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IMAGING AND NON-AD NEURODEGENERATION

Differential associations of amyloid and tau (from PET) with brain volumes (from MRI) by cognitive status

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Abstract

Background: Alzheimer's disease pathology (AD) is an important cause of neurodegeneration and brain atrophy. Non-AD mechanisms can also cause neurodegeneration alone or in conjunction with AD. Harboring combination of AD and non-AD pathologies leads to greater cognitive impairment and dementia. Here, we examined the hypothesis that the association of amyloid and tau burden from positron emission tomography (PET) with brain volumes from magnetic resonance imaging (MRI) is weaker in those with dementia compared to those with mild cognitive impairment (MCI) or normal cognition.

Method: We used data from participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI) who had either florbetapir amyloid PET (N=1320) of flortaucipir tau PET (N=833, 535 of whom had both). We examined the association between volumes of brain structures (FreeSurfer-v7) and standardized uptake value ratios (SUVr) for amyloid (summary cortical region, normalized to whole cerebellum) and tau (meta-temporal region, normalized to inferior cerebellar gray matter) separately, using linear regressions adjusting for age, sex, and education. We report results in overall groups and by cognitive status (normal, MCI, dementia). We display semi-partial correlations (sr, thresholded at $P_{uncorrected}<0.05$), as measures of effect size.

Result: *Table-1* summarizes participant characteristics. The effect of amyloid on brain volumes was modest in the overall cohort, with associations strongest for inferior/middle temporal, inferior parietal, entorhinal, hippocampus, and amygdala regions (sr∼-0.2, P<0.001 all). In those with dementia, however, there were no distinct associations between amyloid and brain atrophy (*Figure-1*). For tau, associations in the overall cohort were similarly strongest for inferior/middle temporal, inferior parietal, entorhinal, hippocampus, and amygdala regions (sr∼-0.3, P<0.001 all). In those with dementia, associations remained strong for inferior/middle temporal regions (sr∼-0.3, P<0.001) but tau was not associated with hippocampus volumes (left, sr=-0.05, P=0.6; right, sr=-0.12, P=0.14, *Figure-2*); this divergence is further highlighted in select regions (inferior temporal and hippocampus) in *Figure-3*.

Conclusion: We found that the relationship between amyloid and tau burden and atrophy was stronger in the overall cohort than in participants with dementia. This

was particularly the case for medial temporal lobe structures. The effect of non-AD pathologies on medial temporal lobe atrophy is a potential explanation for the observed results.

Table-1. Characteristics of ADNI participants.

Amyloid (N=1320)	Dementia (N=337)	MCI (N=504)	Normal (N=479)
Women (%)	193 (57.3%)	212 (42.1%)	270 (56.4%)
Age at Scan (Years)	76.9 (8.10)	76.0 (8.03)	76.2 (7.47)
Education (Years)	15.9 (2.60)	16.0 (2.78)	16.7 (2.47)
SUVr	1.40 (0.229)	1.22 (0.243)	1.13 (0.192)
Amyloid Positive	294 (87.2%)	271 (53.8%)	187 (39.0%)

Tau (N=833)	Dementia (N=116)	MCI (N=272)	Normal (N=445)
Women (%)	193 (57.3%)	212 (42.1%)	270 (56.4%)
Age at Scan (Years)	76.9 (8.10)	76.0 (8.03)	76.2 (7.47)
Education (Years)	15.6 (2.47)	16.2 (2.67)	16.8 (2.31)
SUVr	1.66 (0.471)	1.30 (0.258)	1.21 (0.125)

