Performance of a $[^{18}\text{F}]$Flortaucipir PET Visual Read Method Across the Alzheimer Disease Continuum and in Dementia With Lewy Bodies

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Abstract

**Background and objectives:** Recently, the US Food and Drug Administration approved the tau-binding radiotracer $[^{18}\text{F}]$flortaucipir and an accompanying visual read method to support the diagnostic process in cognitively impaired patients assessed for Alzheimer’s disease (AD). Studies evaluating this visual read method are limited. Here, we evaluated the performance of the visual read method in participants along the AD continuum and dementia with Lewy Bodies (DLB) by determining its reliability, accordance with semi-quantitative analyses and associations with clinically relevant variables.

**Methods:** We included participants who underwent tau-PET at Amsterdam University Medical Center. A subset underwent follow-up tau-PET. Two trained nuclear medicine physicians visually assessed all scans. Inter-reader agreement was calculated using Cohen’s kappa ($\kappa$). To examine the concordance of visual read tau-positivity with semi-quantification, we defined standardized uptake value ratio (SUVr)-positivity using different threshold approaches. To evaluate the prognostic value of tau-PET visual read, we performed linear mixed models with longitudinal Mini-Mental State Examination (MMSE).

**Results:** We included 263 participants (mean age: 68.5, 45.6% female), including 146 cognitively unimpaired (CU), 97 amyloid-positive mild cognitive impairment or AD-dementia (AD), and 19 DLB. The visual read inter-reader agreement was excellent ($\kappa=0.95$ [CI: 0.91-0.99]). None of the amyloid-negative CU (0/92 [0%]) and 1 amyloid-negative DLB (1/12 [8.3%]) were tau-positive. Among amyloid-positive participants, 13 CU (13/52 [25.0%]), 85 AD (85/97 [87.6%]) and 3 DLB (3/7 [42.9%]) were tau-positive. Two-year follow-up visual read status was identical to baseline. Tau-PET visual read corresponded strongly to SUVr status, with up to 90.4% concordance. Visual read tau-positivity was associated with a decline on the MMSE in CU ($\beta=-0.52$ [CI: -0.74, -0.30], $p<0.001$) and AD ($\beta=-0.30$ [CI: -0.58, -0.02], $p=0.04$).

**Discussion:** The excellent inter-reader agreement, strong correspondence with SUVr, and longitudinal stability indicate that the visual read method is reliable and robust, supporting clinical application. Furthermore, visual read tau-positivity was associated with prospective
cognitive decline, highlighting its additional prognostic potential. Future studies in unselected cohorts are needed for a better generalizability to the clinical population.

**Classification of Evidence:** This study provides Class II evidence that $[^{18}\text{F}]$flortaucipir visual read accurately distinguishes patients with low tau-tracer binding from those with high tau-tracer binding, and is associated with amyloid-positivity and cognitive decline.
Introduction

Alzheimer’s disease (AD) is pathologically characterized by amyloid-β plaques and neurofibrillary tau tangles. The clinical application of biomarkers for amyloid-β pathology have substantially improved the diagnostic process of AD dementia, leading to increased diagnostic confidence and changes in treatment strategies. However, positron emission tomography (PET) biomarkers for tau pathology have shown higher specificity for AD dementia, as the presence of incidental or co-morbid amyloid-β pathology is common, especially at older age and in APOE ε4-carriers. Moreover, tau-PET is more strongly associated with cognitive decline and atrophy. Therefore, tau-PET holds potential to become an important diagnostic and prognostic tool in the clinic.

Recently, the US Food and Drug Administration (FDA) approved the tau-binding radiotracer \(^{[18}F\)flortaucipir and an accompanying visual read method to support the diagnostic process in cognitively impaired patients assessed for AD. The FDA-approved visual read method defines increased tracer binding in late-stage tau regions (corresponding to tau-PET Braak stages IV-VI) as tau-positive, whereas increased tracer binding isolated to early-stage tau regions (corresponding to tau-PET Braak stages I-III) or absence of increased tracer binding is defined as tau-negative. As a result, this method has strong specificity for AD given the focus on late-stage tau regions. Moreover, this method provides valuable prognostic information. However, studies evaluating the performance of this visual read method in independent samples are limited.

