Tau PET Visual Reads: Research and Clinical Applications and Future Directions

David N. Soleimani-Meigooni[1] & Gil D. Rabinovici [1,2]

[1]Memory and Aging Center, Department of Neurology, University of California, San Francisco, CA, USA

[2]Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA, USA

Correspondence: David N. Soleimani-Meigooni, MD

Assistant Professor of Neurology

UCSF Memory and Aging Center, Box 1207

675 Nelson Rising Lane, Suite 190

San Francisco, CA 94143

+1-415-353-2427

david.soleimani-meigooni@ucsf.edu

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Biomarkers for tau pathology are essential to the latest Alzheimer's disease (AD) research framework (1). Phosphorylated-tau, the primary component of neurofibrillary tangles, is measurable in cerebrospinal fluid and plasma, but these fluid biomarkers do not capture the spatial dynamics of tau accumulation and spread (Braak staging) (2-4). Over the last decade, radiotracers that selectively bind to aggregated tau in neurofibrillary tangles have been developed, enabling diagnosis, mapping, and quantification of this pathology in living people (2, 4, 5). Tau PET correlates with other regional pathological changes (synaptic loss, hypometabolism, and brain atrophy), domain-specific cognitive scores, and cognitive decline in people with AD (2). In AD clinical trials, tau PET is increasingly used in participant selection, pre-treatment staging, and measuring treatment response (6). In the future, tau PET could become an important diagnostic and prognostic tool in clinical practice.

[18F]Flortaucipir is the most widely used tau PET tracer. Quantitative analysis of [18F]Flortaucipir PET accurately distinguishes clinically diagnosed dementia due to AD from non-AD neurodegenerative diseases and cognitively unimpaired controls (7). Although quantitative analysis has been primarily used in research, newer visual interpretation methods could have important research and clinical applications (8, 9). In a PET-to-autopsy study, majority interpretations of 5 raters applying a binary visual read algorithm (negative or positive AD tau pattern) on 64 antemortem scans showed 92% sensitivity and 80% specificity for detecting advanced tau pathology (Braak stages V-VI) at autopsy (mean PET-to-autopsy interval 2.6 months) (8). Based on these data, the United States Food and Drug Administration (FDA) approved clinical [18F]Flortaucipir PET, "To estimate the density and distribution of aggregated tau neurofibrillary tangles in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease." (10). Importantly, the positive AD tau pattern excluded isolated uptake in medial and anterolateral temporal lobes, which is less specific and may represent early neurofibrillary tangle pathology in AD, age-related tau accumulation in cognitively normal adults, or off-target binding in non-AD neurodegenerative conditions (8). However, accumulation in

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these regions can be clinically significant, indicating Braak stage III-IV tangle pathology, which in clinicopathological studies is often with associated mild cognitive impairment (MCI) or dementia during life (*11*). An alternative visual read method, which classified scans as positive based on uptake in these regions, showed increased sensitivity but lower specificity for MCI and mild dementia due to AD compared to the FDA-approved visual read method (*9*). Both visual read methods were developed for diagnostic purposes, and neither was intended to track disease progression or treatment response on longitudinal imaging.

Several other tau radiotracers have advanced to investigational human studies (*5*). [18F]MK-6240 has high affinity and selectivity for AD neurofibrillary tangles. Compared to [18F]Flortaucipir, [18F]MK-6240 has two-fold higher dynamic range and less off-target binding in choroid plexus, which could be advantageous for detecting early medial temporal neurofibrillary pathology (Braak stages I-II) and small changes in longitudinal studies or clinical trials (*12, 13*). On the other hand, [18F]MK-6240 has more off-target binding in the meninges, which may be misinterpreted as tracer uptake in the medial and inferior temporal lobes (*12*).

In this issue of *The Journal of Nuclear Medicine*, Seibel *et. al.* describe and evaluate a [18F]MK-6240 PET visual read method to assess *in vivo* presence of tau pathology, measure regional pattern and extent of tau, and classify abnormal regional patterns as either AD (temporal and extra-temporal cortical tracer uptake without subcortical uptake) or non-AD neurodegeneration (subcortical tracer uptake with some cortical uptake allowable) patterns (*14*). Three expert nuclear medicine physicians applied this algorithm in blinded reads of cross-sectional, [18F]MK-6240, 60-90-minute post-injection PET data from 102 participants, including healthy controls and patients with clinical diagnoses of MCI, AD dementia, or non-AD neurodegenerative diseases. Scans were read in gray scale, without corresponding structural neuroimaging data, with images scaled to mean activity in a cerebellar gray matter reference region. The majority visual reads were 81% sensitive and 93% specific for distinguishing patients with MCI or dementia due to AD from non-AD patients and controls. Reliability was high

(κ=0.91), with discordant reads occurring because of technical artifacts from scan processing or reconstruction, difficulty distinguishing cortical tracer retention in medial and inferior temporal lobes from nearby meningeal off-target binding, and low inter-rater agreement in regions of early tau accumulation (hippocampus and medial temporal lobes). Majority visual reads had higher accuracy than individual reads and higher sensitivity than various quantitative methods. The high accuracy and reliability support the plausibility of tau PET visual reads performed by experienced readers.

