Université de Montréal

Evaluation of Neurodegenerative Diseases With [^{18}F]flortaucipir :

Comparison of Visual Reads With Tau PET Quantification and Cerebrospinal Fluid Analysis

Par

Karine Provost

Faculté de Médecine

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Présenté par

Karine Provost

A été évalué(e) par un jury composé des personnes suivantes

Matthieu Pelletier-Galarneau
Président-rapporteur

Jean-Paul Soucy
Directeur de recherche

Gil D. Rabinovici
Codirecteur

Hélène Masson
Membre du jury

Résumé

Contexte & objectifs: L'avènement de biomarqueurs *in vivo* pour la maladie d'Alzheimer a révolutionné la recherche clinique dans ce domaine. Nous avons comparé le taux de positivité pour le biomarqueur tau (statut-T) dérivé de l'interprétation visuelle des études TEP au [^{18}F]flortaucipir (FTP), de l'analyse quantitative du FTP et de la mesure de la protéine Tau phosphorylée en position 281 (PTau181) dans le liquide céphalorachidien (LCR). **Méthodologie**: Nous avons inclus 351 participants avec divers diagnostics cliniques provenant de trois cohortes ayant subi une étude TEP au FTP ainsi qu'une mesure du PTau181 dans un délai de 18 mois. Le statut-T a été dérivé de : (1) l'interprétation visuelle à l'aveugle du FTP par deux observateurs; (2) la quantification SUVR (*standardized uptake value ratio*) du FTP d'une région d'intérêt composite temporale (seuil : SUVR ≥ 1.27) ; (3) la concentration dans le LCR de Elecsys® Phospho-Tau (181P) (Roche Diagnostics) (seuil : PTau181 ≥ 24.5 pg/ml). **Résultats:** L'interprétation visuelle du FTP a entraîné le plus haut taux de T+, alors que les T+ par quantification SUVR augmentaient progressivement des sujets cognitivement normaux (CN) vers les sujets avec troubles cognitifs légers (TCL) et ceux avec démence de type Alzheimer (DA). Le taux de T+ par PTau181 était intermédiaire à ceux de l'analyse visuelle et quantitative du FTP pour les CN, similaire à la quantification SUVR pour les TCL et plus faible chez les DA. La concordance entre le statut-T par paire de modalité fluctuait de 68% à 76% et variait selon le diagnostic, étant plus élevé chez les DA. L'interprétation visuelle du FTP offrait la plus haute sensibilité (0.96) pour discriminer entre les sujets avec TCL ou DA amyloïde-positifs des sujets CN et non-Alzheimer, mais une spécificité plus faible (0.60). La spécificité était la plus élevée avec la quantification SUVR (0.91) avec une sensibilité de 0.89, alors que la sensibilité (0.73) et la spécificité (0.72) étaient de même niveau pour le PTau181 dans le LCR. **Conclusion**: Le choix d'un biomarqueur tau pourrait varier selon le stade de la maladie et les objectifs de recherche visant à maximiser la sensibilité ou la spécificité. L'interprétation visuelle des TEP tau augmente la sensibilité en comparaison avec la quantification seule, en particulier dans les stades précoces de la maladie.

Mots-clés : Tau, TEP, Flortaucipir, Alzheimer, biomarqueurs, LCR

Abstract

Background & purpose: The advent of in vivo biomarkers for Alzheimer's disease (AD) pathology has transformed clinical research in this field. The purpose of this study is to compare rates of tau biomarker positivity (T-status) per the 2018 AD Research Framework derived from [^{18}F]flortaucipir (FTP) PET visual assessment, FTP quantification, and cerebrospinal fluid (CSF) phosphorylated Tau-181 (PTau181) concentration. **Methods**: We included 351 subjects with varying clinical diagnoses from three cohorts with available FTP PET and CSF PTau181 within 18 months. T-status was derived from: (1) FTP blinded visual assessment by two raters; (2) FTP standardized uptake value ratio (SUVR) quantification from a temporal meta-ROI (threshold: SUVR ≥ 1.27); (3) Elecsys® Phospho-Tau (181P) CSF (Roche Diagnostics) concentrations (threshold: PTau181 ≥ 24.5 pg/ml). **Results:** FTP visual reads yielded the highest rates of T+, while T+ by SUVR increased progressively from cognitively normal (CN) through mild cognitive impairment (MCI) and to AD dementia. T+ designation by CSF PTau181 was intermediate between FTP visual reads and SUVR values in CN, similar to SUVR in MCI, and lower in AD dementia. Concordance in T-status between modality pairs ranged from 68% to 76% and varied by clinical diagnosis, being highest in patients with AD dementia. In discriminating Aβ+ MCI and AD subjects from healthy controls and non-AD participants, FTP visual assessment was the most sensitive (0.96) but the least specific (0.60) approach. Specificity was highest with FTP SUVR (0.91) with a sensitivity of 0.89. Sensitivity (0.73) and specificity (0.72) were balanced for PTau181. **Conclusion**: The choice of a tau biomarker may differ by disease stage and research goals that seek to maximize sensitivity or specificity. Visual interpretations of tau PET enhance sensitivity compared to quantification alone, particularly in early disease stages.