The aim of this study was to evaluate the performance of the FDA-approved \(^{[18}F\)flortaucipir PET visual read method, by determining its reliability, accordance with semi-quantitative analyses and associations with clinically relevant variables. We included participants along the AD continuum and participants with Lewy Body Dementia (DLB), as AD-type tau tangles are observed in approximately 50% of DLB patients. To evaluate key properties of the method, we assessed inter-reader agreement, examined longitudinal stability of the method, and compared it to a semi-quantitative measure of tracer binding. To evaluate the method in relation to clinically relevant variables, we examined associations with clinical diagnosis, amyloid-β status, demographic factors, and prospective cognitive decline. The primary research questions addressed in this study are: is the visual read method reliable, and is tau-PET visual read associated with clinical diagnosis, amyloid-β status and cognitive decline.
Methods

Participants

We included 263 participants who underwent \([^{18}F]\)flortaucipir PET between 2015 and 2021 for research purposes at Amsterdam University Medical Center (Amsterdam, The Netherlands). The study population largely consisted of participants from the Amsterdam Dementia Cohort,\(^{16,17}\) the Subjective Cognitive Impairment Cohort,\(^{18}\) the Dementia with Lewy Bodies Project,\(^{19}\) and the Amsterdam sub-study of the EMIF-AD PreclinAD study.\(^{20}\) From these cohorts, cognitively normal identical twins (n=82), and cognitively normal participants with subjective cognitive decline (SCD) (n=56) were included, as well as cognitively impaired participants with mild cognitive impairment (MCI) (n=12), probable AD dementia (n=85) and DLB (n=19). All MCI and probable AD dementia participants had positive amyloid-\(\beta\) PET and/or CSF biomarkers.\(^{21,22}\) Furthermore, the study population consisted of n=9 healthy controls who were not part of the aforementioned cohorts, but who underwent tau-PET as control participants in prior PET kinetic modelling studies.\(^{23,24}\) Details are described in the eMethods. Exclusion criteria for undergoing tau-PET included large structural abnormalities on magnetic resonance imaging (MRI), a history of severe traumatic brain injury and (prior) use of amyloid-\(\beta\)- or tau-lowering drugs.

Participants were categorized into three groups based on their clinical presentation: 1) cognitively unimpaired (CU) participants (SCD, twins and healthy controls), 2) cognitively impaired participants with AD (amyloid-\(\beta\) positive MCI and probable AD dementia, hereafter referred to as “AD”) and 3) DLB participants. All participants had cross-sectional Mini-Mental State Examination (MMSE) (global cognitive functioning) available, and 140 participants had prospective 1.5\(\pm\)1.7 year follow-up MMSE available. A total of 594 MMSE scores (number of visits per participant: 1-7 [median: 2], time between visits varied per participant) were included.

Standard Protocol Approvals, Registrations, and Patient Consents

All participants provided written informed consent. All studies were approved by the Medical Ethics Review Committee of the VU University Medical Center (Amsterdam, the Netherlands).
Amyloid-β status

Amyloid-β status of CU participants was determined by \(^{18}\text{F}\)florbetapir or \(^{18}\text{F}\)flutemetamol PET visual read according to company guidelines. Amyloid-β status of AD and DLB participants were determined at diagnostic screening by either PET visual read (\(^{18}\text{F}\)florbetapir, \(^{18}\text{F}\)flutemetamol and \(^{18}\text{F}\)florbetaben according to company guidelines, or \(^{11}\text{C}\)PiB according to previously published methods\(^25\)) or CSF using previously determined cutoffs.\(^26\) If both PET and CSF were available, PET was chosen. We used amyloid-β status that was available in closest proximity in time to tau-PET. Amyloid-β status was missing for three CU participants.

Tau-PET and MRI acquisition

All participants underwent baseline tau-PET. A subset (n=50 CU and n=40 AD) underwent 2.1±0.5-year follow-up tau-PET of which n=15 CU additionally underwent 4.5±0.4-year follow-up tau-PET. All scans were acquired using a dual time-point dynamic protocol, starting immediately after \(^{18}\text{F}\)flortaucipir administration and including at least the 0-30 minutes and 80-100 minutes post-injection time interval.\(^27,28\) All scans were acquired on a Philips TF-64 PET/CT scanner (baseline: n=244 Philips Ingenuity and n=19 Philips Gemini; follow-up: n=105 Philips Ingenuity, Philips Medical System, Best, The Netherlands). Low dose CT scans were acquired prior to both parts of the dynamic scan for attenuation correction purposes. Participants underwent three-dimensional T1-weighted MRI on a 3Tesla scanner for co-registration and brain region-of-interest purposes.

