

Network-specific patterns of functional connectivity and amyloid- β align with and precede tau in atypical Alzheimer disease subtypes

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Introduction

- Spatiotemporal patterns of tau differ between distinct AD presentations^{1, 2}
- Tau accumulation may be driven by:
 - Trans-neuronal spread through network connections^{2, 3}
 - Amyloid- β (A β) deposition⁴
- Current project aims:
 - Replicate tau PET subtypes in an independent cohort (Knight ADRC)
 - Test subtype differences in network connectivity (RSFC) and A β PET
 - Evaluate timing of network differences

Methods

- Defined subtypes with **tau PET**
 - 919 ¹⁸F-Flortaucipir scans from 709 participants
 - Standardized SUVRs with GMM
 - Applied Subtype & Stage Inference model (**SuStaln**)⁵ to 5 lobe Z scores
- Tested group differences in **RSFC MRI**
 - Retrospective scans** up to 14 years before tau PET (mostly 0 to 6 years)
 - GSR & censored frames > 0.2 mm FD
 - Seed-based analyses with subtype-specific **early tau regions as seeds**
- Tested group differences in **A β PET**
 - Retrospective scans** up to 14 years before tau PET (mostly 0 to 6 years)
 - ¹¹C-PiB or ¹⁸F-Florbetapir harmonized to regional Centiloid

References

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Results

	Subtype 0: Tau- Negative	Subtype 1: Limbic	Subtype 2: Posterior	Subtype 3: MTL- Sparing
N	522	136	25	23
Age	68.5 (9.2)	74.2 (7.0)	73.0 (6.4)	67.4 (9.2)**
Sex (%F)	54%	61%	76%	43%
Education (Y)	16.4 (2.3)	15.8 (2.5)	16.1 (2.4)	15.2 (2.5)
CDR® (%>0)	5%	40%	44%	70%***
APOE (%ε4+)	35%	61%	44%^	52%^
Centiloid	6.4 (23.7)	58.6 (38.2)	45.5 (49.6)	59.5 (54.7)
Knight PACC	-0.0 (0.8)	-0.7 (1.0)	-1.0 (1.5)	-1.9 (1.3)***
Figure Copy	15.1 (1.2)	14.8 (1.6)	11.5 (6.0)*	11.9 (4.5)*

Table. Demographic characteristics of tau PET subtypes.

