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NEUROIMAGING

APOEε4 drives microglial activation in the medial temporal cortex in individuals across the AD spectrum

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Abstract

Background: Microglial activation is an early phenomenon in Alzheimer's disease (AD) that may occur prior to and independently of amyloid-β (Aβ) aggregation. Compelling experimental evidence suggests that the apolipoprotein E ε4 (*APOE*ε4) allele may be a culprit of early microglial activation in AD. However, it is unclear whether the *APOE*ε4 genotype is associated with microglial reactivity in the living human brain. In individuals across the aging and AD spectrum, we tested the hypothesis that *APOE*ε4 associates with microglial activation.

Method: We studied 118 individuals (79 cognitively unimpaired [CU], 23 with mild cognitive impairment [MCI], and 16 with AD dementia) from the Translational Biomarkers in Aging and Dementia (TRIAD) cohort. Individuals had available [^{18}F]AZD4694 Aβ PET, [^{18}F]MK6240 tau PET, [^{11}C]PBR28 microglial activation PET, and magnetic resonance imaging (MRI), as well as *APOE* genotyping. To increase the reliability of our results, we only included high-affinity binders for the [^{11}C]PBR28 radiotracer. In a subgroup of 42 individuals with longitudinal clinical and MRI data, we further assessed longitudinal hippocampal atrophy and clinical deterioration.

Result: Voxel-wise analysis revealed that *APOE*ε4 carriership was associated with increased [^{11}C]PBR28 uptake mainly in the medial temporal cortex (Figure 1A and B), and this effect of *APOE*ε4 was independent of Aβ and tau accumulation. Region-wise analyses demonstrated that *APOE*ε4 carriers presented increased [^{11}C]PBR28 SUVR relative to noncarriers only in Braak I-II regions (Figure 1C), which further supports that *APOE*ε4-related microglial activation occurs specifically in medial temporal structures. Lastly, we found that [^{11}C]PBR28 uptake in brain regions vulnerable to

APOEε4 effects is associated with subsequent hippocampal atrophy and clinical decline over 2 years (Figure 2).

Conclusion: These results support a model in which APOEε4 plays a role in early AD progression by contributing to microglial activation in medial temporal regions. Our findings provide a rationale for the development of novel AD therapies targeting the interplay between ApoE and neuroinflammation.