Tau-PET visual read

Tau-PET scans were prepared and visually read according to FDA-approved guidelines.\(^13\) First, dynamic PET frames were summed from 80-100 minutes post-injection. T1-weighted MR images were then co-registered to the corresponding summed image using Vinci software (Max Planck Institute, Cologne, Germany). Scans were reoriented to remove head tilt. Background activity was determined by calculating the mean counts in the cerebellum (manually delineated in the transversal plane at the maximum cross-sectional area). Voxels of increased activity were defined as >65% above the cerebellar average. Following FDA-approved guidelines, increased activity in posterolateral temporal, occipital, or parietal/precuneus region(s) in either hemisphere, with or without frontal involvement, resulted in a positive visual read. The absence of increased activity or increased activity
isolated to medial temporal, anterolateral temporal, and/or frontal regions resulted in a negative visual read. Patterns of isolated or small non-confluent foci of increased activity were not defined as tau-positive.

All scans were visually read by two trained nuclear medicine physicians (BvB and EvdG) blinded to clinical information. The two readers gave confidence scores for each scan ranging from 1 (lowest confidence) to 5 (highest confidence). Scans were presented in a random order. The two nuclear medicine physicians were first trained with a test set of 20 randomly selected baseline scans. The 20 test set scans were visually read for a second time within the complete set of 263 baseline scans, from which intra-reader agreement was determined. Subsequently, the 105 follow-up scans were assessed. Scans with between-reader disagreement were re-read by the two nuclear medicine physicians in a joint consensus meeting resulting in a consensus read.

**Tau-PET SUVr**
To compare tau-PET visual read to a semi-quantitative measure of tracer binding, we calculated standardized uptake value ratios (SUVr) using whole cerebellar grey matter as reference region in two regions-of-interests (ROIs) based on the Hammers and Svarer atlases. First, we calculated SUVr in a temporal meta-ROI corresponding to a volume-weighted average of the bilateral entorhinal cortex, amygdala, parahippocampal gyrus, fusiform gyrus and middle, inferior and superior temporal cortices. The temporal meta-ROI is commonly used and has shown high discriminative accuracy between AD and non-AD dementias. However, the temporal meta-ROI also includes medial temporal regions and therefore does not fully correspond to regions most relevant for visual read. Therefore, we additionally calculated SUVr in a temporoparietal ROI (only including regions that can contribute to a positive visual read), including the bilateral inferior, middle, and superior temporal cortices, superior parietal gyrus, inferolateral parietal lobe and the posterior cingulate gyrus.

**Statistical analyses**
Demographical characteristics between groups were compared using t-tests, \( \chi^2 \) and Mann-Whitney \( U \) tests. To assess inter- and intra-reader reliability, Cohen’s kappa coefficients (\( \kappa \)) were calculated. Prevalence of visual read tau-positivity was determined per diagnostic group (CU, AD and DLB) stratified by amyloid-\( \beta \) status. Independent t-tests were performed to
compare tau-PET SUVr between visual read tau-negative and visual read tau-positive participants. To examine the correspondence of tau-status defined by visual read and tau-status defined by SUVr, we obtained SUVr thresholds (ROI-specific) using two approaches: first, by fitting a Gaussian Mixture Model (GMM) with 2 components resulting in a threshold representing the mean of the mu of both components,\(^{32,33}\) and second, by defining the threshold as mean+\([2\times SD]\) of amyloid-β negative CU participants.\(^4\) Percentages of concordance and discordance in tau-status between visual read and the two SUVr thresholds were calculated. Next, we assessed associations of tau-PET visual read with age, sex, \(APOE\) ε4-carriership, and prospective cognitive decline in CU and AD. There was too limited power in the DLB group due to low number of tau-positive DLB cases. Associations of tau-PET visual read (outcome) with age, sex and \(APOE\) ε4 (predictors) were performed using bivariate binary logistic regressions (separate models per predictor). A multivariable logistic regression including all significant predictors was performed to test predictors’ independent effects. Associations of tau-PET visual read (predictor) with prospective decline on the MMSE (outcome) were performed using age-, sex-, and education-adjusted linear mixed models (LMM) with a random intercept (MMSE ~ visual read \(\times\) time + visual read + time + age + sex + education + (1 | participant)). A random slope (time | participant) was added if it improved model fit based on the Akaike information criterion and the \(\chi^2\) statistic (see eMethods). Time reflected time between tau-PET and MMSE. Education was based on the Dutch Verhage score.\(^{34}\) Continuous variables were z-transformed prior to model entry. To test whether SUVr was able to explain additional variance in cognitive decline within visual read tau-positive AD, an additional age-, sex-, and education-adjusted LMM with a subject-specific intercept, and temporal meta-ROI SUVr, time and an interaction term of SUVr \(\times\) time was performed in tau-positive AD participants (MMSE ~ tau-PET SUVr \(\times\) time + tau-PET SUVr + time + age + sex + education + (1 | participant)).

