

Background

Recent evidence demonstrates distinct cortical amyloid- β (A β) accumulation subtypes with different epicenters and progression patterns in Alzheimer's disease (AD).

Aim

We aimed to identify such subtypes in a preclinical population and determine whether longitudinal A β accumulation follows shared or distinct network propagation mechanisms.

Methods

Cohort: 4082 cognitively unimpaired subjects (AMYPAD, A4, ADNI)

Imaging: A β -PET (regional SUVR), fMRI (functional connectivity), DWI (structural connectivity) using Schaefer 100-region atlas

Disease progression modeling: SuStaln to identify data-driven A β subtypes and stages

Longitudinal modeling : LMMs estimating annual A β change (random intercepts/slopes; adjusted for age, sex, education, eTIV, cortical thickness, SuStaln-derived disease stage) per subtype

Network properties: Trans-synaptic spread (Connectivity-weighted neighbourhood accumulation, shortest path to epicenter), hub stress (Betweenness), trophic failure (Inverse Clustering), spatial proximity (Euclidean distance). Subtype-level network properties derived from group-average connectomes

Spatial correlation: Spearman spatial correlation with spin permutation testing

Results

1. Demographics and Clinical Characteristics at Baseline.

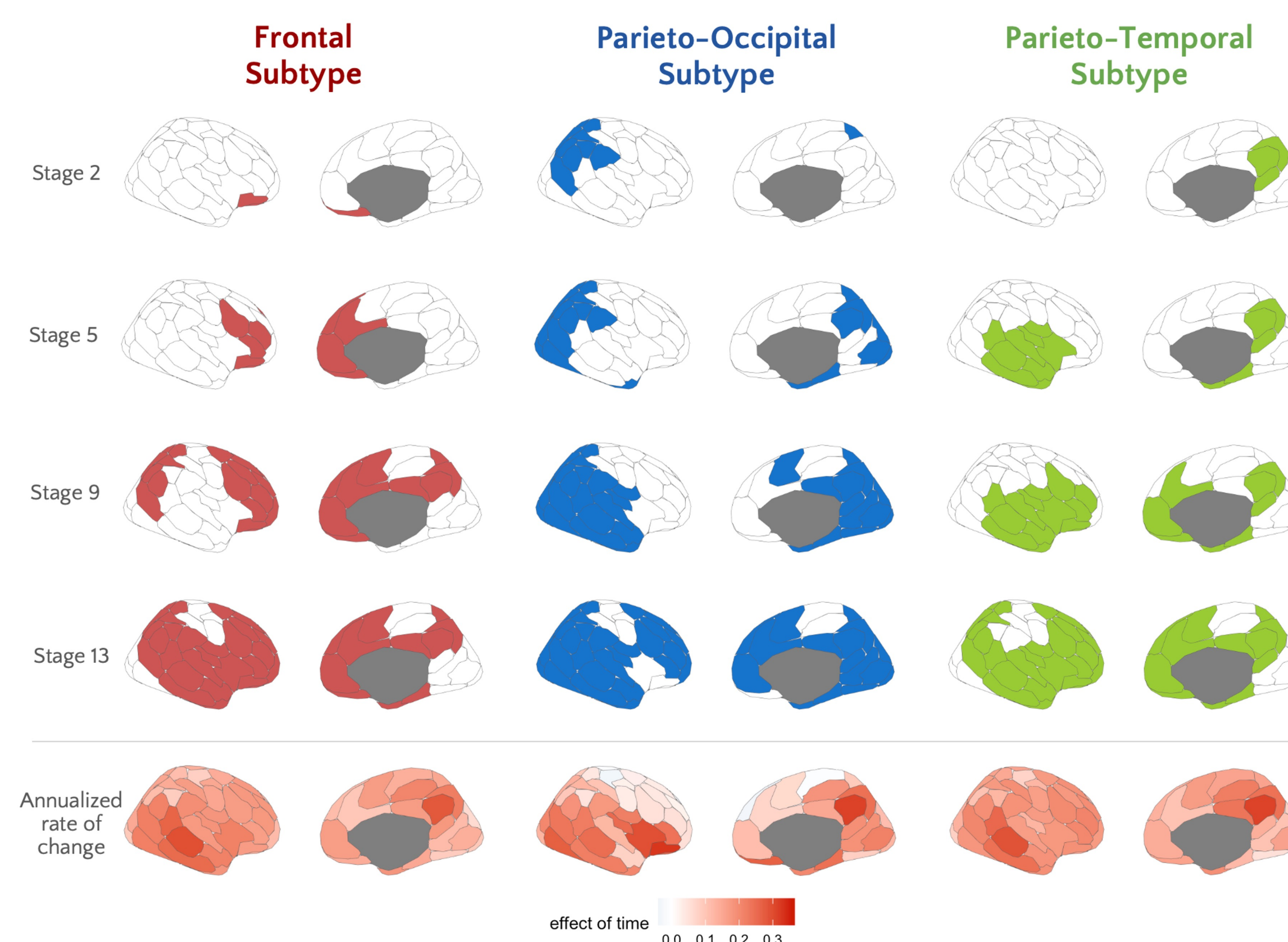
	Frontal N = 788 ¹	Parieto-Occipital N = 174 ¹	Parieto-Temporal N = 487 ¹	p-value ²
Age (years)	72.3 (6.9)	71.9 (7.2)	71.4 (6.0)	0.066
Sex, Female	449 (57%)	119 (68%)	257 (53%)	0.002
Education (years)	15.9 (3.4)	16.2 (3.2)	16.5 (3.3)	0.006
APOE ϵ 4, Carriers	457 (60%)	68 (41%)	241 (51%)	<0.001
CDR				0.018
0	652 (83%)	150 (86%)	431 (89%)	
0.5	136 (17%)	24 (14%)	56 (11%)	
Centiloid (CL)	51.0 (28.9)	33.0 (18.3)	46.9 (27.9)	<0.001
Amyloid Positive	653 (83%)	102 (59%)	377 (77%)	<0.001
Disease stage	10.8 (4.8)	7.0 (4.1)	8.7 (5.3)	<0.001
Follow-up visits				0.18
0	488 (62%)	110 (63%)	324 (67%)	
1	274 (35%)	55 (32%)	154 (31%)	
>1	26 (3%)	9 (5%)	9 (2%)	
Follow-up time (years)	3.73 (1.42)	3.67 (1.42)	4.17 (1.32)	0.002

¹Mean (SD); n (%)

²One-way analysis of means; Pearson's Chi-squared test

Abbreviations: CDR = Clinical Dementia Rating; PET = Positron Emission Tomography

2. Subtypes of A β deposition and subtype-specific A β accumulation.



Conclusion

Early A β progression relates to subtype-specific network mechanisms:

- Across all subtypes**, structural connectivity-mediated neighbour accumulation and distance to epicentres was the most consistent mechanism, supporting trans-synaptic propagation together with a geometric component of spread ($r = -0.16^*$, -0.25^* , -0.25^*).
- Frontal** and **Parieto-Temporal** subtypes were associated with robust functional connectivity-mediated neighbour accumulation patterns and trophic vulnerability.
- Parieto-Occipital** subtype showed predominantly structural connectivity- and proximity-driven accumulation, but no evidence functional network-mediated spread.

3. Subtype-specific network mechanisms of A β accumulation.

