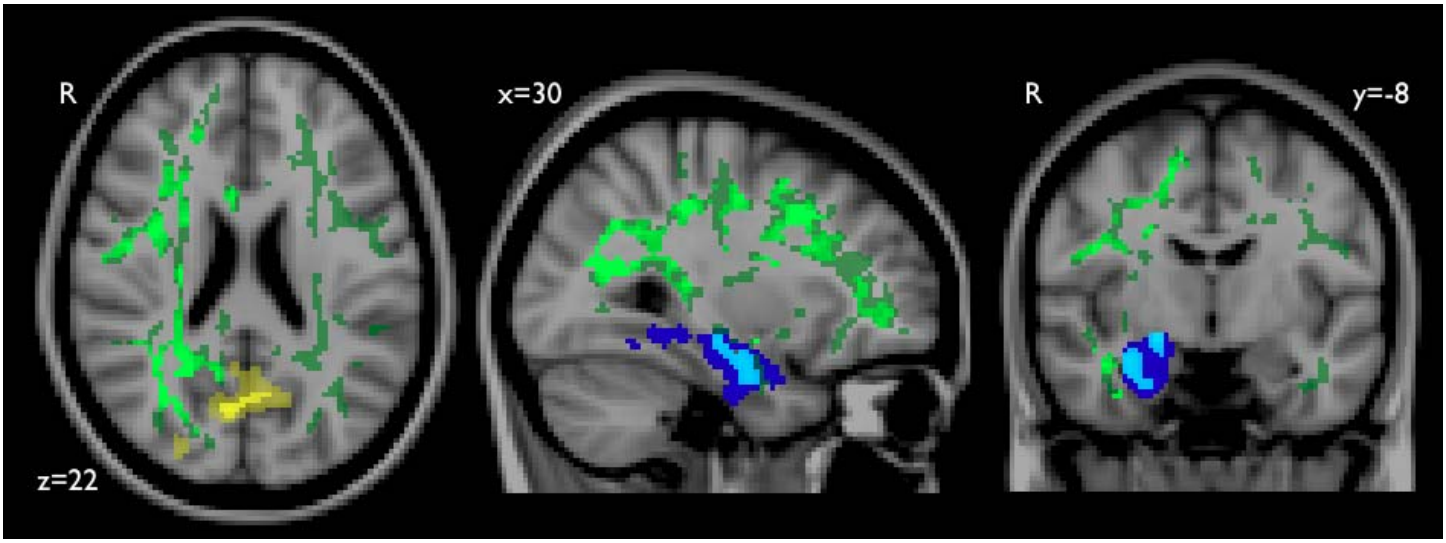
N. FILIPPINI[1,2], A. GASS[3], A. U. MONSCH[4], A. RAO[5], B. WHITCHER[5], P. M. MATTHEWS[5], AND S. SMITH[1]

[1]OXFORD UNIVERSITY FMRIB CENTRE, OXFORD, OXON, UNITED KINGDOM, [2]DEPT. PSYCHIATRY, OXFORD UNIVERSITY, UNITED KINGDOM, [3]DEPTS. NEUROLOGY AND NEURORADIOLOGY, UNIVERSITY HOSPITAL BASEL, SWITZERLAND, [4]MEMORY CLINIC BASEL, SWITZERLAND, [5]GLAXOSMITHKLINE, CLINICAL IMAGING CENTRE, LONDON, UNITED KINGDOM

INTRODUCTION Several reports have documented effects of the apolipoprotein E (*APOE*) allelic variants on the brain in health and disease. The *APOE* ε4 allele (*APOE*4) is the strongest genetic risk factor for sporadic Alzheimer's disease (AD)[1,2] and is also associated with greater cognitive impairment in AD patients, particularly in memory and learning[3,4]. Brain imaging studies allow brain tissue volumes to be used as quantitative traits in genetic association studies[5]. Neuroimaging studies on *APOE*4 carriers in AD have largely focused on grey matter (GM) changes in medial temporal lobe (MTL) structures, as they are particularly vulnerable to effects of *APOE*4. While the association between GM changes and the presence of *APOE*4 has been fairly well studied, little is known about the effect of *APOE*4 on WM in AD. To better define specific influences on neurodegenerative processes played by *APOE*4, we studied GM and WM changes in a well-characterised group of AD patients.

DATA & METHODS The EAGLE study of AD and mild cognitive impairment (MCI) includes structural, diffusion and perfusion MR imaging, *APOE* allele identification, blood and CSF chemistry and behavioural tests on over 200 subjects. We analysed a subset of 50 AD subjects (16 ε3ε3, 25 ε3ε4, 9 ε4ε4; clinical dementia rating (CDR) 0.7±0.3, age 75±8y, disease duration 3±1y). In order to investigate the effect of *APOE* polymorphism on structural and diffusion MRI data, we applied FSLVBM (Voxel-Based Morphometry using FSL tools, to test for differences across groups in grey matter density, as imaged by structural MRI) and TBSS (Tract-Based Spatial Statistics, part of FSL, to test for differences in white matter microstructure across groups, as imaged by diffusion MRI). In all analyses the multiple regression model included age, disease duration and CDR, as well as a separate group membership covariate for each of the 6 gender × *APOE* subgroup combinations. Inference was carried out using permutation testing, using TFCE (Threshold-Free Cluster Enhancement) thresholding, correcting for multiple comparisons.

RESULTS The figure integrates results of FSLVBM and TBSS analyses. Bright colours show P<0.05 fully corrected for multiple comparisons across voxels; darker colours show the same contrasts more liberally thresholded at P<0.2 corrected. Yellow: ε3ε3>ε3ε4, showing differences in grey matter density in precuneus. Blue: ε3ε3>ε4ε4, showing differences in grey matter density in right amygdala/hippocampus. Green: ε4ε4>ε3ε3, showing differences in white matter mean diffusivity (ε3ε4>ε3ε3 is similar). Tracts showing affected diffusivity (green) are clearly connecting to areas of grey matter change (yellow and blue). A further analysis correlating GM density against the cross-subject "timecourse" of mean diffusivity (averaged over voxels of significantly different MD as found above) showed a significant negative correlation with GM density in the hippocampus/parahippocampal gyrus. The white matter and grey matter measures described had approximately equal discriminative power to separate the 3 *APOE* groups.



CONCLUSIONS We have shown that *APOE*4 in AD patients is associated with both GM and WM changes. An *increase* in white matter diffusivity is often seen as one possible diffusion-related marker of pathology/aging, hence the increase seen here is consistent with a decrease in GM density, and, like the GM MTL changes, is more substantial on the right side. Changes in WM associated with *APOE4* were widespread, including extending to precuneus and temporal regions. It may not be surprising that the MD differences correlate (across subjects) more strongly with the MTL GM differences than the precuneus, given that the disease is often described as "starting" in the MTL and "spreading outwards" from there. The observed effect on WM changes may be associated indirectly with neurodegeneration or could reflect the key role played by *APOE* in lipid metabolism, mobilisation and redistribution of cholesterol, phospholipids and fatty acids, which are abundant in WM tissue[6]. We have also confirmed previous findings showing that homozygous *APOE*4 carriers (ε4ε4) show an even more severe effect on GM in medio-temporal lobe regions than heterozygous (ε3ε4), when compared with non-carriers (ε3ε3)[7]. The relative group differences are not the same in grey matter in precuneus, where ε3ε3>ε3ε4 is the strongest inter-group contrast, and the ε4ε4 group appears to take an intermediate position.

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