We used R version 4.0.3 for statistical analyses. \(P\)-value<0.05 was considered significant.
Data availability
Anonymized data that support the findings of this study are available upon reasonable request from a qualified investigator.

Results

Participants
We included 263 participants, among which 147 CU, 97 AD and 19 DLB participants (Table). By design, all AD participants were amyloid-β positive. Furthermore, 52 CU (36.1%) and 7 DLB (36.8%) were amyloid-β positive. AD participants were significantly younger (65.6±7.6 years) compared to CU (70.2±7.7, p<0.001) and DLB (69.5±5.6, p=0.03). There were fewer female participants in DLB (15.8%) compared to CU (49.7%, p=0.01) and AD (45.4%, p=0.03) groups. Moreover, there were more APOE ε4 carriers in AD (72.0%) compared to CU (55.9%, p<0.001) and DLB (35.3%, p=0.01) groups. As expected, MMSE was lower in AD (21.9±4.5) and DLB (23.8±4.6) compared to CU (28.8±1.3, both p<0.005).

Among the 97 AD participants, there were nine participants with an atypical AD variant (five posterior cortical atrophy, two logopenic progressive aphasia, and two behavioral AD).

Inter- and intra-reader agreement
Across all tau-PET scans (368 scans), the inter-reader agreement between the two nuclear medicine physicians for visual read was excellent (κ=0.95 [CI: 0.91-0.99]). For baseline (263 scans), 2-year follow-up (90 scans) and 4-year follow-up (15 scans) separately, comparable Cohen’s kappa coefficients were observed (baseline: κ=0.95 [CI: 0.91-0.99]; 2-year follow-up: κ=0.96 [CI: 0.89-1.0]; 4-year follow-up: κ=1.00 [CI: 1.0-1.0]). There was disagreement between readers in only eight scans (2.2%; six baseline and two 2-year follow-up scans), for which consensus reads were obtained for subsequent analyses. The eight scans with between-reader disagreement belonged to n=4 CU, n=2 AD and n=1 DLB participants, of which 1 AD participant had between-reader disagreement on both baseline and 2-year follow-up (consensus reads were obtained independently of each other). The final consensus read was in line with the initial read of reader 1 for 2/8 scans.

Intra-reader agreement (i.e., between training set and baseline set) was excellent (κ=0.90 [CI: 0.71-0.90] for both readers).
Prevalence of tau-PET visual read positivity

We examined the prevalence of tau-PET visual read positivity stratified according to diagnosis (CU, AD and DLB) and amyloid-β status (negative/positive) (Figure 1A). Among amyloid-β negative participants, 1 DLB participant was visually read as tau-positive (1/12 DLB [8.3%]). None of the amyloid-β negative CU participants (0/92 [0%]) were visually read as tau-positive. Among amyloid-β positive participants, 13 CU (13/52 [25.0%]), 85 AD (85/97 [87.6%]) and 3 DLB (3/7 [42.9%]) participants were visually read as tau-positive. There were 3 CU participants with unknown amyloid-β status, who were all tau-negative. Among the 9 participants with an atypical AD variant, all except one participant with logopenic progressive aphasia were tau-positive.

We next examined stability in tau-PET visual read status over time for the subset with 2-year follow-up (n=90) and 4-year follow-up (n=15) available. For all participants, tau-PET visual read at 2-year follow-up was identical to tau-PET visual read at baseline. At 4-year follow-up, there was 1 amyloid-β positive CU participant that changed from tau-negative to tau-positive (Figure 1B).

Comparing tau-PET visual read to tau-PET SUVr

We next compared tau-PET visual read to a semi-quantitative measure of tau-tracer binding (SUVr). Four scans (4/263 [1.5%], n=3 tau-positive AD and n=1 tau-negative DLB) did not meet scan quality criteria for SUVr due to severe motion during the scan. Reported in the text are results for temporal meta-ROI SUVr, whereas eFigure 1 shows results for temporoparietal ROI SUVr.

