Tau beats amyloid in predicting brain atrophy in Alzheimer's disease: implications for prognosis and clinical trials

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Several biomarkers have emerged in the past decades to quantify pathological brain changes related to Alzheimer's disease (AD). In particular, positron emission tomography (PET) radiotracers that bind selectively to amyloid-β plaques and tau neurofibrillary tangles have advanced AD research and drug development by enabling the detection and quantification of the neuropathologic lesions that define AD in living people.

Among amyloid-β PET tracers, 11C-PiB was the first to be developed, followed by fluorine-18 labelled tracers approved for clinical use (i.e., 18F-florbetapir, 18F-florbetaben, 18F-flutametamol). Cumulative evidence has demonstrated the diagnostic utility of amyloid-PET in differentiating AD from non-amyloid neurodegenerative diseases (*1*,*2*). However, amyloid-PET retention begins two decades before the onset of clinical symptoms and reaches a relative plateau throughout most of neocortex early in the evolution of AD (prior to, or coincident with early clinical symptoms). As a result, the distribution and burden of amyloid correlate poorly with disease stage or clinical measures in symptomatic patients, and do not co-localize with markers of regional neurodegeneration (*3*,*4*).

18F-flortaucipir was the first PET tracer to show high affinity and selectivity for AD neurofibrillary tangles, followed by next generation tau tracers like 18F-MK6240, 18F-RO948, 18F-PI2620, 18F-GTP1 and 18F-PM-PBB3. 18F-flortaucipir is to date the only tau PET tracer to receive FDA approval for clinical use in the U.S. 18F-flortaucipir PET distinguishes AD from other underlying neuropathologies, including non-AD tauopathies to which the tracer shows a low binding affinity (*5*–*8*). In contrast with the early widespread distribution of amyloid PET binding, tau-PET signal originates in entorhinal cortex and other medial

temporal regions. In the presence of amyloid, signal progressively spreads into inferior temporal gyrus, followed by lateral occipital cortex, posterior cingulate/precuneus, lateral temporoparietal regions and finally prefrontal cortex. This evolution is similar (though not identical) to Braak neuropathological staging of tau neurofibrillary tangles, and closely co-localizes with brain atrophy and hypometabolism patterns as measured by MRI or FDG-PET (*3*,*9*). Increasing spread of tau is associated with clinical impairment (*10*–*12*), with tau-PET binding topography associated with domain-specific cognitive deficits (*13*,*14*) and distinct AD clinical variants (*9*,*15*,*16*),

The relationships between amyloid- and tau-PET and clinical measures largely replicate clinicopathological studies which show that the stage and extent of neurofibrillary tau tangles are strongly associated with *ante-mortem* clinical status and cognitive deficits (*17*,*18*), while amyloid neuropathology correlates weakly with ante-mortem clinical impairment. Moreover, the regional distribution of neurofibrillary tau tangles at *post-mortem* also relates to distinct clinical presentations and syndromes (*19*), while amyloid-β plaques distribution generally does not. *Post-mortem* pathology and *in vivo* imaging evidence together suggest a spatial and temporal decoupling between amyloid-β plaques accumulation and neurodegeneration, while neurofibrillary tangles are more closely associated with regional neurodegeneration and clinical impairment. These observations support the hypothesis that amyloid-β may influence neuronal integrity only indirectly by facilitating tau spreading (see (*20*) for review), leading to synaptic and cell loss, and ultimately translating into cognitive and functional decline.

In cross-sectional multimodal imaging studies along the clinical AD spectrum, tau accumulation has also been observed in areas without overt neurodegeneration (*3*,*9*,*15*,*21*). These findings support the hypothesis that tau elevation may locally precede neurodegeneration, which would be a downstream event in the cascade associated with AD. Such hypotheses are reinforced by significant associations between baseline tau-PET patterns and prospective MRI atrophy (*22*,*23*). A recent study conducted by La Joie et al. (*22*) showed that in patients with clinically mild AD, the burden and regional distribution of tau pathology at baseline, as measured with 18F-flortaucipir PET, can forecast the severity and topography of prospective brain atrophy over the following 15 months. In contrast, neither the severity nor topography of amyloid-PET was found to be informative of atrophy progression. At a group level, regional tau-PET uptake at baseline explained >40% of unique variance in atrophy at follow-up, even when corrected for baseline cortical thickness, versus 3% of variance explained by regional amyloid-PET. Importantly, the close association between baseline tau-PET and subsequent atrophy was found not only at the group level but also in each individual patient (***Figure 1***). In line with this, tau-PET also correlates strongly with retrospective longitudinal atrophy (years preceding PET) in both cognitively unimpaired individuals and patients with clinical AD (*24*,*25*).

