00396 Greater Longitudinal White Matter Microstructure and Extracellular Free-water Changes in Healthy Elderly APOE4 Allele Carriers

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Aims: The apolipoprotein E4 (APOE4) allele is a key Alzheimer's disease risk factor with preliminary evidence indicating poorer white matter integrity in APOE4 carriers. However, the longitudinal link between APOE4 and white matter microstructure remains unexplored. Thus, we used free water (FW) corrected diffusion MRI measures in healthy older adults to differentiate longitudinal APOE4-related alterations in brain tissue fractional anisotropy (FAt) from extracellular FW increase. We hypothesized that APOE4 carriers would show larger FW increases and FAt declines over time.

Methodology: We used dMRI data from healthy elderly subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI: 23/73 APOE4 carriers/non-carriers; 2-4 time-points) and Singapore Longitudinal Ageing Brain Study (S-LABS: 21/83 APOE4 carriers/non-carriers; 2-3 time-points). We derived subject-specific FW and FAt maps from diffusion MRI data and averaged over the whole-brain white matter and 18 major white matter fibres traced using the TRACULA method.

Linear mixed models assessed the contribution of cross-sectional age, time and APOE genotype (e4 carrier/non-carrier) on FW and FAt longitudinal trajectories. Covariates included gender, years of education and estimated total intracranial volume.

Result: APOE4 carriers had higher baseline FW in the bilateral superior longitudinal fasciculus (temporal part) for S-LABS ($p<0.05$) and greater increases in FW over time in bilateral cingulum angular bundle for ADNI ($p<0.05$). APOE4 carriers also showed steeper reduction in left CAB FAt over time in S-LABS and in the right CAB FAt over time in ADNI (APOE4*time; $p<0.05$). Moreover, APOE4 carriers had faster age-dependent FW increases in the right inferior longitudinal fasciculus, bilateral cingulum cingulate gyrus and right uncinate fasciculus over time in ADNI (APOE4*Age*Time; $p<0.05$).

Conclusion: Across the two datasets, we consistently demonstrated that the presence of APOE4 allele in the healthy elderly appears to be associated with greater neuroinflammation, mild vascular changes and excessive white matter degeneration over time in temporal-parietal and temporal-occipital fibres.