Keywords : Tau, PET, Flortaucipir, Alzheimer's disease, biomarkers, CSF

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Legend

Aβ: amyloid-beta

AD : Alzheimer's disease

AD_c : Alzheimer's disease clinical diagnosis

ADNI: Alzheimer's Disease Neuroimaging Initiative

ADNC: Alzheimer's disease neuropathological changes

AT(N): Amyloid Tau Neurodegeneration

AUC: area-under-the-curve

bvFTD: behavioral variant frontotemporal dementia

CBS: corticobasal syndrome

CN: cognitively normal

CSF: cerebrospinal fluid

FDA: Food and Drug Administration

FDG: [^{18}F]fluorodeoxyglucose

FTP : [^{18}F]flortaucipir

IWG: International Working Group

κ: Cohen's kappa

MBq: Megabecquerels

MCI: mild cognitive impairment

MMSE: Mini-mental status exam

MRI: magnetic resonance imaging

OPA: overall percent agreement

PART: primary age-related tauopathy

PET: positron emission tomography

PTau217: phosphorylated Tau-217

PTau181: phosphorylated Tau-181

PVC: partial volume correction

ROI: region of interest

SD: standard deviation

SUVR: standardized uptake value ratio

TDP-43: TAR DNA binding protein 43

UCSF ADRC: University of California San Francisco Alzheimer's Disease Research Centre

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Section 1 – Introduction

1.1 Epidemiology of Alzheimer's disease

Alzheimer's disease (AD) is by far the most frequent etiology of dementia in older adults, affecting an estimated 60-80% of individuals afflicted with this condition("2021 Alzheimer's disease facts and figures," 2021). In the United States, it is estimated that there are currently more than 6 million individuals with clinical AD, representing about 1 in 9 people over 65 years old("2021 Alzheimer's disease facts and figures," 2021; Rajan et al., 2021). In Canada, most recent estimates indicate at least 500,000 Canadians living with Alzheimer's or another dementia(Alzheimer Society of Canada, 2016). These numbers are expected to reach 13,85 million in the United States by 2060 and over 900,000 in Canada by 2031 (Alzheimer Society of Canada, 2016; Rajan et al., 2021), illustrating the utmost importance of this disease and its impact on public health.

Although there is no single identifiable cause for AD, there are multiple established risk factors including age, genetics and family history, as well as potentially modifiable risk factors such as lifestyle, cardiovascular disease, education, social/cognitive engagement, traumatic brain injury, sleep, alcohol use and exposure to air pollutants("2021 Alzheimer's disease facts and figures," 2021).

In addition to the emotional and social burden inflicted on patients and their families, AD has enormous economic implications, in part due to healthcare costs (estimated at US$355 billion in 2021 in the United States alone), but also indirectly through the costs of caregiving provided by relatives("2021 Alzheimer's disease facts and figures," 2021). In Canada, total health care system costs and out-of-pocket caregiver costs were over $10 billion in 2016(Alzheimer Society of Canada). It is not surprising therefore, that significant financial and scientific resources worldwide have been devoted in the past decades to "finding a cure" to Alzheimer's.

1.2 Definition of Alzheimer's disease

Pathologically, AD is defined by the presence of two protein aggregates, namely amyloid plaques in the extracellular space and tau tangles which accumulate inside neuronal cells(Montine et al., 2012). Accumulation of these proteins temporally follow a typical topographical distribution as described by Braak and Braak(1991; Hyman et al., 2012), ultimately leading to neuronal death and onset of clinical deficits. Previously, the diagnosis of AD could only be confirmed at autopsy, however, the advent of biomarkers (described in detail in section 1.4) now allows diagnosis of the disease in living patients.

