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NEUROIMAGING

Microglial Activation and Tau Accumulation in the Alzheimer's Disease Spectrum: Insights from Longitudinal PET Imaging

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Abstract

Background: Recent evidence suggests that microglial activation mirrors tau accumulation along highly connected brain regions, but their relation remains unclear. We examined (a) longitudinal changes in microglial activation in Alzheimer's disease spectrum (ADS) compared to healthy controls (HC) (b) whether these changes are linked to tau levels and their functional connectivity (FC), and (c) the relation of microglia and tau across CDR-based groups.

Method: As part of the longitudinal ActiGliA prospective cohort study, ADS ($n = 36$, defined by CSF Aβ42/Aβ40 ratio or an Aβ PET composite of ADS) and HC ($n = 20$, with CDR=0 and no Aβ pathology) underwent [18F]GE-180 (TSPO) imaging to assess microglial activation and resting-state fMRI to determine FC, alongside structural T1 MRI. After 18 months, a subset of participants received follow-up TAU-PET ([18F]Flutemetamol) and TSPO-PET.

Results: TSPO ratios (FU/BL SUVRs) increased from baseline to follow-up in ADS when compared to HC (paired median difference 0.0718, $p <0.001$), and were negatively correlated with TAU (ρ=-0.207, $p = 0.003$) or TSPO SUVRs (ρ=-0.152, $p = 0.032$), while HCs showed positive correlations. For ADS participants, the TSPO SUVR ratio (ρ=-0.19, $p = 0.008$) and ADS-HC TSPO ratio difference (ρ=-0.27, $p <0.001$) were inversely associated with FC distance from the TAU hotspot, a pattern opposite in HCs. Braak-like stage analysis showed TSPO SUVR increases in ADS at advanced stages (Braak 5: 0.011, Braak 6: 0.0115) but decreases in HC. TAU SUVRs in CDR=0 ($n = 13$) were better predicted by TSPO SUVRs in CDR=0.5 ($n = 6$) (β=1.16, R^2=0.79, AIC=-509) than CDR=0 TSPO SUVRs (β=1.3, R^2=0.64, AIC=-307). Similarly, the TAU SUVRs in CDR=0.5 were better estimated by CDR=0.5 TSPO SUVRs (β=0.79, R2=0.64, AIC=-400), than in CDR=0 (β=0.89, R2=0.5, AIC=-239).

Conclusion: These findings suggest microglial activation increases in ADS and correlates inversely with TAU, with spatial and temporal patterns supporting a mild pseudotemporal precedence of microglial activation over tau accumulation.