Compared to visual read tau-negative participants of the same diagnostic group, temporal meta-ROI SUVr was higher in visual read tau-positive CU (p<0.001), AD (p<0.001) and DLB (p=0.03) participants. However, there was also overlap in temporal meta-ROI SUVr between visual read tau-negative and visual read tau-positive participants, as highlighted in grey in Figure 2A. A total of 81 scans (81/259 [31.3%]) fell within this overlapping “grey zone” (SUVr 1.19-1.59). The two readers showed significantly lower confidence scores for scans within the grey zone compared to scans below (p<0.001 for both readers) or above the grey zone (p<0.001 for both readers) (Figure 2B). Out of 8 scans with initial between-reader disagreement, 6 scans had SUVr values falling within the grey zone, and 2 scans had SUVr values slightly below the grey zone (SUVr 1.12 and 1.17).
To define tau-PET status based on temporal meta-ROI SUVr, we identified a threshold of 1.41 SUVr derived from a GMM with 2 components (short-dashed line in Figure 2A), and a threshold of 1.28 SUVr derived from the mean+2×SD of amyloid-β negative CU (long-dashed line in Figure 2A). When comparing visual read tau-status to SUVr tau-status (taking both SUVr thresholds into account), the majority of scans were concordant on tau-status (234 scans concordant on all three tau-status measures [90.4%]) (Figure 2C). Discordant visual read tau-negative SUVr tau-positive scans were observed more often when using the mean+2×SD threshold (9 scans) compared to when using the GMM threshold (2 scans). To the contrary, discordant visual read tau-positive SUVr tau-negative scans were observed more often when using the GMM threshold (16 scans) compared to when using the mean+2×SD threshold (6 scans). Discordance was especially noticeable in the DLB group, where visual read tau-positive DLB participants showed generally low SUVr values.

In Figure 3, we highlighted four representative scans with concordant or discordant tau-status. The discordant DLB participant (visual read tau-positive, SUVr tau-negative) showed tracer uptake in a relatively small region, potentially resulting in a low SUVr. The discordant AD participant (visual read tau-negative, SUVr tau-positive) showed tracer uptake predominantly in the medial temporal lobe, which does not contribute to a positive visual read.

Results for temporoparietal SUVr (eFigure 1) were similar, but showed a slightly lower concordance between visual read and SUVr status (224 scans concordant on all three tau-status measures [86.5%]).

**Demographic factors associated with tau-PET visual read status**

We next examined associations of age, sex, and APOE ε4 with tau-PET visual read in CU and AD participants (eTable 1). Due to the low number of tau-positive DLB cases, these analyses could not be performed for DLB. In CU, APOE ε4-carriership was associated with a higher odds for tau-positivity (OR: 4.15 [CI: 1.17-19.41], p=0.04), but this effect disappeared when restricting the analysis to amyloid-β positive CU (OR: 1.56 [CI: 0.39-7.94], p=0.55). In AD, both younger age (OR: 0.82 [CI: 0.72-0.92], p=0.001) and female sex (OR: 11.26 [CI: 2.05-210.40], p=0.02) were individually associated with a higher odds for tau-positivity. When including age and sex in the same model, younger age remained associated with a higher odds for tau-positivity (OR: 0.84 [CI: 0.73-0.93], p=0.004) and a trend was observed for female sex (OR: 8.44 [CI: 1.41-162.83], p=0.052). In Figure 4, we modelled the estimated
probabilities of tau-PET visual read positivity according to age, showing a strong negative association between age and tau-positivity in AD and a trend towards a positive association between age and tau-positivity in CU.

**Association with prospective cognitive decline**

Finally, we tested the association of tau-PET visual read status with prospective longitudinal trajectories of cognitive decline in CU and AD participants. These analyses could not be performed in DLB participants due to the low number of tau-positive DLB cases.

A positive tau-PET visual read was associated with worse cross-sectional MMSE in CU ($\beta=-0.85$ [CI: -1.35, -0.35], $p=0.001$), but no significant cross-sectional association was observed in AD ($\beta=-0.48$ [CI: -1.05, 0.08], $p=0.10$). Over time, a positive tau-PET visual read was associated with a steeper decline in MMSE in both CU ($\beta=-0.52$ [CI: -0.74, -0.30], $p<0.001$) and AD ($\beta=-0.30$ [CI: -0.58, -0.02], $p=0.04$) (Figure 5A-B). For sensitivity analyses, we restricted analyses in the CU group to CU amyloid-\(\beta\) positive participants and observed a trend-level association between a positive tau-PET visual read with worse cross-sectional MMSE ($\beta=-0.55$ [CI: -1.09, -0.01], $p=0.06$), and a significant association with steeper decline in MMSE ($\beta=-0.40$ [CI: -0.64, -0.16], $p=0.002$).

Last, we examined whether semi-quantification (temporal meta-ROI SUVr) could provide prognostic information within visual read tau-positive AD participants. Within visual read tau-positive AD participants, higher temporal meta-ROI SUVr was associated with worse cross-sectional performance on the MMSE ($\beta=-0.29$ [CI: -0.50, -0.09], $p=0.008$) and worse prospective decline on the MMSE ($\beta=-0.14$ [CI: -0.20, -0.08], $p<0.001$) (Figure 5C).

