From clinical trials to memory clinics, tau PET visual reads can help diagnosis and patient stratification

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With the emergence of disease-modifying therapies for Alzheimer's disease (AD), it is imperative that standardized approaches to interpret relevant biomarkers are validated and clinically available. 18F-flortaucipir was the first PET tracer to show high affinity and selectivity for AD tau neurofibrillary tangles. 18F-flortaucipir binding has higher specificity for determining dementia due to underlying AD than amyloid biomarkers, as these can detect incidental or secondary amyloid-β pathology. The topography of 18F-flortaucipir binding is strongly associated with distinct clinical variants, neurodegeneration, and clinical decline in AD[1]. Furthermore, in recent drug trials, patients with low-medium 18F-flortaucipir binding at baseline derived greater clinical benefit from amyloid plaque lowering than those with baseline high tau-PET signal.

18F-flortaucipir is the only tau-PET tracer approved for clinical use by the U.S. Food and Drug Administration, with a visual read method designed to detect tau pathology in patients with suspected AD. This method defines 18F-flortaucipir patterns as "moderate AD" when binding is increased in posterolateral temporal or occipital cortex, and as "advanced AD" when binding extends to cingulate, parietal and frontal cortex. A scan is defined as "negative" for AD when binding is absent or limited to mesial and anteromedial temporal cortex. This approach was validated in a PET-to-postmortem study in end-of-life patients with mostly severe dementia[2]. The positive reads showed high sensitivity (~92%) and specificity (~80%) for Braak stages

V/VI, which are often associated with dementia, but low sensitivity for Braak stages III/IV, which represent the median stages underlying mild cognitive impairment (MCI)[3]. The visual-read method was shown to predict clinical deterioration over 18 months among patients with advanced AD-tau patterns, but not with moderate tau pathology or negative tau-PET[4]. The validation of visual-read methods in clinically relevant populations can enable broader clinical and trial applications, as 18F-flortaucipir PET could be crucial to disease staging and predict response to anti-amyloid-β therapies[5].

In this issue of NEUROLOGY, Coomans et al[6] provide additional evidence on translation of 18F-Flortaucipir visual reads into clinical practice. Following FDA-approved guidelines, the authors evaluated its performance in a memory-clinic cohort of 97 amyloid-positive patients (mostly with AD dementia, only 12 with MCI), compared to 146 cognitively-unimpaired adults. Importantly, 19 patients with dementia with Lewy Bodies (DLB) were included, as AD-like tau tangles are observed in approximately half of DLB cases[7]. Tau-PET visual reads were compared between *two raters* and with *semiquantitative classification*, which defined tau-positivity based on standardized uptake value ratio (SUVr) at two thresholds. Across all participants, high inter-reader agreement (~98%), and high concordance (~90%) between visual-read and semiquantitative classifications were found. Across the aging-AD continuum, tau-positivity correlated with worse cognitive decline. Within tau-positive patients, tau-PET SUVr was associated with prospective decline, adding prognostic value.

The *clinical relevance* of the visual-read approach was further tested in association with clinical diagnosis and amyloid-β status. Among amyloid-negative participants, only one in 12 DLB patients were tau-positive; within the amyloid-positive cohort, 25.0% of cognitively unimpaired adults, 87.6% and 42.9% of patients with AD and DLB respectively were tau-positive. However, the study lacks post-mortem pathology confirmation, and low-level 18F-flortaucipir signal may not be specific for tau pathology, being described also in TDP43 cases[8]. This, together with spatially restricted low-level tau pathology in DLB, makes early tau-positive DLB cases difficult to interpret.

Longitudinal stability of the method was tested in 40 patients with AD and 50 controls with a follow-up tau-PET (~2 years). As visual reads were unchanged, tau-positive visual reads may be

stable over time in clinically impaired patients. However, this could also be related to the severe and extensive tau pathology pattern required for positive visual reads, and inclusion of patients mostly at dementia stage.

Coomans and colleagues provide an independent validation of the FDA-approved tau-PET visual-read method, recruiting patients from tertiary memory clinics. The main strengths of the study are (i) evaluating concordance between visual-read and semiquantitative classifications, (ii) testing visual read reproducibility with longitudinal scans, and (iii) inclusion of DLB cases. While this study represents an important first step, further studies are needed to test the generalizability of the tau-PET visual-read method, especially in unselected "real-world" cohorts, larger groups of non-amnestic patients with AD (here 9 of 97), and among more diverse participants and raters.

Importantly, this study included relatively young AD patients who were previously shown to have a high tau burden, and only few cases with MCI. Towards clinical implementation of tau-PET visual reads, it will be important to test the accuracy in older cohorts that are more representative of dementia demographics, across a broader range of clinical impairment. Studies that classified tau-PET based on semi-quantification have generally shown lower sensitivity for detecting tau pathology in older and less impaired patient cohorts. The baseline characteristics of patients in this study may thus over-estimate sensitivity of the FDA-approved visual-read method, which is geared towards addressing more advanced pathology, but may be less useful for early detection and preclinical diagnosis.

Alternative tau-PET visual-read approaches have been proposed that include medial temporal lobe, and may be more sensitive to earlier, clinically meaningful tau pathology[9]. However, tau isolated to the medial temporal lobe is not specific for AD, and can be seen in Primary Age Related Tauopathy with absent-low amyloid-β pathology. A future diagnostic approach could include combining emerging blood biomarkers alongside tau-PET. For example, plasma P-tau measures could be used to establish presence or absence of amyloid-β[10], while tau-PET could be performed in patients with positive plasma P-tau as a complementary tool for tau staging, while the addition of semi-quantification to visual reads could provide more accurate prognosis and potentially predict therapy response.

Overall, this study represents an important step toward implementation of 18F-flortaucipir in memory clinics. TauPET may play important future clinical roles in diagnosis, prognosis and treatment selection for patients with underlying AD.

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