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PODIUM PRESENTATION

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A generalizable data-driven model of atrophy heterogeneity and progression in a memory clinic setting

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Abstract

Background: Memory clinic patients are a heterogeneous population representing various aetiologies of pathological aging. It is unknown if divergent spatiotemporal progression patterns of brain atrophy, as previously described in Alzheimer's disease (AD) patients, are prevalent and clinically meaningful in this group of older adults.

Method: To uncover atrophy subtypes, we applied the Subtype and Stage Inference (SuStaIn) algorithm to structural MRI data from 813 participants (mean ± SD age = 70.67 ± 6.07 years, 52% females) from the DELCODE cohort. Participants were cognitively unimpaired (CU; n = 285) or patients with subjective cognitive decline (SCD; n = 342), mild cognitive impairment (MCI; n = 118), or dementia of the Alzheimer's type (n = 68). Atrophy subtypes were compared in baseline demographics,

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fluid AD biomarkers, and domain-specific cognitive performance. PACC-5 trajectories over up to 240 weeks were examined. Clinical trajectories (PACC-5 scores and MCI conversion rates) in only CU and SCD participants were analysed. SuStaIn modelling was repeated in participants from the Swedish BioFINDER-2 study for replication and generalizability testing.

Result: Limbic-predominant and hippocampal-sparing atrophy subtypes were identified (Figure 1). Limbic-predominant atrophy first affected the medial temporal lobes, followed by further temporal and, finally, the remaining cortical regions. This subtype was related to older age, more pathological AD biomarkers, APOE ε4 carriership, and an amnestic cognitive impairment. Hippocampal-sparing atrophy initially occurred outside the temporal lobe and spared the medial temporal lobe until advanced stages. This atrophy pattern also affected individuals with positive AD biomarkers and was associated with more generalised cognitive impairment. Limbic-predominant atrophy, in all and in only unimpaired participants, was linked to more negative longitudinal PACC-5 slopes than observed in participants without or with hippocampal-sparing atrophy (Figure 2) and increased the risk of MCI conversion. In BioFINDER-2, analogous atrophy subtypes and cognitive correlates were identified. Group- and subject-level model generalizability were excellent, indicating reliable performance in novel data (Figure 3).

Conclusion: The proposed model is a promising tool for capturing heterogeneity among older adults at early at-risk states for AD in applied settings. The implementation of atrophy subtype- and stage-specific end-points may increase the statistical power of pharmacological trials targeting early AD.