Regional brain volume changes correlate with functional differences between APOE-e4+ and APOE-e4-

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

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

INTRODUCTION: 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 (AD) or age-related memory loss in later life but, 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 to identify differences in the brain volume of groups of young e4 carriers (e4+) and those that do not carry the e4 polymorphism (e4−) and find that areas of volume difference correlate with fMRI differences when completing cognitive tasks.

METHODS: *Subjects and equipment.* 93 healthy young participants were recruited (mean age 20 years, range 18 – 30 years, 64 females, 29 males) as well as 78 health mid-aged participants (mean age, range 43-58, 44 females, 34 males). APOE genotypes were determined from cheek swab samples and used to randomly select the e4+ and e4− groups. *Selected Young group:* 20 participants to enter the e4+ group and 21 to enter the e4− group; *Selected Middle-age group:* 17 participants to enter e4+ group, 22 to enter e4− group. All scans were performed on a Siemens Avanto 1.5 T scanner.
Acquisition. The imaging protocol included a **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, acquisition time=5 min; **fMRI**: BOLD EPI, TR= 3300 ms, TE=50 ms, FoV=192x192 mm^2, matrix=64x64, voxel size=3x3x3mm^3, slices=36; **fMRI tasks**: (1) Prospective memory (PM) card-sorting task. (2) Covert attention (CA) task using a combination of congruent and incongruent cues. Speed and accuracy of participants' responses were recorded.
Analysis. Cortical reconstruction and volumetric segmentation were performed with the Freesurfer image analysis suite [5-7]. The fMRI analysis was completed using the standard hierarchal model approach employed in SPM8 (FIL, UCL London).

RESULTS AND DISCUSSION: In the **young group**, the volumetric segmentation revealed that there is a significant bilateral increase in white matter volume in the cuneus and in right-side inferiorparietal areas for e4+ group compared to e4− (Table 1). These findings correlate with our fMRI study that reveals increased activation in the cuneus and parietal regions among e4+[8]. In the **middle-age group** there was bilateral increase in parahippocamal cortical thickness for e4+ compared to e4−, this correlates with increased activation seen by Fillipini et al [9] with the suggestion that this is a compensation mechanism among e4+. There was reduced thickness in the right-sided occipital areas that correlates with decreased activity in occipital regions.

Comparison	e4+ Δ(Volume)	p-value
Young group (e4+ v e4−)		
Cuneus volume	+14%	0.004
Inferior parietal volume	+16%	0.003
Middle age group (e4 v e4−)		
Parahippocampus thickness	+6%	0.02
Occipital volume	−6%	0.002

Table 1. Summary of brain volume differences Δ(Volume). Positive percentage differences indicate increased volume in e4+. Negative differences indicate decreased volume in e4+. Volume changes correlate with regions showing significantly different response to fMRI tasks.

CONCLUSIONS: This work demonstrates that subtle regional brain volume differences can be detected between healthy e4+ and e4− at young and middle age. The volumetric data from this work positively correlates with areas of activation found in functional imaging studies conducted by our group and others. This work also suggests there is a detectable link between brain structure and activity within these populations.

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