This research represents a major advance by introducing the first systematic approach to visual interpretation of [18F]MK-6240 PET. The study also raises a number of important follow-up questions:

First, is this an optimal [18F]MK-6240 visual read algorithm? Visual read approaches require standardization of many image visualization and classification parameters (i.e., color scale, thresholds, image scaling, target regions, classification rules). The parameters selected for [18F]MK-6240 were notably different than for [18F]Flortaucipir. Most important was the decision to consider scans showing focal temporal uptake as AD positive. The initial proposed criteria considered these scans negative based on concerns for inaccurate classification due to possible misinterpretation of meningeal off-target binding. However, the researchers found that visual raters could be trained to distinguish off-target binding from on-target temporal signal by applying multiple planar views, which could theoretically increase sensitivity for detecting earlier Braak stages. However, even without choroid plexus contamination, many concerns around specificity of signal in temporal regions observed with [18F]Flortaucipir also apply to [18F]MK-6240. Ultimately, PET-to-autopsy studies are needed to determine the trade-off between increased sensitivity and potentially decreased specificity associated with interpretation of isolated temporal lobe signal as consistent with AD-related tau.

Second, how will this visual read method generalize to less experienced brain PET readers? While most readers in the present study were naïve to [18F]MK-6240, all had

substantial experience with amyloid PET and other tau radiotracers. As tau radiotracers are rolled-out into broader research and clinical use, the reliability of visual reads by less experienced clinicians will need to be established. Encouraging early data from the Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) study found high agreement between visual reads of amyloid PET scans performed and interpreted in the community and scan classification by image quantification (15). However, unlike amyloid PET radiotracers, which all show similar off-target binding in white matter, each tau PET tracer has unique off-target binding patterns, which can complicate visual interpretation (5, 9, 12, 16). Novice readers may need additional radiotracer-specific training to accurately identify/discriminate off-target binding, especially near the medial temporal lobes, with the same accuracy and reproducibility as experts.

Third, should a single clinician's qualitative read be the standard for tau PET interpretation? For both [^{18}F]MK-6240 and [^{18}F]Flortaucipir, majority visual reads show generally higher accuracy than individual visual reads, but requiring multiple expert reads for each scan is not practical (8, 14). Hybrid read approaches, which incorporate both a visual read and quantitative information from the image, have been proposed to leverage the complementary strengths, and counter-balance the weaknesses, of qualitative versus quantitative approaches to image classification (17). Further research is needed to measure the effect of additional quantitative information on accuracy and reliability of tau PET visual reads.

Fourth, will visual ratings be useful for measuring longitudinal changes in tau in individual patients? The authors propose this as a potential application of their visual read algorithm, but validation in longitudinal observational research or clinical trials is needed. The proposed region-based method may be too time consuming for routine clinical or research purposes, and there are a variety of challenges (e.g., variable reliability of reads in different regions of interest; difficulty grading the extent of tracer binding in regions without complementary structural neuroimaging) that may impact reliability of this method, even in the hands of expert readers. Given these challenges, quantitative approaches to measuring signal

intensity and spatial spread will likely be necessary to most precisely evaluate longitudinal changes in tau PET signal.

Lastly, how well will the visual read algorithm perform in MCI? The present study included only 21 MCI patients in the visual read test group, yet this early clinical stage represents one of the highest priority populations for tau PET in clinical trials and future clinical practice. Patients with MCI are functionally independent and have subtle symptoms that overlap with non-AD neurodegenerative diseases; thus, accurate and timely identification of these patients is important, and may be particularly crucial for administration of future disease-modifying therapies (18). At autopsy, MCI patients have on average intermediate Braak stage III-IV neurofibrillary pathology, and antemortem tau PET signal can be modest and subtle at this stage (8, 11, 19). A more sensitive visual read schema, which identifies early signal in medial temporal lobes, may be particularly beneficial for detection of AD tau pathology in MCI.

Ultimately, visual reads will need to be applied to large numbers of longitudinally scanned patients, with a broad range of neurodegenerative disease diagnoses, who have excellent clinical characterization and amyloid biomarker data, and who eventually undergo autopsy. These data will clarify the sensitivity and specificity of tau tracers to neurofibrillary tangle pathology, elucidate causes of off-target binding, and determine how longitudinal visual tracking of regional tracer uptake corresponds to pathological progression of AD. Another area of interest is head-to-head comparisons of different tau PET ligands in the same patients, which may lead to development and validation of unified approaches for tau PET quantification and visual reads (20). While each tau radiotracer has its idiosyncrasies, the overall spatial pattern of binding is remarkably consistent, suggesting that standardized approaches will be feasible (7). The maturation of tau PET as a powerful biomarker for diagnosis, staging, and prognosis in AD is occurring hand-in-hand with the emergence of novel molecular therapies that modify the course of AD pathophysiology. Collectively, the field seems to be at an inflection point, heralding a new era of early detection, biomarker-based diagnosis, and disease modifying therapy.

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