**Classification of Evidence**

This study provides Class II evidence that \(^{18}\text{F}\)flortaucipir visual read accurately distinguishes patients with low tau-tracer binding from those with high tau-tracer binding, and is associated with amyloid-positivity and cognitive decline.
Discussion

This study aimed to evaluate the performance of the FDA-approved \([^{18}\text{F}]\text{flortaucipir PET visual read method}\). Our results showed that the method had excellent inter- and intra-reader agreements, corresponded strongly with a semi-quantitative approach, and was stable over time. Furthermore, a positive tau-PET visual read status was almost exclusively observed in amyloid-\(\beta\) positive participants, and was associated with prospective decline on the MMSE. Our results indicate that the visual read method is reliable and robust, and that outcome of this method shows expected associations with clinically relevant variables, supporting the application of this method in clinical practice.

First, for clinical implementation, it is important that the method is reliable and accurate. A recent study validated the method to accurately detect post-mortem neurofibrillary tangle pathology, as positive visual reads were typically observed in post-mortem Braak stage IV or higher.\(^{13}\) We add to this by showing reliability of the method with several findings. We observed a strong degree of agreement between two independent readers, with agreement observed in 97.8\% of scans. Moreover, tau-status based on visual read corresponded strongly to tau-status based on a semi-quantitative approach (SUVr) with concordance in tau-status observed in 90.4\% of scans. In addition, none of the AD patients with available follow-up tau-PET changed in tau-PET visual read status over 2-year follow-up, indicating that outcome of the method is stable over time in clinically impaired patients. Altogether, this indicates that the visual read method accurately detects tau pathology and is reliable for clinical implementation.

Second, for clinical implementation, it is important to understand which clinically relevant factors are associated with tau-PET visual read status. Previous studies suggested that cortical amyloid-\(\beta\) is required for tau to spread beyond Braak stage IV,\(^{35}\) resulting in the expectation that a positive tau-PET visual read will be accompanied by the presence of neocortical amyloid-\(\beta\). In line with this expectation, none of the amyloid-\(\beta\) negative CU participants were visually read as tau-positive. However, there was 1 amyloid-\(\beta\) negative DLB participant visually read as tau-positive. Tau-positivity in amyloid-\(\beta\) negative DLB patients was also observed previously,\(^{4}\) and post-mortem studies are needed to establish whether the tracer is truly binding to AD-type tau in these cases. As expected, tau-positivity among the amyloid-\(\beta\) positive groups was highest in AD, with 87.6\% of AD patients being visually read as tau-positive. Notably, 12.4\% of AD patients were thus tau-negative. In AD, we observed a strong decrease in prevalence of tau-positivity with older age, which has also
been reported previously (with comparable effect sizes) using quantitative thresholds.\textsuperscript{36,37} Potential explanations could be that with older age, there may be additional development of co-pathologies or less resilience to tau, and therefore a lower tau-threshold may be needed to result in cognitive impairment. For implementation of tau-PET visual reads in clinical practice, it will be important to further characterize these tau-negative AD patients.

Since tau-PET is clinically expected to show strong diagnostic performance at the dementia stage of AD, it is important to note that in our study, a substantial proportion of amyloid-\(\beta\) positive DLB participants (42.9\%) were visual read tau-positive. Post-mortem studies indicated that approximately 50\% of DLB patients also have amyloid-\(\beta\) and tau pathology.\textsuperscript{15} Interestingly, previous tau-PET studies in DLB using quantitative PET measures have generally shown minimal tracer uptake in DLB patients.\textsuperscript{38,39} Here, we also observed that SUVr of visual read tau-positive DLB patients was low and indistinguishable from SUVr of visual read tau-negative DLB patients. A potential explanation could be that DLB patients have relatively focal and low amounts of tau, which is detectable by visual read, but this signal may be attenuated when assessed quantitatively within a larger region-of-interest. Future studies may look into potential differences in spatial patterns of tau-positive DLB and tau-positive AD, to examine whether spatial information may help in the differentiation.

