White Matter Changes in Cognitively Healthy Adults With the APOE E4 Gene

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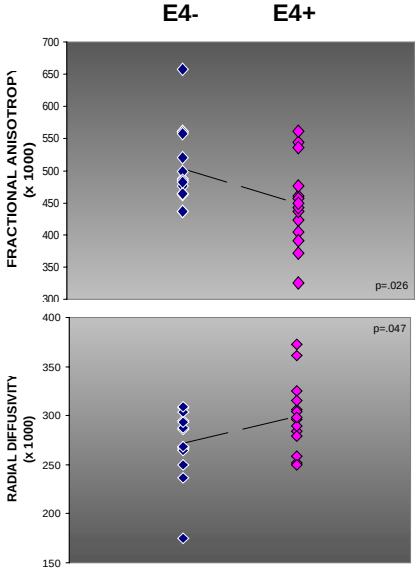
INTRODUCTION- APOE ε4 is a gene on chromosome 19 that confers a 4-6 fold heightened risk for developing Alzheimer's disease (AD). No preclinical MRI markers are available for the early diagnosis of AD. Diffusion Tensor Imaging (DTI) studies have shown decreased white matter (WM) diffusion anisotropy and increased diffusivity in patients with AD and minimal cognitive impairment, a disorder which often progresses to AD. Here we present the first known report of WM abnormalities using DTI in cognitively intact older adults with (ε4+) and without (ε4-) the APOE ε4 gene.

METHODS- All participants (aged 60-77) were medically healthy with no laboratory abnormalities and no evidence of dementia (CDR=0), neurological, or psychiatric illness and had mini mental status scores ≥ 28. 14 ε4+ subjects (mean age 66.9±5.3) and 15 ε4- subjects without (mean age 65.6±3.1) were group-matched for age (p=.78) and years of education (p=.89). The *ε4-* group consisted of genotypes *ε2/ε3* (N=5) and *ε3/ε3* (N=10). *ε4+* subjects were primarily *ε4/ε3* (N=12) with *ε4/ε4* (N=1) and *ε4/ε2* (N=1). Imaging was conducted on a 1.5 T Siemens Vision system. A 3D T1-weighted sagittal MP-RAGE scan was acquired (matrix 256 x 256, FOV 300mm, 172 partitions for a nominal slice thickness of 1.686mm, 0mm gap). Oblique axial DTI scans (AC-PC aligned at acquisition) were acquired with a pulsed gradient, double spin echo, EPI sequence (TR/TE 6000/100 ms, 128 x 128 matrix, FOV 240 mm, *b*=900s/mm2, NEX=4, 20 slices, 5mm slice thickness, 0mm gap). The double spin echo method substantially reduces image distortion artifacts due to eddy currents. Diffusion was measured along six equally spaced non-collinear directions. For each of these six gradient directions, four acquisitions were averaged. Two acquisitions without diffusion weighting (*b*=0) were also averaged. Blind to genotype, small (~15mm^2) graphical ROIs were placed on DTI-derived maps of fractional anisotropy (FA), trace diffusivity, axial (DAx) and radial [$(\lambda_2+\lambda_3)/2$] diffusivity (DRa) in the right and left WM of the parahippocampal gyrus, at slice positions -5mm, -10mm and -15mm relative to the AC-PC plane. FA and diffusivity measures were each evaluated with repeated measures ANOVA with one between-subject variable (genotype), and two within subject variables (slice and side).

RESULTS- No main effects of genotype were observed for any DTI metric. However, ANOVA for FA showed a main effect of slice [F(2,52)=6.39; (p=.003)] and a genotype by slice interaction [F(2,52)=4.87, p=.011]. Profile plots revealed a ventral > dorsal trend for mean FA differences across the three slice regions with the largest group differences occurring at AC-PC -15mm. At this level mean (±SD) FA (averaged across both sides) was significantly less [t(27)=2.35, p=.026)] in parahippocampal ROIs in ε4+ subjects (.448± 66) relative to ROIs in ε4- subjects for E4+ (.503±59). These data are shown in Figure 1 (top). For trace a marginally significant genotype by slice interaction was observed [F(2,52)=2.79; (p.070)] and for the Dax no genotype by slice interaction was observed. For DRa, an effect of slice [F(2,52)=4.75, p=.013] and genotype by slice interaction [F(2,52)=5.19, (p=.009)] were observed. Only the most ventral ROIs (averaged across sides) showed significant group differences [t(27)=2.09, p=.047] for DRa, which was higher in ε4+ subjects (.299± .036) than in ε4- subjects (.271± 034). These data are displayed in Figure 1 (bottom). Region-specific genotype effects were present even when age was used as a covariate in the main ANOVAs. Individual and group data for FA and RA are displayed in Figure 1. Dashed lines connect the group means.

Figure 1 Parahippocampal WM Deficits in APOE ε4 Carriers at AC-PC -15mm



CONCLUSIONS- Targeting the WM of the medial temporal lobe, where the earliest neuropathological changes of AD have been characterized, we found white matter abnormalities in cognitively intact older adults with heightened genetic risk for AD using DTI. That the differences were greatest in the basal regions of the parahippocampal gyrus reinforces its potential relationship to postmortem studies of AD neurofibrillary pathology. The combination of decreased FA and increased DRa is similar to the profile observed in myelin basic protein-deficient mice, which has been observed in our lab as well as the lab of others. Myelin defects have also been observed in postmortem AD brain, with a neuroanatomical distribution consistent with that observed in the present study. These data argue for more intensive investigation of WM MRI measures as potential early diagnostic indicators of progression to AD.