Tau-PET is a sensitive predictor not only of structural brain changes in AD, but also of prospective cognitive decline. Several studies have described strong associations between baseline tau-PET and cognitive changes over time across the AD clinical spectrum. In head-to-head comparisons, tau-PET binding in temporo-parietal regions outperformed amyloid-PET and structural MRI measures in predicting cognitive decline (*26–28*), especially in patients at early AD stages (*26*). This was replicated by local and multicenter studies, using different tau-PET tracers (i.e., 18F-Flortaucipir and 18F-RO948), with retrospective and prospective longitudinal cognitive assessments, and including participants with different severity of impairment. These converging findings suggest that tau-PET is a promising prognostic tool for predicting cognitive decline, and tau pathology may be the main driver of neurodegeneration and cognitive symptoms.

Tau-PET may play an important role in future precision medicine approaches to AD care by enabling prediction of specific neurodegeneration and cognitive trajectories in individual patients. A recent study that evaluated tau PET patterns in a large, multi-site dataset (N=1,612) revealed substantial variability across patients, highlighting four distinct spatiotemporal patterns, each associated with specific demographic and clinical features (*29*). This heterogeneity highlights the limitations of a "one size fits all" approach to predicting tau, neurodegeneration or clinical change. Furthermore, individual factors modify the relationship between tau accumulation and cognition, with younger age, female sex, higher educational attainment and higher baseline cortical thickness all associated with increased resistance against the deleterious effect of pathology on cognitive performance (*30*). Some studies suggest that the relationship between tau, neurodegeneration and cognition may also vary based on race and ethnicity as proxies for social determinants of health (see (*31*) for review), though much more work in diverse cohorts is needed to better understand these relationships. Finally, the development of biomarkers that measure common non-AD pathologies (e.g. , vascular lesions; TDP43 and α-synuclein aggregates) will be critical for achieving more adequate prognosis, as these processes are highly prevalent in patients with AD (*32*) and contribute significantly to neurodegeneration and cognitive decline.

Plasma biomarkers have recently emerged as promising and accessible biomarkers for tau pathology in AD (*33*). Plasma p-tau181, p-tau217 and p-tau 231 increase in early stages of AD, discriminate patients with AD from non-AD conditions, and show moderate correlations with tau-PET uptake (*34*,*35*). While plasma p-tau measures Aβ-induced changes in tau phosphorylation and secretion, tau-PET measures the overall burden and topographic distribution of neurofibrillary tangles. Therefore, plasma p-Tau measures and tau-PET provide additive and complementary information on tau pathology and prognosis. In a recent head-to-head study, baseline plasma p-Tau217 best predicted longitudinal increases in tau PET in preclinical AD, while baseline tau-PET was the better predictor in symptomatic patients (*36*). Future work will determine whether baseline patterns of tau PET can also predict domain-specific changes in cognition (e.g., medial temporal tau predicting changes in episodic memory; occipital tau predicting changes in visuospatial function).

The close relationship between tau burden, prospective neurodegeneration and consequent clinical decline is particularly important in the development of novel AD therapies. Effective treatments to AD may ultimately require combination therapies targeting both amyloid-β and tau pathology as well as other elements of AD pathophysiology. Anti-tau therapies could be effective in preventing synaptic loss and atrophy thus slowing clinical decline; while anti-amyloid therapies in early stages could prevent tau spreading. Thus, tau-PET may be a good tool to stratify patients in clinical trials of disease-modifying therapies, with personalized estimations of neurodegeneration and cognitive trajectories, enhancing the chance to identify the best time window and cohort where a given therapy can be most effective. In a recent Phase 2 trial of donanemab (*37*), a monoclonal antibody targeting the pyroglutamate epitope on Aβ plaques, 18F-flortaucipir PET was used to limit trial inclusion to patients with intermediate tau deposition. This innovative approach for patient stratification shifts the focus from amyloid to tau pathology, enabling more accurate prediction of clinical progression. Including patients with intermediate amount of tau pathology addresses the concern that anti-amyloid therapies may not be beneficial at advanced disease stages (high tau), but also reduces the risk of including patients who may not progress clinically during the course of the trial (low tau). In the trial, significant amyloid PET lowering by donanemab was associated with slower tau PET progression in frontal and temporal cortex and modestly slower cognitive and functional decline compared to placebo. This successful trial foreshadows a future in which tau-PET may have an important role in establishing eligibility and evaluating response to novel disease modifying therapies. However, future clinical trials also need to evaluate alternative tau-PET tracers, which may be more sensitive than 18F-flortaucipir PET for early Braak tau stages, in order to ensure the inclusion of patients with early AD-tau pathology - as these patients may benefit most from anti-amyloid and other therapeutic approaches.