To compare tau-PET visual read status to tau-PET SUVr status, we utilized two threshold approaches, since there is no consensus yet on the optimal threshold for defining SUVr positivity. For both approaches, a high percentage of concordance with tau-PET visual read was observed. However, differences between the SUVr approaches in the composition of concordant and discordant groups were also observed. This indicates potential difficulty when defining tau-positivity based on quantification. In addition, our results showed that there was a certain amount of overlap in tau-PET SUVr (the “grey zone”) between visual read negative and visual read positive scans. Overlap in tau-PET SUVr may not be unexpected, since tau-PET binding tends to have a more continuous (albeit skewed) distribution, which is in contrast to e.g. amyloid-PET which tends to have a more bimodal distribution. Therefore, a larger “grey zone” may be expected for tau-PET than for amyloid-PET. Moreover, 6 out of 8 scans with initial between-reader disagreement had SUVr values within this grey zone, and the readers’ certainty was lower for scans in this grey zone. It would be of interest to examine whether providing tau-PET SUVr to the readers could result in higher confidence scores for visual assessment, and thus whether SUVr could aid in the diagnostic process.
Tau-PET is expected to provide not only diagnostic, but also accurate prognostic information in the clinic. Previous studies have indicated the utility of tau-PET as a prognostic marker, and we add to this by showing that tau-positivity assessed by visual read is also associated with prospective cognitive decline. This is of clinical relevance, given that biomarkers that are currently used clinically (e.g. amyloid-β PET) show weaker associations with cognitive decline and brain atrophy, especially at the dementia-stage.

However, also within tau-positive AD patients large variation in cognition exists. Our results showed that within visual read tau-positive AD patients, tau-PET SUVr was associated with prospective cognitive decline. This indicates that SUVr has potential to provide prognostic information beyond visual read, which is of interest to investigate further.

Although the visual read method is not approved for use in cognitively normal individuals, we also examined this method in a relatively large CU sample. Among amyloid-β positive CU participants, 25.0% was visually read as tau-positive. This is higher compared to what has been reported using semi-quantitative thresholds, which showed around 5-10% tau-positivity in amyloid-β positive individuals. A potential explanation could be that our CU group partly consisted of individuals with SCD, which has been associated with increased risk for dementia. Moreover, it must be noted that the cohorts from which CU individuals were included were enriched for amyloid-β positivity. Over 2-year follow-up, none of the CU tau-negative participants (n=46, of which 13 were amyloid-β positive) converted to tau-positive. There was 1 CU tau-negative (amyloid-β positive) participant (out of n=15, of which 2 were amyloid-β positive) that converted to tau-positive at 4-year follow-up. This may indicate a limited sensitivity of the visual read method to detect the earliest changes in tau pathology. Previous studies have proposed similar, though not identical, visual read schemes which (in contrast to the FDA-approved visual read method) also include isolated medial temporal lobe binding. All methods seem to correspond well with quantitative measures of tracer binding. Head-to-head comparisons are needed to examine differences in sensitivity and specificity between the visual read schemes.

Strengths include the relatively large sample size, longitudinal data, and the use of both visual read and quantification. This study also has limitations. Our DLB cohort was relatively small and did not have follow-up, and we did not include other non-AD dementias, limiting the ability to test diagnostic accuracies. In addition, our cohort consisted of few atypical AD cases. Future studies with more non-AD dementia and atypical AD cases are of interest. Furthermore, all clinically impaired participants were recruited from a tertiary memory clinic, which may limit generalizability to the general population. In addition,
participants come from selected research populations, which may limit generalizability to daily practice. Future studies are encouraged to evaluate tau-PET visual reads in large, unselected cohorts, as has been done with amyloid-PET.\(^2\) Also, less than 50% of AD patients were female which may be lower than the general population with clinical AD and should be taken into account when interpreting the data. Furthermore, we and others observed that some AD patients are tau-negative.\(^4\) However, we were not able to validate whether these individuals were devoid of tau using post-mortem data. Examining post-mortem data of tau-negative AD patients is important to confirm the absence of tau pathology in these cases. Finally, the inter-reader and intra-reader agreement in this study have to be cautiously interpreted, as this study included highly specialized readers, and therefore the reliability metrics may not generalize to the broader community of nuclear medicine physicians. Furthermore, the intra-reader agreement may contain a learning effect.

**Conclusion**

The excellent inter-reader agreement, strong correspondence with a semi-quantitative approach, and longitudinal stability indicate that the FDA-approved visual read method is reliable and robust, supporting its clinical application. Furthermore, tau-PET visual read was associated with prospective cognitive decline, highlighting its additional prognostic potential.

