

Atrophy Signature For Alpha-synuclein Copathology In Alzheimer's Disease

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BACKGROUND

Alpha-synuclein (α -syn) copathology is common in Alzheimer's disease (AD) and has been associated with worse clinical trajectories. With α -syn seed amplification assays (qSAA) enabling in vivo detection of misfolded α -syn, we investigated whether α -syn copathology is associated with distinct MRI atrophy patterns.

METHODS

Retrospective neuroimaging study with two independent cohorts: Clínic Barcelona (91 AD-qSAA⁻, 17 AD-qSAA⁺, 31 controls) and Alzheimer's Disease Neuroimaging Initiative (ADNI; 53 AD-qSAA⁻, 31 AD-qSAA⁺, 107 controls). Participants underwent T1-weighted MRI and cerebrospinal fluid testing for qSAA and AD biomarkers. Cortical thickness and subcortical gray-matter volumes were obtained with FreeSurfer. Region-wise group comparisons were performed using permutation tests adjusting for age and sex, and effect sizes were summarized with Cohen's distance ($|d|$).

RESULTS

Versus controls, AD-qSAA⁻ showed widespread cortical thinning with relative sparing of medial occipital and anterior cingulate regions alongside lateral ventricular enlargement in both cohorts. Clínic Barcelona displayed a predominantly parietal-centered pattern (inferior/superior parietal cortex and precuneus; $|d|$ up to ~ 1.51) with prominent hippocampal and amygdalar involvement. ADNI showed higher peak effects ($|d|$ up to ~ 1.78) led by temporal–medial temporal and limbic regions (fusiform/entorhinal, hippocampus, amygdala) with additional orbitofrontal involvement.

RESULTS

Compared with controls, AD-qSAA⁺ exhibited broader and more severe atrophy ($|d| \approx 0.82$ – 2.71) than AD-qSAA⁻ across parietal–temporal–limbic regions, with additional frontal, cingulate, insular, lateral occipital involvement, basal ganglia (putamen, thalamus, and caudate) and greater ventricular enlargement. Intercohorts differences were similar than in the previous comparison, with broader subcortical involvement in the Clínic Barcelona.

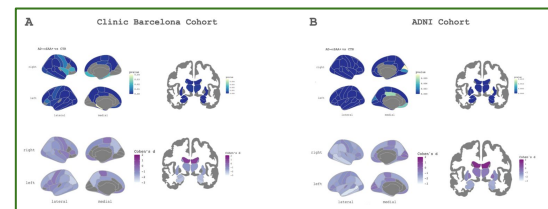


Fig.2: Brain maps show cortical thickness differences between AD-qSAA⁻ and AD-qSAA⁺, displaying only significant regions after multiple-comparison correction ($p < 0.05$). Upper panels show significance levels; lower panels show Cohen's d effect sizes. Negative values indicate cortical thinning in AD-qSAA⁻.

Direct AD-qSAA⁺ vs AD-qSAA⁻ comparisons showed consistent differential involvement of insula, entorhinal, superior temporal/bankssts, pre- and postcentral gyri, orbitofrontal, rostral middle and superior frontal regions, and amygdala, but effect sizes were low-to-medium (≤ 0.6); Clínic Barcelona additionally showed broader subcortical differences, whereas ADNI emphasized frontal regions.

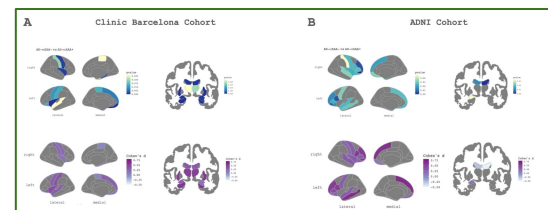


Fig.3: Brain maps show cortical thickness differences between AD-qSAA⁺ and controls, displaying only significant regions after multiple-comparison correction ($p < 0.05$). Upper panels show significance levels; lower panels show Cohen's d effect sizes. Negative values indicate cortical thinning in AD-qSAA⁺.

CONCLUSIONS

In vivo α -syn copathology was associated with more extensive and pronounced atrophy, especially in frontal, lateral temporal, entorhinal, and amygdalar regions. This suggests that α -syn acts as an accelerator of neurodegeneration beyond typical AD patterns.