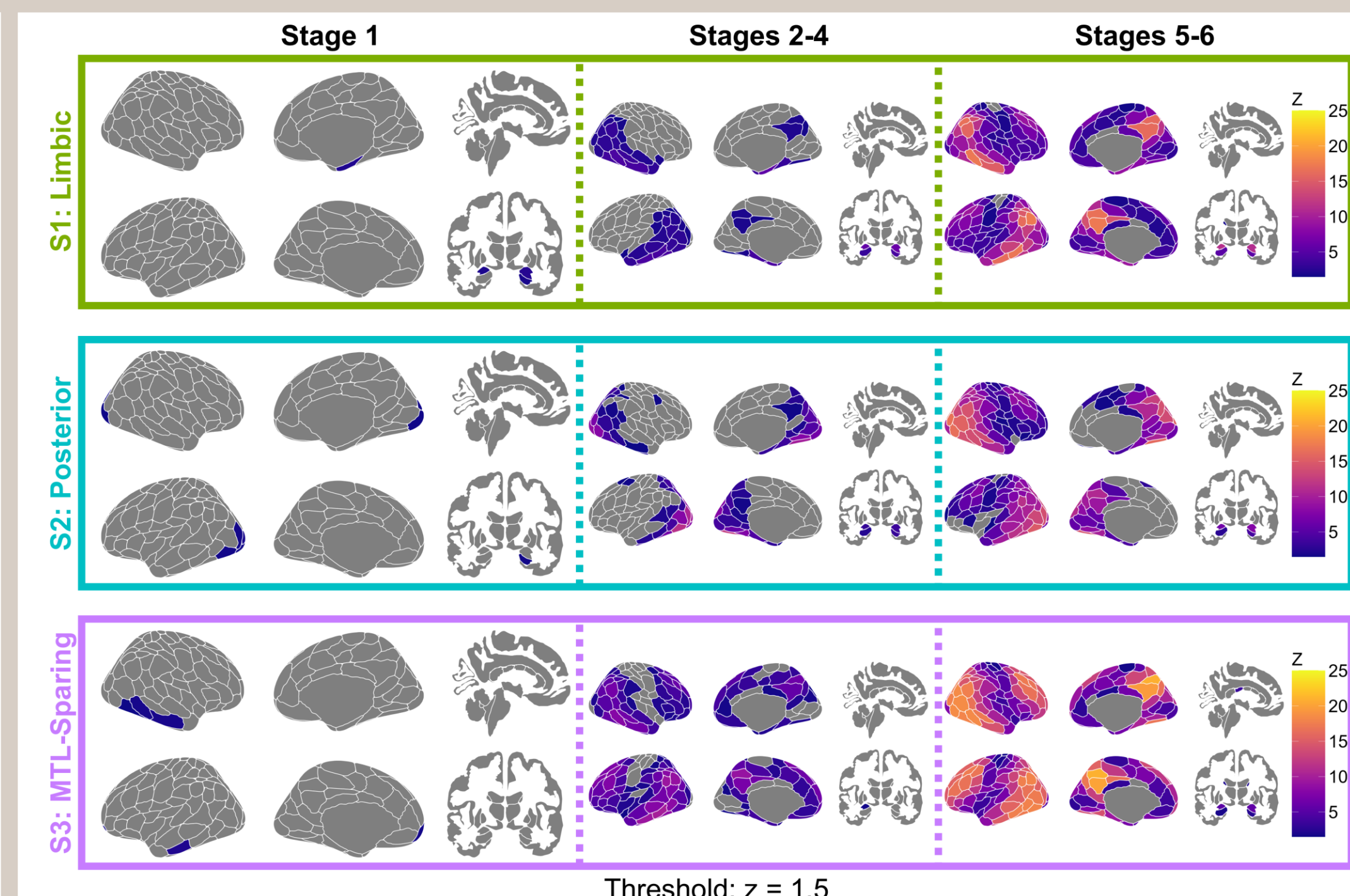


Fig 1. Tau PET subtype and stage spatiotemporal patterns.