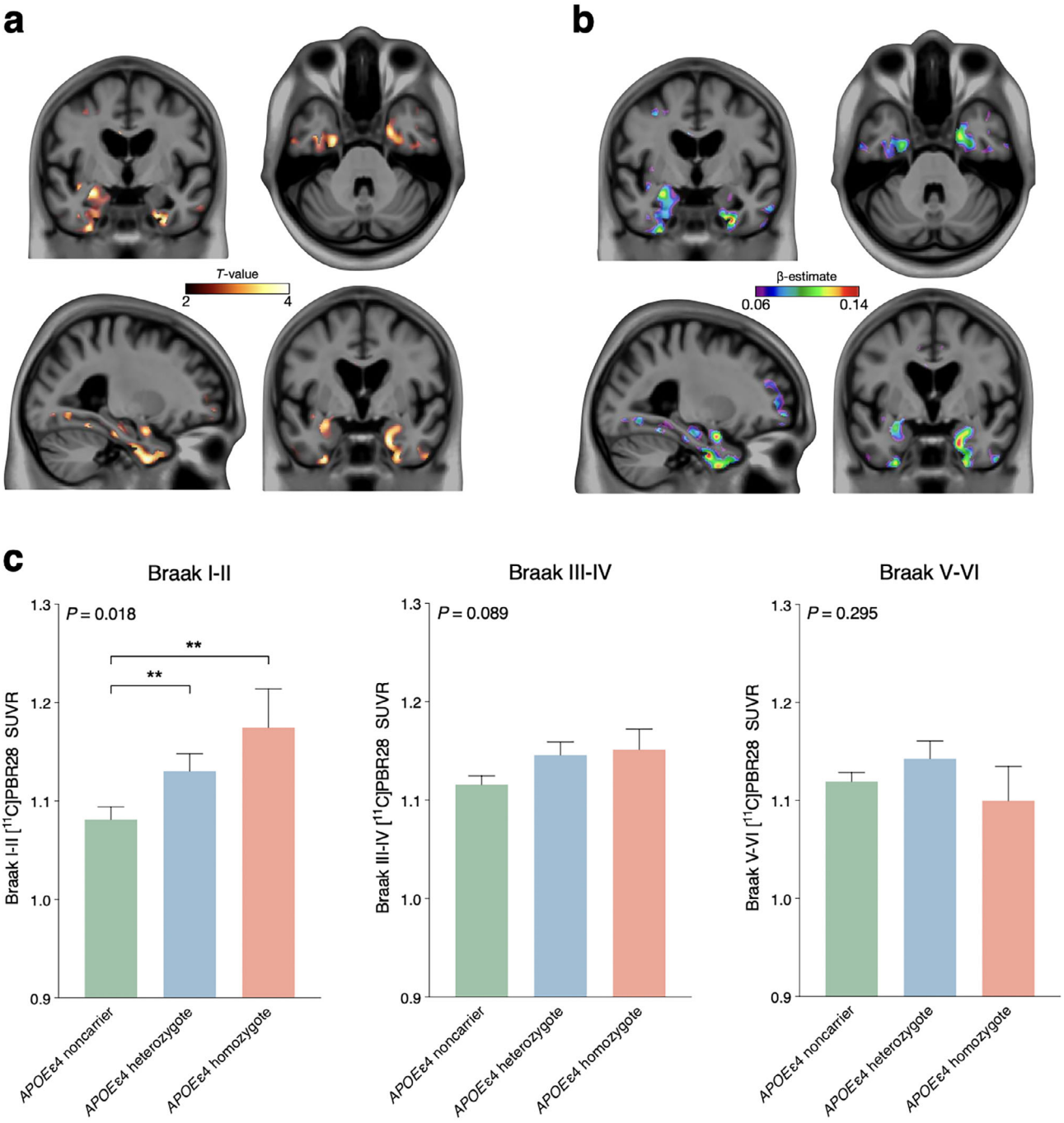

Figure 1. *APOE*ε4 is associated with microglial activation in the medial temporal cortex. (**a**) T-map and (**b**) β-map show the result of voxel-wise linear regression testing the association of *APOE*ε4 carriership with [11C]PBR28 SUVR accounting for age, sex, and clinical diagnosis. (**c**) Bars show the mean and SEM of [11C]PBR28 standardized uptake value ratio (SUVR) in *APOE*ε4 noncarriers, *APOE*ε4 heterozygotes and *APOE*ε4 homozygotes. Groups were compared using analysis of covariance with Tukey's multiple comparisons test (**$P < 0.05$). All regression models were adjusted for age, sex, and clinical diagnosis.

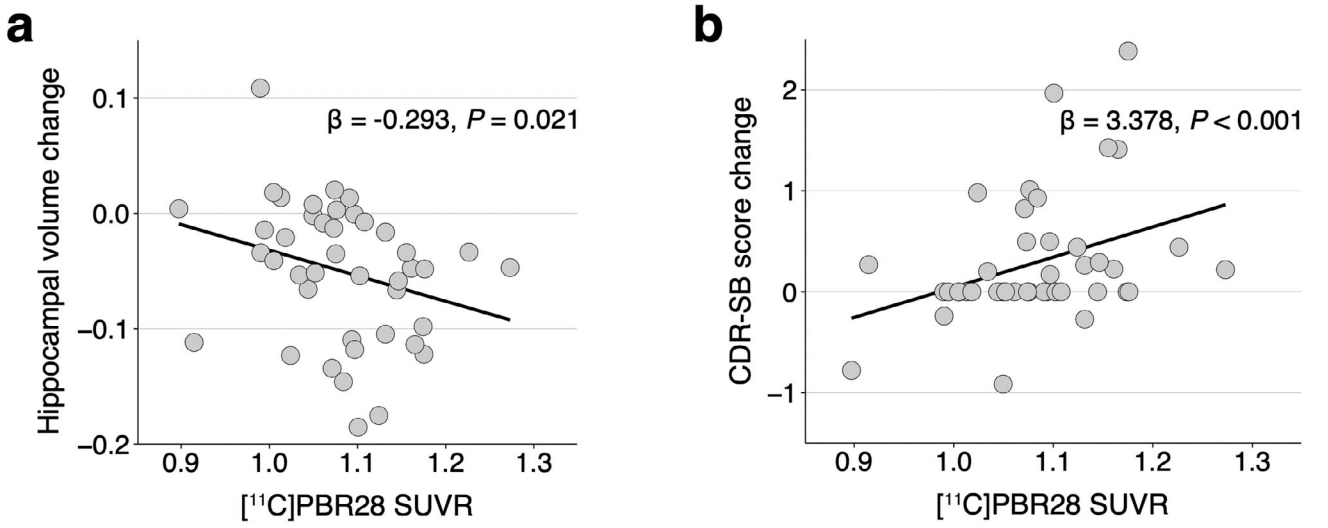

Figure 2. Microglial activation in *APOE*ε4-vulnerable regions associates with longitudinal hippocampal atrophy and clinical decline. The scatter plots shows the association of [^{11}C]PBR28 SUVR with annual changes in (**a**) hippocampal volume (mean [SD] follow-up, 2.1 [0.7] years) and (**b**) CDR-SB score (mean [SD] follow- up, 1.8 [0.5] years). These analyses were conducted in a subset of 42 individuals (31 CU, 6 with MCI, and 3 with AD dementia). [^{11}C]PBR28 SUVR values were extracted from the brain regions showing *APOE*ε4 effects on microglial activation. The β-estimates and P-values were computed from regression models accounting for age, sex, and clinical diagnosis.