

## 2 **Wherever tau pathology starts, propagation will follow brain** 3 **connections**

4 **This scientific commentary refers to ‘Connectivity as a universal predictor of tau**  
5 **progression in atypical Alzheimer’s disease’ by de Bruin *et al.***  
6 **(<https://doi.org/10.1093/brain/awaf279>).**

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8 Predicting future tau propagation is critical for providing accurate prognoses to patients with  
9 Alzheimer’s disease (AD), as neurological symptoms depend on which brain regions are  
10 affected. However, the mechanisms driving tau propagation are still largely unknown. Different  
11 propagation patterns may originate from distinct starting points in the brain, contributing to inter-  
12 individual variability in symptoms, rates of cognitive decline, and possibly treatment responses.  
13 Identifying modulators of tau spread, whether genetic, molecular, cellular, or network-level,  
14 could reveal actionable targets to limit tau propagation before irreversible neurodegeneration  
15 occurs.<sup>1</sup> In this context, studying patients with atypical AD, in whom varying brain regions are  
16 affected and spared by tau pathology, is of particular interest to understand the biological  
17 mechanisms driving tau propagation. Moreover, addressing the generalizability of tau  
18 propagation models from typical to atypical AD could enhance the development of personalised  
19 therapeutic strategies tailored to each individual’s unique pattern of tau pathology.

20 Contributing to this endeavour, de Bruin and colleagues<sup>2</sup> leveraged a large-scale multicentre  
21 dataset including four atypical AD variants to investigate whether tau pathology preferentially  
22 propagates along functionally connected networks. The cross-sectional cohort included 320  
23 individuals from 14 international sites: 139 with posterior cortical atrophy (PCA-AD), 103 with  
24 logopenic variant primary progressive aphasia (lvPPA-AD), 35 with behavioural variant AD  
25 (bvAD), and 43 with corticobasal syndrome (CBS-AD). Longitudinal tau-PET data were  
26 available for a subset of 78 participants, while an independent validation sample included  
27 regional post-mortem tau staining data from 93 atypical AD patients across two sites.

Using functional connectivity matrices derived from 42 cognitively normal, amyloid- $\beta$ -negative individuals from the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset, the authors computed connectivity distances from tau epicentres, defined as the top 5% of regions with the highest tau-PET standardized uptake value ratios (SUVR) at the individual subject level. Across all AD variants, brain regions with stronger functional connectivity to tau epicentres displayed higher covariance in both concurrent tau-PET deposition and longitudinal tau-PET change. This network-based pattern was further replicated in the post-mortem dataset. Notably, tau pathology was assessed in only one hemisphere per individual, which may not fully capture lateralised pathology, especially in syndromes such as lvPPA-AD and CBS-AD. Future neuropathology studies should consider bilateral analyses to better characterise atypical AD variants.

This study advances our understanding of tau propagation in atypical AD. The findings align with prior functional and diffusion MRI studies in typical AD, which similarly suggest that tau spreads along structurally and functionally connected networks.<sup>3,4</sup> Taken together, these lines of evidence highlight the complementary roles of tau-PET and functional MRI in modelling the future extent of tau pathology at the individual level.

Developing personalised connectome-based prediction models that account for subject-specific brain connectivity would be the logical next step. Indeed, a growing body of work has demonstrated that everyone exhibits a unique connectome 'fingerprint'. While individual differences in network organisation are subtle relative to the highly conserved architecture shared across people, they are sufficiently distinctive to reliably identify individuals based solely on their brain network properties.<sup>1</sup> Of note, de Bruin and colleagues<sup>2</sup> were able to replicate their findings in a subset of participants using subject-specific functional connectivity data. However, individualised network metrics are not yet widely available as they can be susceptible to noise, especially in functional MRI, where longer acquisition times are often needed for reliable estimation. Future work should explore whether individual differences in the brain connectome result in different tau spreading patterns in patients with a similar tau epicentre, and whether combining subject-specific and group template connectomes might help improve tau propagation prediction.

While using connectivity from tau epicentres to estimate subsequent accumulation represents a useful model of tau propagation, the addition of local vulnerability (*i.e.* intrinsic tissue properties) will help refine future models of AD progression.<sup>5</sup> First, because functional connectivity between regions might overlap with shared tissue properties, whose respective roles in tau propagation will need to be disentangled. Second, because tau extent (*i.e.* the presence of tauopathy over a certain threshold throughout the brain) and tau load (as quantified by SUVR) might not be explained by the same set of underlying factors, and considering additional brain-derived metrics beyond functional connectivity could help dissociate them (Figure 1).<sup>6</sup> Accounting for such factors could better explain the anatomical variability of tau epicentres across (a)typical AD. A non-exhaustive list of metrics to consider for refining connectome-based models of tau propagation includes gene expression, neurotransmission marker density, cellular morphology, glucose metabolism, haemodynamic activity, electrophysiology, and the presence of co-pathologies.<sup>6,7</sup>