**Tables**

**Table. Demographics**

<table>
<thead>
<tr>
<th></th>
<th>CU</th>
<th>AD</th>
<th>DLB</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>147</td>
<td>97</td>
<td>19</td>
</tr>
<tr>
<td>Age, years</td>
<td>70.2 ± 7.7(^b)</td>
<td>65.6 ± 7.6(^{a,c})</td>
<td>69.5 ± 5.6(^b)</td>
</tr>
<tr>
<td>Sex, n female (%)</td>
<td>73 (49.7)(^c)</td>
<td>44 (45.4)(^b)</td>
<td>3 (15.8)(^{a,b})</td>
</tr>
<tr>
<td>Education, Verhage</td>
<td>6.00 [5.00, 6.00]</td>
<td>6.00 [5.00, 6.00]</td>
<td>5.00 [5.00, 6.00]</td>
</tr>
<tr>
<td>(APOE\ \varepsilon4) status, n carrier (%)</td>
<td>61 (44.9)(^b)</td>
<td>67 (72.0)(^{a,c})</td>
<td>6 (35.3)(^b)</td>
</tr>
<tr>
<td>Amyloid-(\beta) status, n positive (%)</td>
<td>52 (36.1)(^b)</td>
<td>97 (100.0)(^{a,c})</td>
<td>7 (36.8)(^b)</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.8 ± 1.3(^{b,c})</td>
<td>21.9 ± 4.5(^a)</td>
<td>23.8 ± 4.6(^a)</td>
</tr>
</tbody>
</table>

Age and MMSE are shown as mean ± standard deviation, whereas education is shown as median [interquartile range]. Education reflects the Dutch Verhage score. Education was missing for n=6 CU. \(APOE\ \varepsilon4\) status was missing for n=11 CU, n=4 AD and n=2 DLB. Amyloid-\(\beta\) status was missing for n=3 CU participants.
\(^a\) significantly different from CU  
\(^b\) significantly different from AD  
\(^c\) significantly different from DLB
Figure Legends

Figure 1 Cross-sectional and longitudinal tau-PET visual read status. A) The prevalence of baseline tau-PET positivity stratified according to diagnostic group (CU, AD and DLB) and amyloid-β status (unknown, negative and positive) is shown. Numbers indicate the number of participants visually read as tau-negative or tau-positive within each group. B) Tau-PET visual read status (positive (+) or negative (-)) for each diagnostic group at baseline, 2-year follow-up and 4-year follow-up indicates that outcome of the visual read method is stable over time. The single CU participant that converted to tau-positive at 4-year follow-up was amyloid-β positive.
Figure 2 Comparing tau-PET visual read to tau-PET SUVr. A) Tau-PET SUVr in the temporal meta-ROI is plotted, stratified by diagnostic group (CU, AD and DLB) and tau-PET visual read status (negative and positive). The short-dashed line represents the SUVr cut-off derived from a Gaussian Mixture Model (GMM) with the two Gaussian distributions plotted on the right. The long-dashed line represents the SUVr cut-off defined as 2 SD’s above the mean of amyloid-β negative CU participants. The grey zone represents visual read positive and visual read negative scans with overlapping SUVr. B) The confidence of the two readers (ranging from 1-5) is shown for scans below the grey zone, within the grey zone, and above the grey zone. C) The number of scans with concordant or discordant visual read (VR) and SUVr status (based both GMM and mean+[2×SD]) is shown.
Figure 3 Example [\textsuperscript{18}F]flortaucipir PET scans for visual read. Shown are [\textsuperscript{18}F]flortaucipir PET scans of four participants. (A) A CU participant defined as tau-negative on both visual read and SUVr. (B) a DLB participant defined as visual read tau-positive, but SUVr negative. Increased tracer uptake was observed in only a small region, potentially resulting in low SUVr. (C) An AD participant defined as visual read negative, but SUVr positive. Increase tracer uptake was observed isolated to the medial temporal lobe, which does not contribute to a positive tau-PET visual read. (D) An AD participant defined as tau-positive on both visual read and SUVr.
Figure 4 Estimated probabilities of tau-PET visual read positivity according to age. Plotted are the predicted probabilities of tau-PET visual read positivity according to age obtained from a logistic regression between tau-PET visual read (outcome) and age (predictor). We additionally superimposed individual data-points to better visualize the distribution of tau-negative and tau-positive cases according to age. A trend towards a positive association between age and probability of tau-PET positivity was observed in CU (A), whereas a strong negative association between age and probability of tau-PET positivity was observed in AD (B) participants.
Figure 5 Association of tau-PET visual read and tau-PET SUVr with prospective MMSE. Spaghetti plots of longitudinal MMSE are shown. Association of tau-PET visual read status with longitudinal performance on the MMSE is shown for A) CU and B) AD participants, with slopes from linear mixed models superimposed on the graphs. In C) the association of temporal meta-ROI tau-PET SUVr with longitudinal performance on the MMSE in visual read tau-positive AD participants is shown. For visualization purposes, slopes from linear mixed models with SUVr in tertiles are superimposed on the graph.

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Performance of a $^{18}$F-Flortaucipir PET Visual Read Method Across the Alzheimer Disease Continuum and in Dementia With Lewy Bodies
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