



## Spatial cognition is associated with levels of phosphorylated-tau and $\beta$ -amyloid in clinically normal older adults

*Gillian Coughlan, Brennan DeSouza, Peter Zhukovsky, Michael Hornberger, Cheryl Grady, Rachel F. Buckley, for the European Prevention of Alzheimer's Disease (EPAD) Consortium*

Spatial cognition is associated with Alzheimer's disease (AD) biomarkers in the symptomatic stages of the disease. We investigated whether cerebrospinal fluid (CSF) biomarkers (phosphorylated-tau [p-tau] and  $\beta$ -amyloid) are associated with poorer spatial cognition in clinically normal older adults. Participants were 1875 clinically normal adults (age 67.8 [8.5] years) from the European Prevention of Alzheimer's Dementia Consortium. Mixed effect models assessed the cross-sectional association between p-tau181,  $\beta$ -amyloid1–42 ( $A\beta$ 1–42) and p-tau181/ $A\beta$ 1–42 ratio and spatial cognition measured using semi-automated Supermarket Task and the 4 Mountains Task. Levels of p-tau181,  $A\beta$ 1–42, and p-tau181/ $A\beta$ 1–42 ratio were significantly associated with spatial cognition scores on both tasks. The p-tau181/ $A\beta$ 1–42 ratio showed the largest effect sizes ( $\beta = -0.04/0.05$ ,  $p < 0.001$ ). Lower entorhinal cortical volume was associated with poorer outcomes on both tasks ( $\beta = 0.06$ ,  $p < 0.002$ ) and accounted for 18%–22% of the direct association between p-tau181 and spatial cognition scores. In conclusion, degeneration of the entorhinal cortex mediates a significant proportion of the association between p-tau181 and spatial assessments in cognitively normal adults. Future studies should focus on increasing the sensitivity of digital spatial assessments.

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