Figure-1. Effect of amyloid PET SUVr on brain volumes from MRI

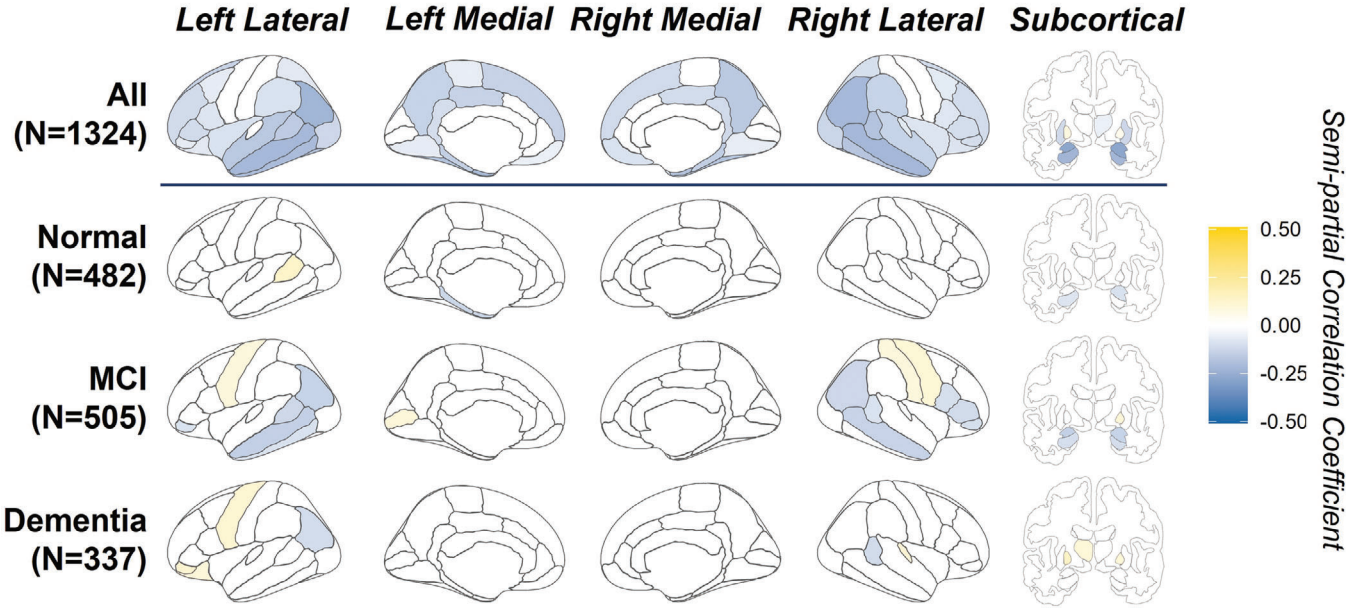

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Figure-2. Effect of tau PET SUVr on brain volumes from MRI

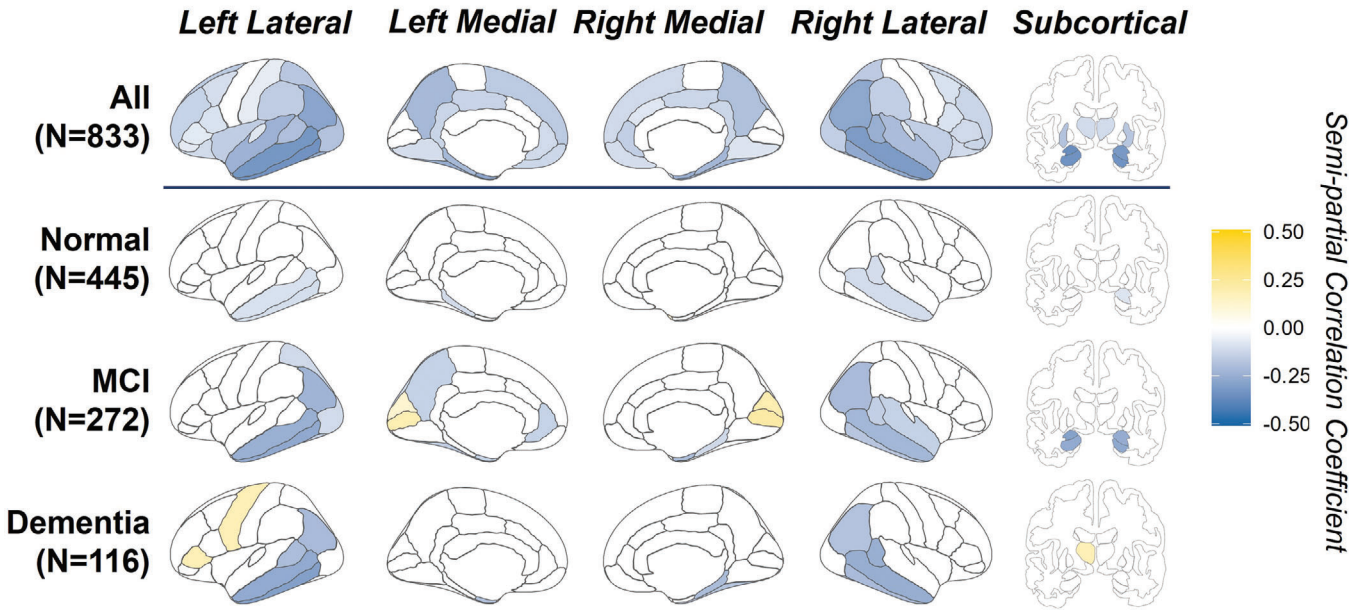

Figure-3. Regressions of brain volumes to amyloid or tau SUVr for select regions.