

Multimodal Modelling of Early Alzheimer's Disease-
Related Change in Adults with Down Syndrome

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Mina Idris¹, Fedal Saini¹, Phoebe Ivain¹, Leda Bianchi¹, Henrik Zetterberg², Peter Wijeratne³ & André Strydom¹ | mina.idris@kcl.ac.uk
¹King's College London, UK, ²University of Gothenburg, Sweden, & ³University of Sussex, UK.

Multimodal modelling suggests structural MRI and plasma biomarker abnormalities emerge before cognitive and functional decline in adults with Down syndrome.

INTRODUCTION

- Adults with **Down syndrome (DS)** are at high risk of **Alzheimer's disease (AD)** due to triplication of the amyloid precursor protein gene.¹
- Although AD neuropathology is common by mid-adulthood, the relative timing of **biological, cognitive, and functional changes** is unclear.
- Aim:** To integrate structural MRI, plasma, cognition measures within a single AD progression model.

METHODS

Multimodal marker assessment

- MRI:** Hippocampus, Thalamus, Caudate, Precuneus, Posterior cingulate cortex, Mean cortical thickness, Lateral ventricles
- Plasma :** GFAP, NfL, pTau217
- Cognition:** CANTAB PAL
- Informant report:** DLD

Analysis

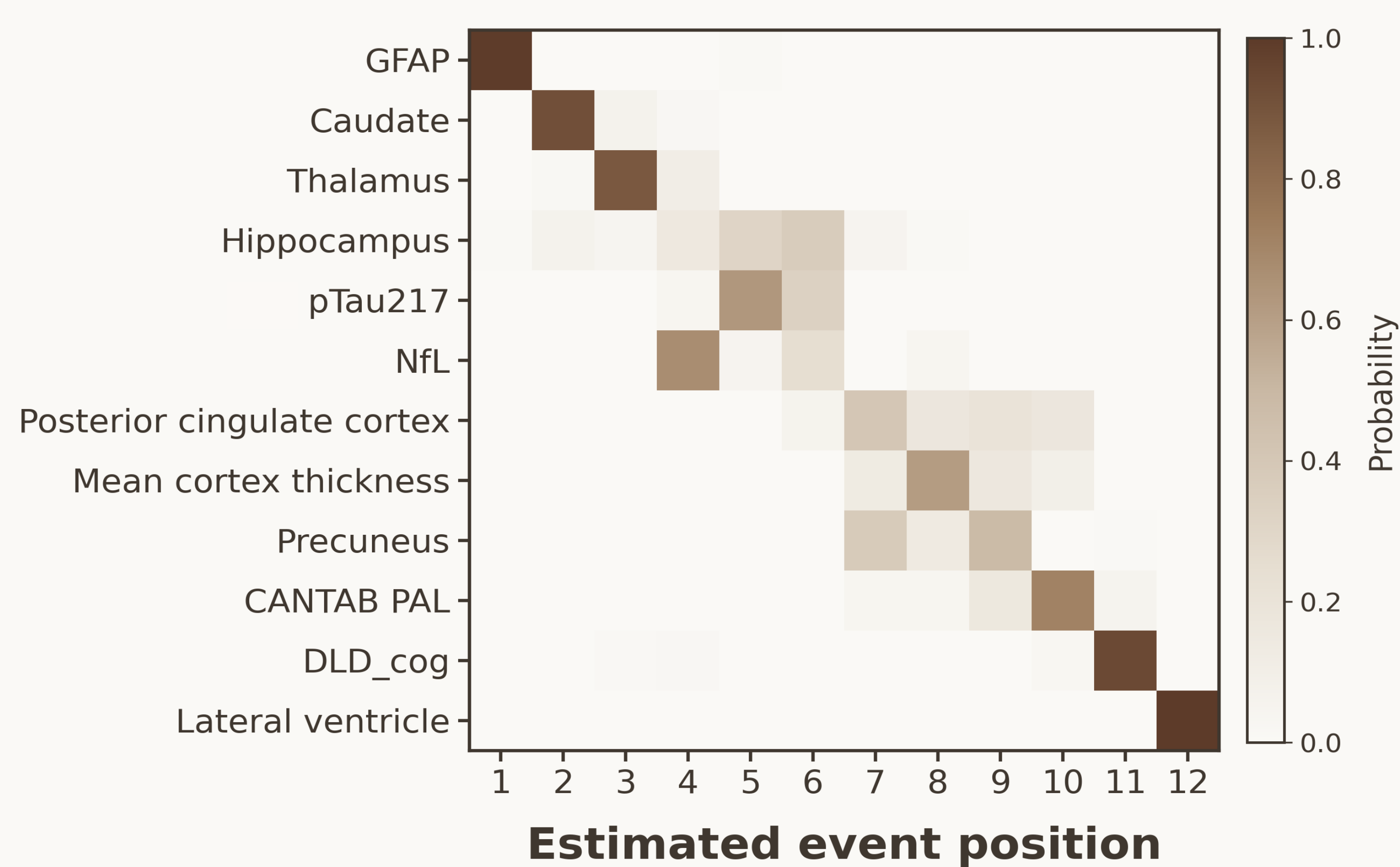
- Markers showing age-related disease signal were entered into an **Event-Based Model (EBM)**, which estimates the most likely sequence of marker abnormality.²