1.3 Clinical diagnosis of Alzheimer's disease

From a clinical standpoint, AD is considered as a continuum, ranging from preclinical disease during which patients are asymptomatic, to mild cognitive impairment (MCI) where symptoms are only mild and do not yet interfere with patients' daily activities, and finally to dementia, where patients face difficulties in multiple domains including memory, language and executive functions, affecting everyday life(Albert et al., 2011; McKhann et al., 2011; Sperling et al., 2011). Dementia in itself is nonspecific and can be caused by multiple disorders, the most frequent being AD, but also other neurodegenerative diseases, for example Lewy body disease, frontotemporal lobar degeneration, limbic-predominant age-related TDP-43 encephalopathy, as well as vascular causes(Barker et al., 2002; Nelson et al., 2019). Clinical diagnosis of AD thus remains probabilistic, based on established criteria which mostly rely on history and neuropsychological examination(McKhann et al., 2011).

Even in specialized centres, misdiagnosis of AD based on clinical criteria is common, with specificity as low as 44.3% to 70.8% compared to autopsy (Beach et al., 2012). In a recent large-scale multi-center study on the use of amyloid positron emission tomography (PET), 36% of 8742 patients with a clinical diagnosis of AD were amyloid-negative, suggesting that they were misdiagnosed(Rabinovici et al., 2019). Misdiagnosis is especially frequent in patients with early onset disease or in patients with atypical variants of Alzheimer's, such as patients with non-

amnestic phenotypes presenting with predominant language, executive, behavioral or visual difficulties(Graff-Radford et al., 2021). Furthermore, with aging, the occurrence of multiple concomitant pathologies in the brain becomes very frequent (Brenowitz et al., 2017; Kapasi et al., 2017; Karanth et al., 2020). For example, in a recent study by Karanth and colleagues (2020) in which autopsy was conducted in a sample of 375 subjects (mean age 86.9 years), up to 12.3% of individuals had 4 concomitant proteinopathies, and 38.1% had 3 proteinopathies. The frequency of mixed pathology was even higher in patients with dementia, with 89.1% of patients having quadruple proteinopathies. It becomes increasingly challenging and important to accurately diagnose the presence of AD in this context.

In view of this, the International Working Group (IWG) has recently published in June of 2021 novel recommendations for clinical diagnosis of AD, which now include a combined clinical-biological approach: "*The diagnosis of Alzheimer's disease is clinical–biological. It requires the presence of both a specific clinical phenotype of Alzheimer's disease (phenotype positive) and biomarker evidence of Alzheimer's disease pathology (amyloid-positive and tau positive).*" (Dubois et al., 2021). These new recommendations represent a shift in clinical paradigm since biomarkers had been until very recently restricted to use in the research setting, as detailed in the following section.

1.4 Biomarkers

The accumulation of amyloid and tau in the brain occurs many years before onset of symptoms(Jack et al., 2010). With disease progression, the more extensive deposition of neurofibrillary tau tangles (usually starting at Braak stages III and IV) leads to the onset of clinical deficits. Local deposition of tau (much more than amyloid) correlates well with both disease severity and the expected topography of lesions as inferred from symptoms(Delacourte et al., 1999; Giannakopoulos et al., 2003; Moloney et al., 2021; Nelson et al., 2012; Ossenkoppele et al., 2016). Detecting the presence of these proteins in the brain of living patients, before they can be seen during autopsy, is therefore of capital importance, not only to allow for early and accurate

diagnosis, but also in an attempt to treat or halt the neuropathological processes responsible for patients' cognitive decline while patients are still in the pre-symptomatic stage.

Biomarkers are biological indicators that can be detected through various means in living subjects and reflect underlying accumulation of pathological processes, for instance the accumulation of amyloid plaques, tau tangles, and downstream neuronal degeneration which occur in AD. There are multiple types of biomarkers, the most frequently studied and currently used including fluid biomarkers and imaging biomarkers.

1.4.1 Fluid biomarkers

The most common and extensively validated fluid biomarkers studied to date involve analysis of cerebrospinal fluid (CSF) for the presence of pathological hallmarks of AD, such as levels of amyloid-beta (Aβ), more specifically low Aβ42 and Aβ42/Aβ40 ratio, elevated phosphorylated tau and total tau, as well as other substances released during neuronal degeneration such as neurofilament light chain or neuroinflammation-related microglial activation like YKL-40 (Hansson et al., 2019; Olsson et al., 2016). Emerging evidence is now growing on biomarkers in other, more easily collected bodily fluids, especially blood (plasma) biomarkers, and even saliva(Olsson et al., 2016; Villa et al., 2020).