In conclusion, tau-PET is a highly promising tool that will likely play an important role in future precision medicine approaches to AD care. Tau-PET is both highly specific for AD neuropathology and (in contrast to amyloid PET) strongly associated with neurodegeneration and clinical outcomes. Further work is needed to fully leverage the potential of tau PET to predict individual patient trajectories, understand the complex pathophysiology of the disease and ultimately accelerate the development of effective therapies.

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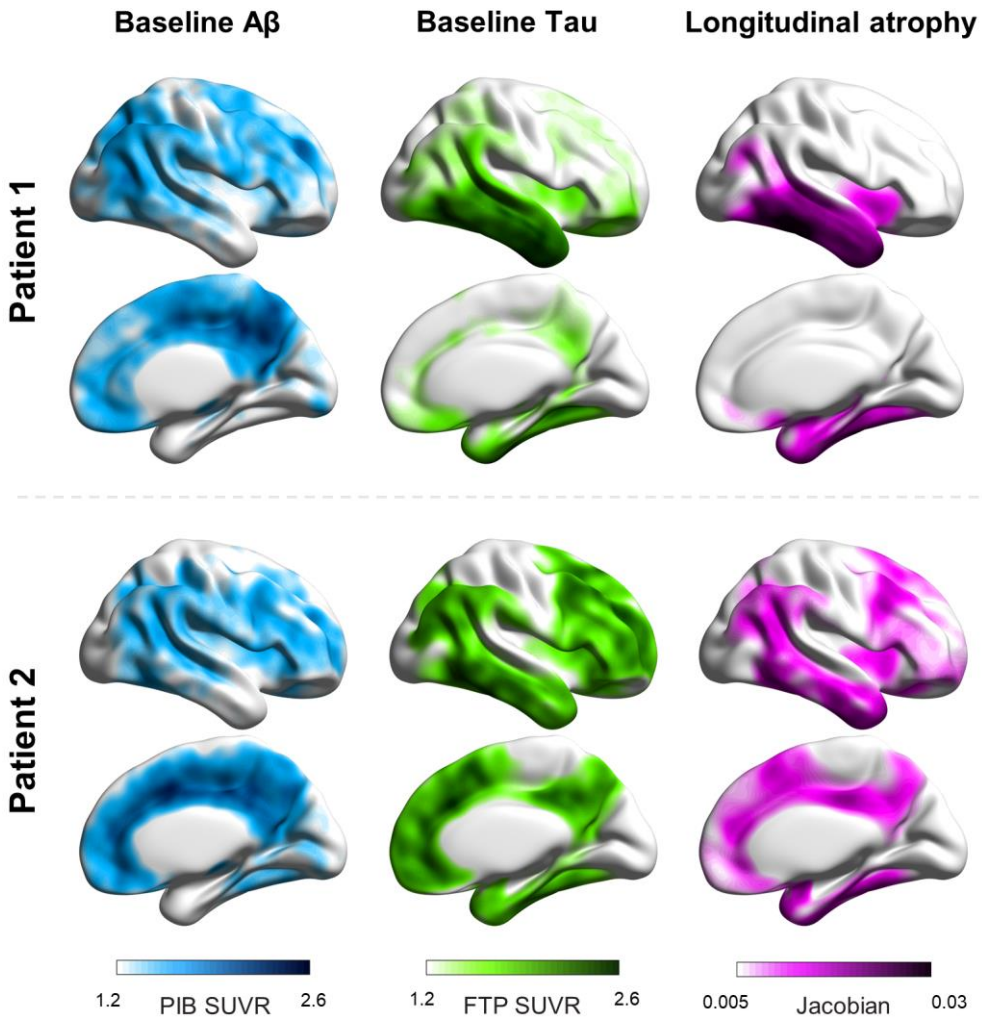
FIGURE 1. Single-subject amyloid and tau PET patterns at baseline and cortical atrophy over time. Left and central panels: 11C-Pittsburgh compound B (PIB) and 18F-flortaucipir (FTP) PET standardized uptake value ratio maps, higher values indicate more severe pathology. Right panel: patterns derived from prospective longitudinal structural MRI scans following PET, positive Jacobians indicate shrinkage over time. Patient 1: 71 year-old with mild AD dementia; Patient 2: year-old with mild AD dementia.



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