Table 1. London Down Syndrome consortium (LonDownS) MRI cohort

Characteristic	Total cohort
N	51
Age, years	35.3 ± 11.3
Female, n (%)	31 (61%)
Mild ID, n (%)	27 (47%)
Moderate ID, n (%)	30 (53%)
Younger adults (≤35y)	28
Older adults (>35y)	23

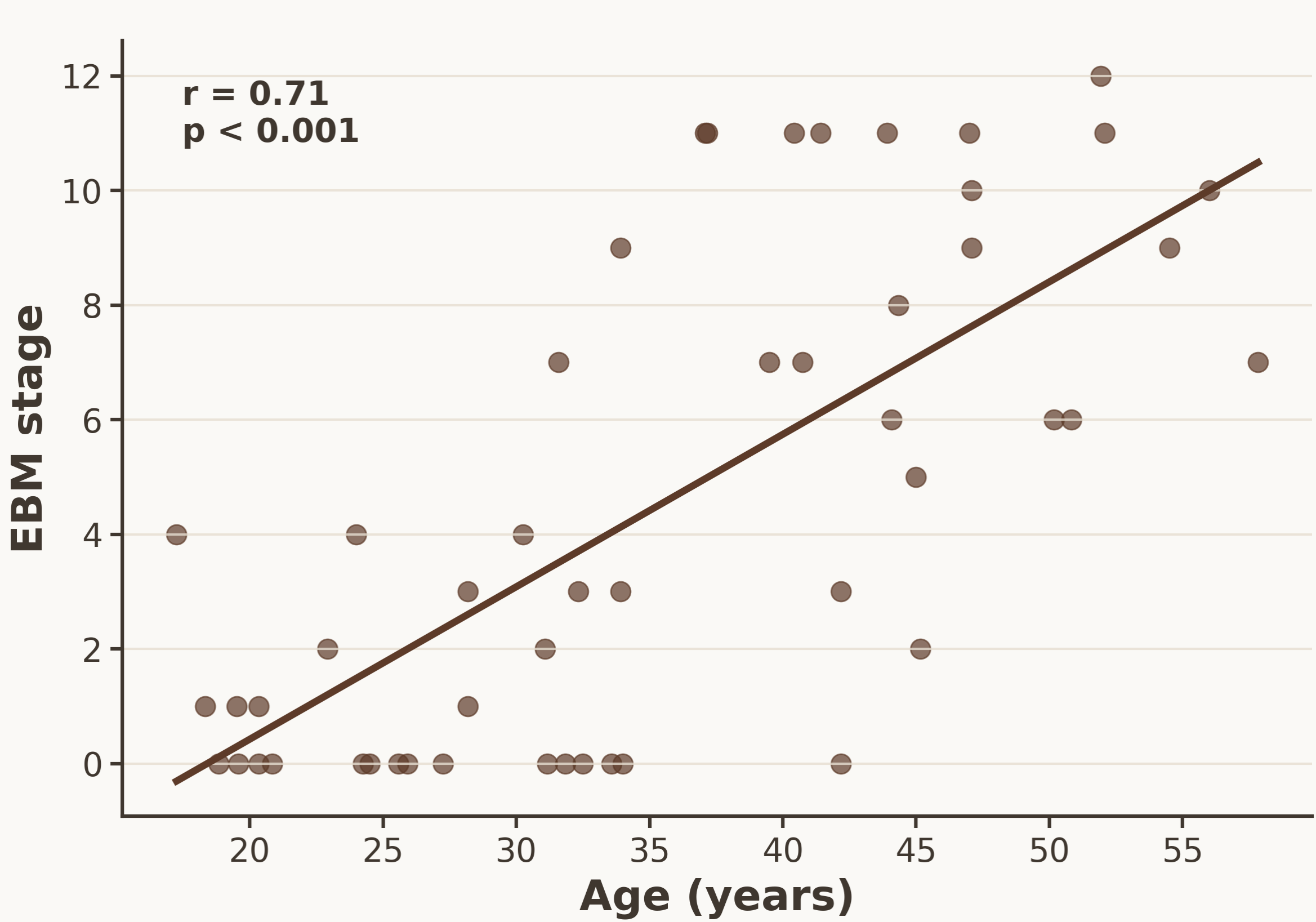
RESULTS

Figure 1. EBM positional variance diagram of AD-related markers



Increased GFAP → Deep grey matter atrophy → Increased pTau217 & NfL → Cortical thinning → Memory decline → Functional decline → Ventricular enlargement

Figure 2. Stage increases with age but varies between individuals



KEY OBSERVATIONS

- Plasma biomarkers** showed early age-related abnormalities.
- MRI abnormalities** were detected in AD-vulnerable regions.
- Memory-related measures** became abnormal before functional decline.
- Informant-reported decline** occurred later in the AD cascade.

CONCLUSIONS

- Early changes:** Structural MRI and plasma abnormalities emerged first; followed by cognitive and functional decline later.
- Disease sequence:** Multimodal EBM identified a biologically plausible sequence of AD-related change in DS.
- Clinical utility:** Multimodal disease staging may support early detection and clinical trial enrichment.

CLINICAL IMPLICATIONS

- Early detection:** Blood biomarkers and MRI may identify disease-related change decades before AD diagnosis.
- Participant stratification:** Disease staging may help identify individuals at elevated risk for prevention trials.
- Precision medicine:** Multimodal staging captures heterogeneity between individuals of the same age.



THE
LonDownS
CONSORTIUM

REFERENCES

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- Fonteyjn HM, et al. Neuroimage. 2012;60(3):1880-1889.

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