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TAU IMAGING

# A longitudinal analysis of depressive symptoms in relation to repeated measurements of regional tau

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## Abstract

**Background:** Depressive symptoms are commonly observed early in Alzheimer's disease (AD), but their temporal association with progression along the AD continuum is less clear. We sought to determine if initial measurements of regional tau were predictive of increasing depressive symptoms, and if changes in depressive symptoms predicted later tau levels. We examined these relationships in a region of early tau accumulation (i.e., entorhinal cortex (EC)), and in regions of later neocortical tau spread commonly involved in affective regulation (amygdala and medial and lateral orbitofrontal cortex (mOFC, lOFC)).

**Method:** Participants (n=257; mean age=70.7; 61% female) came from the Harvard Aging Brain Study, a longitudinal observational cohort of cognitively unimpaired adults with no/low depression at baseline (mean years of follow-up=7.2). All participants completed the self-reported 30-item Geriatric Depression Scale (GDS) annually and tau PET imaging (Flortaucipir-FTP) every 3 years. On average, initial tau PET scans occurred 2.3 years after enrollment and the latest available scan occurred 5.1 years after enrollment. Separate linear mixed effects models investigated relationships between longitudinal GDS and cross-sectional regional tau (FTP PET SUVr), at initial scan and at the latest scan available, in the following regions of interest: EC, amygdala, mOFC, and lOFC. Covariates included age, sex, and education.

**Result:** Higher initial FTP levels were associated with significant increases in GDS score over time in temporal cortex (amygdala: b=0.29,p=0.0002; EC: b=0.21,p=0.0006) and mOFC (b=0.30,p=0.004), with marginal significance in lOFC (b=0.21,p=0.07). However, the reverse temporal sequence was only observed between GDS scores over all

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time points and later measurement of amygdala FTP, such that increasing depressive symptoms over time preceded higher final amygdala tau levels (b=0.15,p=0.02).

**Conclusion:** Higher tau in EC, amygdala and OFC regions predicted increasing depressive symptoms over time in older adults. Only for the amygdala did we also observe the converse relationship: increasing depressive symptoms predicting higher final tau. These results suggest early tau proliferation in affective regions is associated with increased depressive symptoms, though the question of causality is still unclear. Further work is needed to dissect possible temporal relationships across whole brain voxels to better understand depressive symptoms in AD progression.