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Differential white matter extracellular water increase in APOE e4 carriers and non-carriers among healthy normal, mild cognitive impairment, and Alzheimer's disease

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Abstract:
Introduction: Alzheimer's disease (AD) is associated with white matter (WM) microstructure abnormalities revealed by diffusion tensor imaging (DTI) method. The apolipoprotein-E epsilon4 (APOE-ε4) allele is a major genetic risk factor for AD, which may also impact WM microstructure such as demyelination and axonal damage. However, the current DTI model suffers from the partial volume effect, therefore preventing accurate quantification of WM abnormalities in AD patients. Free-water (FW) imaging can solve this problem by differentiating the water compartment in the extracellular space from the tissue compartment in a voxel-based manner using DTI data. Here, using FW techniques in subjects with no cognitive impairment (NCI), mild cognitive impairment (MCI), and AD, we hypothesized that APOE-ε4 carriers and non-carriers would have differential trajectories of WM damage along the AD progression.
Methods: 167 subjects (13 NCI carriers, 50 non-carriers; 22 MCI carriers, 35 non-carriers; and 18 AD carriers, 29 non-carriers) underwent DTI scans (Siemens Tim Trio, 3T, 61 diffusion directions at b=1150 s/mm^{2}and 7 b0 maps). The DTI data were preprocessed using FSL. FW method was applied to derive the individual FW and tissue compartment maps. To access the group difference in FW and tissue compartments (carriers vs. non-carriers in NCI, MCI and AD), we carried out voxel-wise statistics on the FW and tissue compartments images using two-sample t-tests. All analyses were controlled for age, gender, handedness, and ethnicity.
Results: There was no difference in FW and tissue compartments between carriers and non-carriers in AD and NCI group. In MCI group, carriers had higher WM FW mostly at posterior temporal/parietal and occipital regions compared to non-carriers. Tissue compartment did not differ. Moreover, we extracted the mean FW values of these significant regions identified from the MCI group and compared the carriers and non-carriers across the three groups. Differential trajectories of WM FW in carriers and non-carriers across the three groups were observed: in carriers, there was WM FW increase in MCI compared to the NCI; in contrast, in non-carriers, there was WM FW increase in AD compared to MCI stage but not MCI compared to NCI.
Conclusion: Our findings suggest that APOE genotype influences the FW concentration of WM in MCI. APOE-ε4 carriers may feature an early increase in neuroinflammation, making them more vulnerable to Alzheimer's disease.