Spatial-Temporal Patterns of β-Amyloid Accumulation
A Subtype and Stage Inference Model Analysis

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Study Question
Is there data-driven evidence for the existence of β-amyloid (Aβ) accumulation subtypes?

What Is Known and What This Paper Adds
Subject heterogeneity in amyloid spatial-temporal progression remains unresolved and could reflect different disease pathways. Previous work applying the Subtype and Stage Inference (SuStaIn) model on tau-PET imaging showed its value for improving individualized prognosis in Alzheimer disease (AD). This study identified 3 trajectories of Aβ accumulation associated with distinct AD risk factors and disease progression, suggesting that subtype assignment may have clinical relevance or could support individualized risk assessment.

Methods
These retrospective analyses used data from 3,010 participants from 5 cohorts with amyloid-PET (ALFA+, EMIF-AD, ABIDE, OASIS, and ADNI). Across participants, mean age was 68.7 years (SD 9.1), 42% were APOE ε4 carriers, 52% were female, and 68% were cognitively unimpaired. Standardized uptake value ratios were calculated for 17 regions and standardized to cohort-, radiotracer-, and region-specific z scores. We applied SuStaIn to the pooled regional z-scored PET data and the optimal number of subtypes was selected based on the lowest cross-validation information criterion value. A multinomial logistic regression (MLR) was used to determine the effect of demographics and risk factors on subtype assignment, including age, sex, cohort, APOE ε4 and ε2 carriership, baseline Mini-Mental State Examination, and diagnostic group. Next, 2 MLRs were used to determine the relationship between subtypes and amyloid and p-tau. Descriptive statistics were used to determine subtype stability and stage progression in a subset of participants with longitudinal PET data.

Results and Study Limitations
SuStaIn identified 3 subtypes, referred to as frontal, parietal, and occipital based on the first regions to show abnormality (Figure). Of the 788 (26.2%) with strong subtype assignment (>50% probability), the majority was assigned to frontal (n = 415 [52.5%]) followed by parietal (n = 199 [25.3%]) and occipital subtypes (n = 175 [22.2%]). Differences across subtypes included distinct proportions of APOE ε4 carriers (frontal: 61.8%, parietal: 57.1%, occipital: 49.4%; p < 0.001) and dementia diagnosis (frontal: 19.7%, parietal: 19.1%, occipital: 31.0%; p = 0.02) and lower age for the parietal subtype (frontal/occipital: 72.1 years, parietal: 69.3 years; p = 0.005). Higher amyloid (Centiloid) and CSF p-tau burden were observed for the frontal subtype. At follow-up, most participants (n = 421 [81.1%]) maintained their baseline subtype assignment, and 25.6% progressed to a later stage. Limitations of this study include the absence of an independent training and test set and the smaller sample size of the longitudinal cohort.

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CORRECTION

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In the Research Article “Spatial-Temporal Patterns of β-Amyloid Accumulation: A Subtype and Stage Inference Model Analysis” by Collij et al., the following information was mistakenly omitted from the Acknowledgements section:

“Data were provided by OASIS OASIS-3: Principal Investigators: T. Benzinger, D. Marcus, J. Morris; NIH P50 AG00561, P30 NS09857781, P01 AG026276, P01 AG003991, R01 AG043434, UL1 TR000448, R01 EB009352. AV-45 doses were provided by Avid Radiopharmaceuticals, a wholly owned subsidiary of Eli Lilly. OASIS-3: https://doi.org/10.1101/2019.12.13.19014902.”

The authors regret the omission.

REFERENCE