Microstructural differences in the aging white matter of APOE allele ε4 carriers: a diffusional kurtosis imaging and diffusion tensor imaging study

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INTRODUCTION: Being a carrier of the allele ε4 of the apolipoprotein E (APOE) gene is a risk factor for cerebrovascular disease and sporadic Alzheimer's disease. Diffusion tensor imaging (DTI) has previously been used to investigate microstructural differences between carriers and non-carriers of the risk allele; one study revealed mean differences in fractional anisotropy (FA) in young adults and mean diffusivity in older adults separately [1], while another observed genotype by age interaction across the brain in mean diffusivity (MD) and in some regions in FA [2]. Diffusional kurtosis imaging (DKI) is a recently developed neuroimaging technique [3] enabling the additional characterization of the tissue diffusional heterogeneity that has not been applied yet to explore differences between APOE allele ε4 carriers and non-carriers. The goal of our study was to use these novel diffusion metrics to investigate microstructural differences in the aging white matter tissue of carriers of APOE allele ε4 compared to non-carriers that could potentially be linked to its involvement as a risk factor. Secondary goals included identifying whether these changes are observed early as previous studies had few middle-age adults in their sample and suggesting potential tissue correlates based on the integrated diffusion metrics to guide further histological research.

METHODS: 75 generally healthy and non-demented participants (41-91 yo, 29M/46F) were divided in two groups of 55 APOE ε3/ε3 (non-carriers) and 20 APOE ε3/ε4 (carriers) had a whole-head DKI scan (2 mm isotropic, 24 directions with b-values of 700, 1400 and 2100 s/mm^2 and 10 T_2-weighted (b_0) images with b-value = 0 s/mm^2). DTI metrics (fractional anisotropy: FA, mean diffusivity: MD, axial diffusivity: AD, radial diffusivity: RD) were obtained using FSL dtifit from the first b-value measurements. Mean, axial and radial kurtoses (MK, AK and RK) were fit using the FanDTasia toolbox [4,5]. The FSL Tract-Based Spatial Statistics (TBSS) procedure and FSL randomise were used to create a white matter skeleton and to analyze cross-sectionally the group by age interaction with the diffusion metrics on a per-voxel basis on this skeleton, using threshold-free cluster enhancement (TFCE) as the correction for multiple comparisons [6,7].

RESULTS: There was a group by age interaction with MD and RD (corrected p<0.05) in the right hemisphere and bilaterally for AD, corresponding to a greater increase in diffusivity with increasing age in carriers. Broad statistical trends were also observed for a greater decrease in MK and RK with age across the white matter skeleton of carriers, with RK spanning a larger region which is compared in Figure 1a with MD at the corrected p<0.10 level. Trends were also observed for greater increases in AD and RD with age in carriers in complementary regions, with the former spanning the anterior limb of the internal capsule and splenium while the latter was present in regions similar to the RK effects as shown in Figure 1b. A statistical trend for a greater decrease in FA was found in a small prefrontal region and no group by age interaction was found for AK. Figure 2a shows that there was a significantly greater increase in MD and decrease in RK in carriers with age in similar regions using a subsample of middle-aged adults (< 60 yo, 9 carriers and 23 non-carriers). Significantly greater increases in AD and RD with age were also observed in similar regions as shown in Figure 2b but with greater overlap compared to the trends seen in the full sample in Figure 1b. A trend for a greater decrease in MK in similar regions and FA in the left temporal lobe was also observed. The same analysis in a similar subsample including only older adults showed no significant difference or trend.

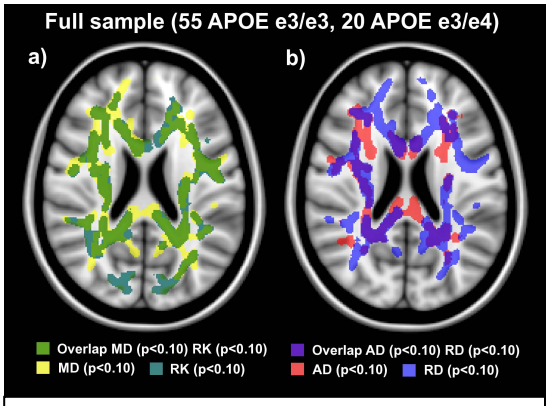

Figure 1 Statistical trends in group by age interaction with a) MD and RK and b) AD and RD in the full sample. Significant interactions were present with MD and RD unilaterally and with AD bilaterally but trends are shown for easier comparison. All p-values are corrected for multiple comparisons and results have been dilated out of the TBSS skeleton for easier visualization.

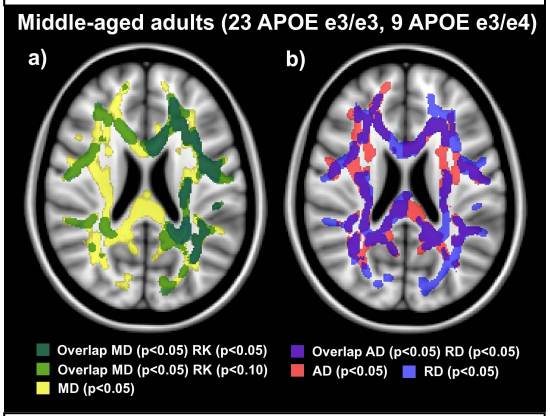

Figure 2 Significant group by age interactions with a) MD and RK and b) AD and RD in the middle-aged adults only. All p-values are corrected for multiple comparisons and results have been dilated out of the TBSS skeleton for easier visualization.

DISCUSSION: Trends for a group by age interaction were observed with all DTI and DKI metrics, except AK and minimally with FA, pointing to a greater cross-sectional increase in diffusivity and decline in the radial diffusional heterogeneity with increasing age, broadly across the white matter of APOE allele ε4 carriers. These trends were significant when we alternatively investigated the group by age interaction in a subsample reduced to 60 subjects to roughly match for both sex and age, pointing to possible confounds. The presence of significant group by age interactions with diffusion metrics in middle-aged adults suggests potentially very early white matter changes in carriers possibly related with their predisposition to Alzheimer's disease, although results need to be replicated with a larger sample size. A previous study corroborates the observed group by age interaction with MD in the full sample, but also found a similar interaction with FA in fewer regions [2]. Another study showed similar white matter regions to have a higher MD in older carriers [1], which is consistent with our observed greater increase in MD in middle-age carriers; however we did not find any significant difference in the MD of our older carriers. Speculatively, decreases in mean, axial and radial diffusivities suggest an increasing extracellular space compartment. However, a decrease in RK increases the possibility of myelin sheath or axonal membrane damage as this metric is minimally affected by an increase in extra-cellular space. It can be noted however that several tissue correlates might be at work as overlapping differences in both RK and AD can hardly be explained by a single underlying cause. Histological studies and longitudinal design would allow more precise investigation and integration of the diffusion metrics to identify tissue correlates linked to the microstructural differences observed.

CONCLUSION: Our study suggests that small differences in aging trends for white matter microstructure can be detected in APOE allele ε4 carriers using DKI and DTI procedures and that such changes may be detectable as early as middle age.

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