Evidence for structural differences in normal appearing brain tissue of those carrying different alleles of APOE

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AIM: (1) To identify whether structural differences exist in the brains of those that carry the e4 allele of the APOE gene, and those that do not. (2) To determine whether these changes correlate with cognitive performance.

TARGET AUDIENCE: of interest to those investigating subtle brain changes in those genetically predisposed to Alzheimer's Disease.

INTRODUCTION: Apolipoprotein E (APOE) is a protein involved in cholesterol and lipid transport. The gene coding for this protein has three different alleles: e2, e3 and e4. The e4 allele is recognized as a significant risk factor for developing Alzheimer's disease or age-related memory loss in later life. Paradoxically, behavioural and functional evidence demonstrate the e4 allele may confer a cognitive advantage to the carrier in youth [1-3]. We use high-resolution anatomical images, DTI, and quantitative magnetization transfer (qMT) [4] to identify subtle differences in the brain tissue of groups of young e4 carriers (e4+) and those that do not carry the e4 polymorphism (e4-).

METHODS: *Subjects and equipment*. Ninety-three healthy young participants were recruited (mean age 20 years, range 18 – 30 years, 64 females, 29 males). APOE genotypes were determined from cheek swab samples and used to randomly select 20 participants to enter the e4+ group and 21 to enter the e4- group. All scans were performed on a Siemens Avanto 1.5 T scanner. *Acquisition.* the imaging protocol included **high-resolution anatomical scan**: MP-RAGE, TR=1160 ms, TE=44 ms, TI=600 ms, FoV=230x230 mm^2, matrix=256x256, voxel size=0.9x0.9x0.9 mm^3, acq. time=5 mins; **DTI:** EPI sequence, TR=12.4 s, TE=111 ms, echo spacing=0.83 ms, FOV=240x240 mm^2, matrix size=96 x 96, voxel dimensions = 2.5x2.5x2.5mm^3, acq. time=7 min; **qMT**:, 12 3D-GRE volumes, TR=40 ms, TE=5 ms, excitation FA=5°, FOV=240x180x170 mm^3, matrix = 256x96x32. MT pulse flip angle 212, 843 for offsets 400, 875, 1912, 4182, 9146, 20000 Hz. *Analysis.* Grey- (GM) and white-matter (WM) volumes were assessed using voxel-based morphometry (VBM) of high-resolution structural MR images. Tract-based spatial statistics (TBSS) was used to identify structural differences between the groups on the DTI and qMT measures. *Cognitive Tests.* IQ, episodic memory, verbal fluency and speed of processing test were used to provide baseline data for group comparability. Episodic memory was tested by free recall of a 20 item word list, each word presented every 2 seconds on the computer screen, followed by an immediate written recall.

RESULTS AND DISCUSSION: Our VBM study has revealed that e4+ have significantly higher WM volume ratio than their e4- peers (e4+: 0.39, e4-:0.38, p=0.022). DTI studies identified increases in axial diffusivity ($\lambda_{||}$) in carriers e4+. The significant differences are detected in the left hemisphere (Fig. 1a), whereas the trend to generally higher $\lambda_{||}$ (Fig. 1b) is widespread. In no region was $\lambda_{||}$ decreased in e4+. A significant correlation was found between axial diffusivity and episodic memory (r = 0.329, p = 0.019, 1-tailed test). Mode of anisotropy (MO) was significantly increased in e4+ following a correction for multiple comparisons. These increases were localized to the region of the inferior longitudinal fasciculus and complement the $\lambda_{||}$ measures, suggesting improved axonal coherence in WM. Evidence of a trend towards increased transverse relaxation time of the bound proton pool T_2^B was detected in e4+, indicative of altered WM composition.

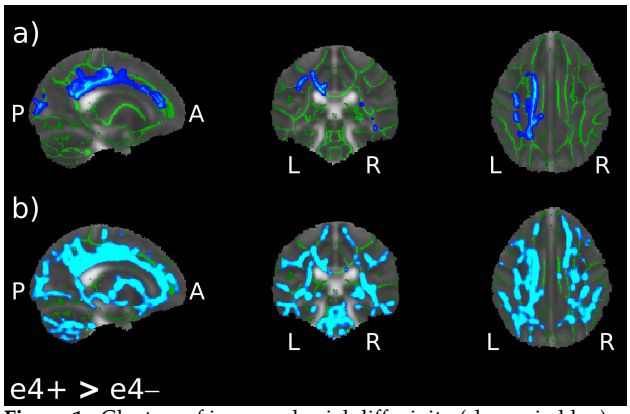

Figure 1 - Clusters of increased axial diffusivity (shown in blue) for e4+ compared to e4-, projected on to the TBSS tract skeleton (in green). The cluster threshold was (a) $p < 0.05$, with TFCE correction and (b) $p < 0.05$, uncorrected for multiple comparisons. Slices shown at MNI co-ordinates x = -19, y = -30, z = 35.

CONCLUSIONS: This study has shown subtle differences in the brains of young healthy adult e4+ and e4- subpopulations. Axial diffusivity was found to correlate with indices of cognitive performance across the two groups. This supports the notion that such subtle differences in WM integrity may confer neural advantages that contribute to cognitive outcomes as observed here in a test of verbal fluency and previously reported by other researchers [1-3].

REFERENCES: [1] Wright RO, et al. Pediatr Res 2003;54(6):819-825. [2] Yu CS, et al. Intelligence 2009;37(2):174-180. [3] Hubacek JA, et al. Neuropsychobiology 2001;43(3):200-203. [4] Cercignani M, et al. Neuroimage 2005;27(2):436-441.