For example, transcriptomic signals can improve models of connectome-based tau spread by capturing selective vulnerability and resilience. Genes such as *MAPT*, *TSPOAP1*, *APOE*, *PRNP*, and *JAZF1* have been shown to increase susceptibility to tau pathology, while others including *BACE1*, *FOXF1*, *SERTAD1*, and *MINDY2* may confer resistance.<sup>8</sup> It is worth noting that some gene expression patterns align with functional networks (*MAPT*, *TSPOAP1*, *APOE*, *BACE1*, *FOXF1*). In contrast, other genes may influence tau spread through local mechanisms, independently from functional networks, making certain regions intrinsically more or less susceptible to pathology (*PRNP*, *JAZF1*, *SERTAD1*, *MINDY2*). Integrating genotype-derived regional expression estimates therefore holds promise for individualised modelling, and emerging studies have proposed using DNA, blood transcripts, or *in vivo* proteomics to infer spatial gene expression patterns.<sup>1</sup> Similarly, co-pathologies such as alpha-synuclein or TDP-43 may accelerate tau accumulation and/or propagation to connected brain regions,<sup>7</sup> while white matter myelination has been shown to modulate the relationship between regional tau-PET covariation and network connectivity.<sup>1</sup> It is also important to consider the presence and quantity of amyloid-beta deposits, since amyloid-related hyperexcitability may trigger tau spread even in

clinically unimpaired individuals.<sup>9</sup> This is particularly relevant since clinically unimpaired A+T+ individuals are at increased risk of progression towards symptomatic AD.<sup>10</sup>

In summary, integrating refined predictive features, including but not limited to connectivity, will enhance our capacity to forecast tau spread and inform the development of personalised therapeutic strategies. Teasing apart the roles of brain connectivity and local vulnerability in explaining variability in both tau extent and load in typical versus atypical AD is therefore an important area for future research.

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# Competing interests

The authors report no competing interests.

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## Figure legend

**Figure 1 While brain connectivity explains the extent of tau pathology, tau load is influenced by a combination of synaptic spread and subject-specific local vulnerability and resilience mechanisms.**

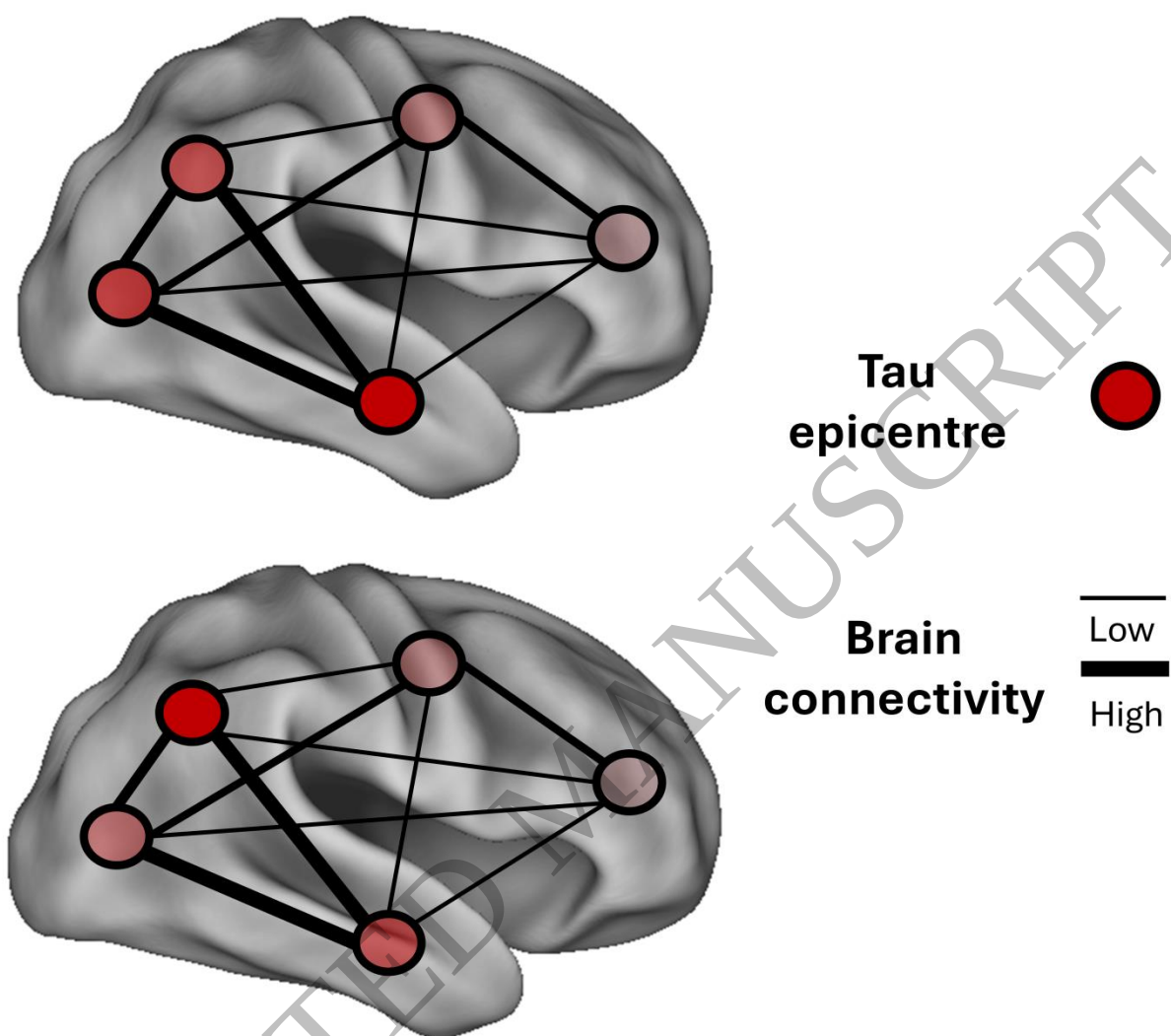


Figure 1  
207x181 mm (x DPI)

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