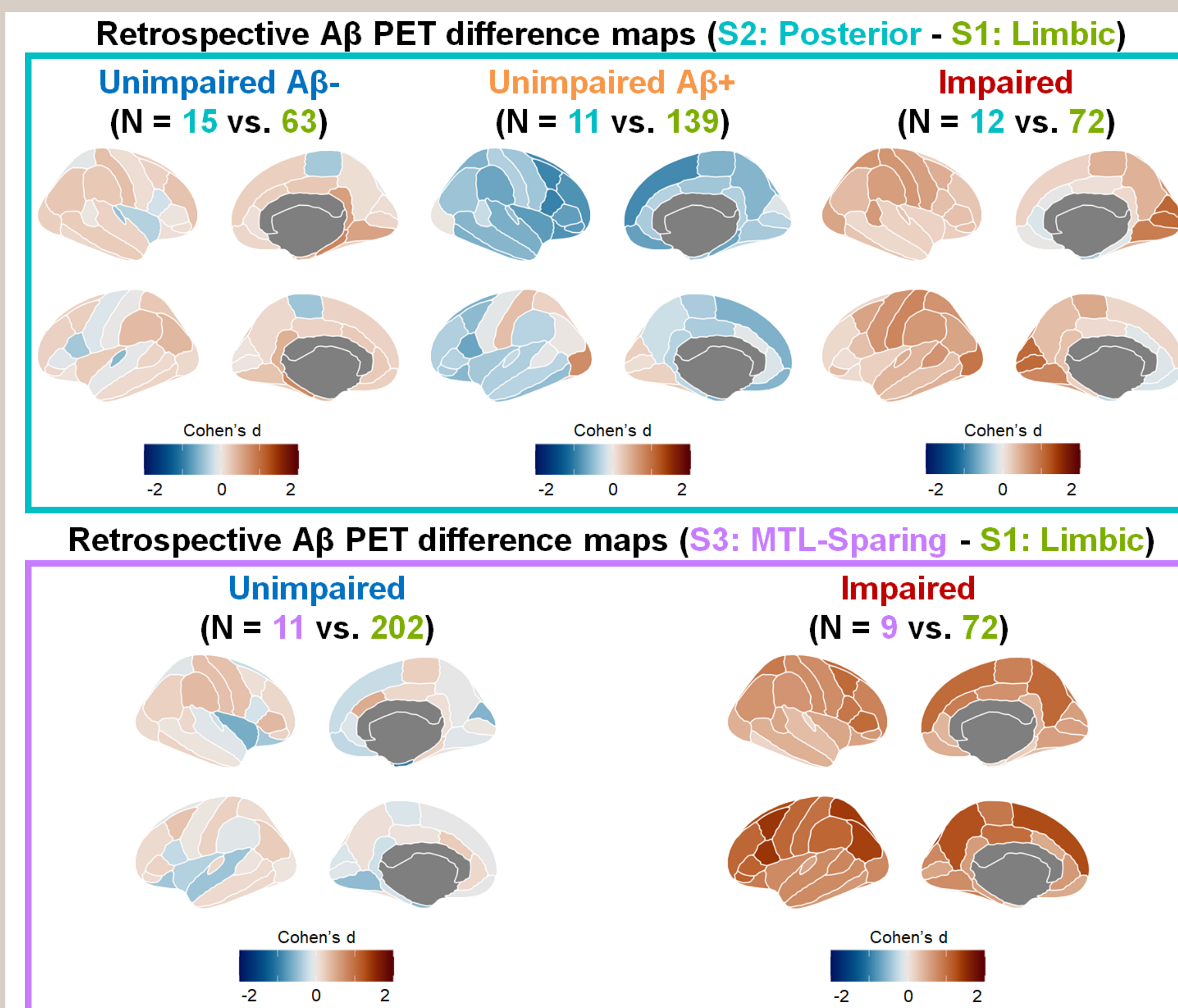


Fig 2. Elevated A β PET in tau regions (Fig 1) detectable when A β +

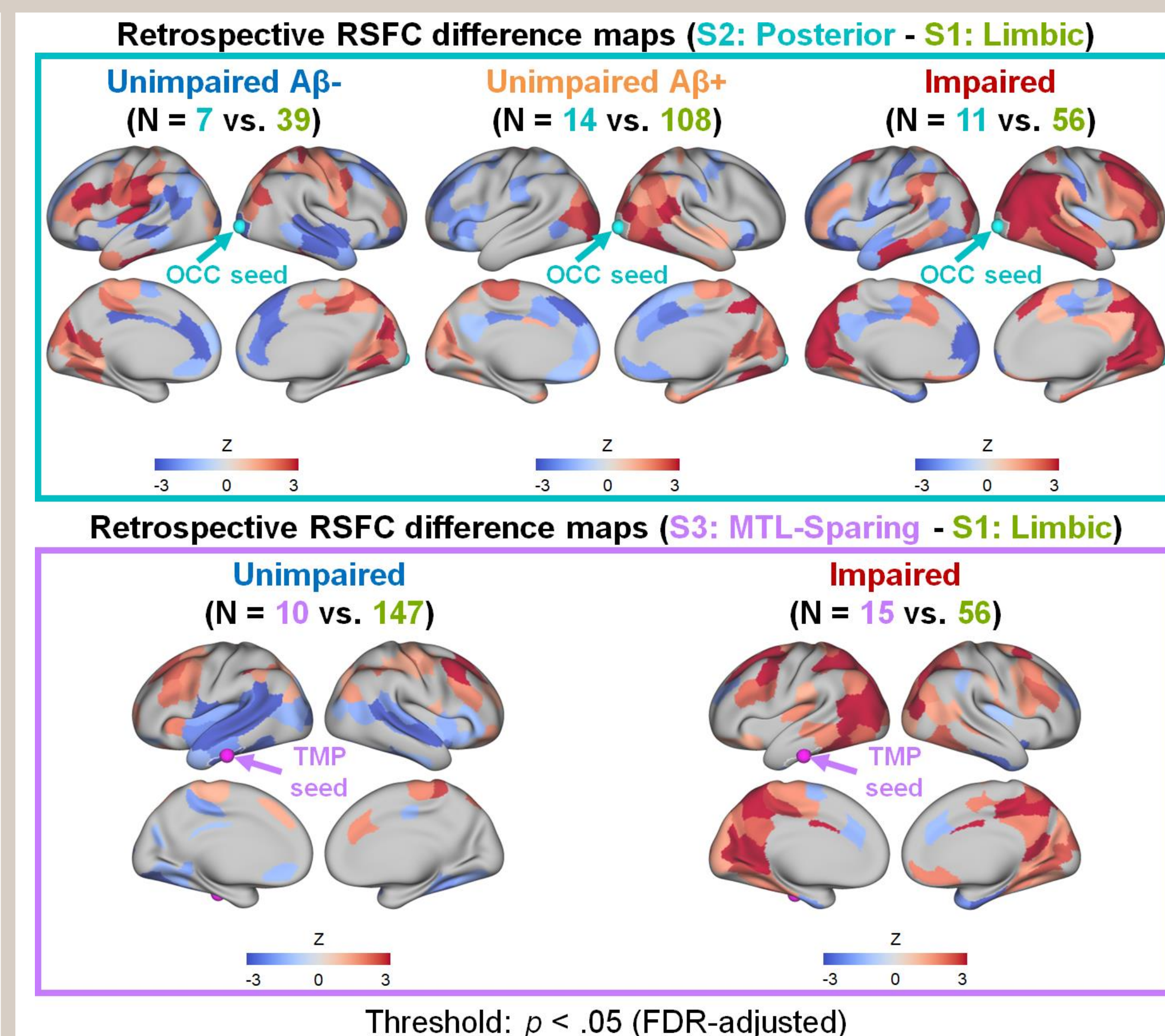


Fig 3. RSFC hyperconnectivity between tau regions (Fig 1) detectable before A β or cognitive impairment.

Conclusions

- Replicated three tau subtypes with distinct clinical, genetic, and cognitive features
 - S1 Limbic** resembles **typical AD**: Most common, Braak-like tau patterns, high APOE ε4+
 - S2 Posterior** resembles **posterior cortical atrophy (PCA)**: Visuospatial deficits, low ε4+
 - S3 MTL-Sparing** resembles **early-onset AD (EOAD)**: Youngest age, low ε4+, most severe impairment in multiple cognitive domains
- Novel subtype differences in **A β** and **RSFC hyperconnectivity** align with patterns of tau
- Hyperconnectivity between tau regions may reflect **network vulnerabilities** that precede A β
- Significance**: Temporal sequence of network abnormality can inform models of AD pathogenesis, clinico-pathological heterogeneity, and precision medicine tools