1.4.2 Imaging biomarkers

Imaging biomarkers include those measured with structural imaging such as magnetic resonance imaging (MRI) which may reveal downstream effects of neuronal loss, namely atrophy. In contrast, imaging with PET allows for functional imaging through injection of various radiotracers specifically designed for the study of metabolism (ex: [^{18}F]fluorodeoxyglucose (FDG), reflecting local glucose metabolism induced by neuronal activity) or reflecting local accumulation of various abnormal proteins, including amyloid (ex: [^{18}F]florbetaben, [^{18}F]florbetapir, [^{18}F]flutemetamol, [^{11}C]PiB) and tau (ex: [^{18}F]THK5317, [^{18}F]THK5351, [^{18}F]MK-6240 and [^{18}F]AV1451 or flortaucipir (FTP))(Beyer & Brendel, 2021; van Waarde et al., 2021). As such, molecular imaging is often used as a screening tool for participants in clinical research for confirmation of disease biology(Schwarz, 2021).

FTP is of particular interest, allowing for *in vivo* detection of Alzheimer's tau pathology with high accuracy, as shown in autoradiographic and autopsy studies(Fleisher et al., 2020; Lowe et al., 2016; Lowe et al., 2020; Marquie et al., 2015; Marquie et al., 2017; Pontecorvo et al., 2020). Although tau generally accumulates slightly later than amyloid in the pathophysiologic process of AD(Jack et al., 2013; Jack et al., 2010), imaging of tau provides incremental value over amyloid PET, given that it correlates more closely with symptomatology and severity of cognitive deficits in patients(Ossenkoppele et al., 2016). Imaging with Tau PET as opposed to amyloid also reduces the likelihood of detecting incidental amyloidosis, a probability that increases with age(Ossenkoppele et al., 2015). High accuracy of FTP in identifying neuropathologically-defined AD(Fleisher et al., 2020) led to the recent regulatory approval of this compound by the Food and Drug Administration (FDA) in the United States, making it the first tau-PET imaging agent available for clinical use.

1.4.3. AT(N) Research framework

In the AD research setting, correct identification of biomarker status is important for screening participants and for outcome evaluation in clinical trials of novel disease-modifying therapies(Blennow & Zetterberg, 2018; Cummings, 2019; Hampel et al., 2021). As such, Jack et al. (2016) proposed a binary classification of all individuals as positive or negative for amyloid (A), tau (T) and neurodegeneration (N). This classification allows interchangeable use of CSF or imaging measures, although reflecting different aspects of amyloid and tau biology, as shown in Table 1.

	CSF	**Imaging**
Amyloid (A)	Aβ42 or Aβ42/Aβ40 ratio (↓)	amyloid PET (↑)
Tau (T)	Phosphorylated tau (↑)	tau PET (↑)
Neurodegeneration (N)	Total tau (↑) Neurofilament light chain (↑)	FDG PET (↓) Structural MRI (↓)

Table 1. - Summary of AT(N) Research classification

The combined information from different biomarkers allows classification of subjects into one of eight possible profiles, indicating whether a given subject is on the Alzheimer's continuum or not. Since the presence of amyloid is required for a diagnosis of AD, only subjects who are A+ (A+T-N-, A+T+N-, A+T-N+, A+T+N+) are considered to be on the Alzheimer's continuum, either in the preclinical phase or in various more advanced pathological stages. In contrast, A- profiles are either normal (A-T-N-) or considered to be indicative of non-AD pathological changes (A-T+N-, A-T+N+, A-T-N+)(Hampel et al., 2021; Jack et al., 2018).

1.4.3.1 Definition of T-status

To date, there is no widely accepted consensus on how to define T-status given large variability owing to methodological differences between techniques and study populations. Tau PET is frequently analyzed using semi-quantitative metrics such as standardized uptake value ratio (SUVR), often considering a region-of-interest (ROI) consisting of brain regions involved early in disease course. The most commonly described ROI for defining T-status using this method is an aggregate temporal lobe region-of-interest (meta-ROI)(Jack et al., 2017; Maass et al., 2017; Ossenkoppele et al., 2018). Independent studies have proposed different SUVR thresholds for positivity, typically ranging between SUVR 1.2-1.4, as summarized in Table 2, and are often not directly comparable, owing to methodological differences. The accuracy of semi-quantitative metrics, however, can be affected by multiple determinants, including partial volume, threshold effects and spillover from off-target areas of tracer accumulation, including choroid plexi, dural venous sinuses, white matter and basal ganglia (Baker et al., 2019; Beyer & Brendel, 2021; Lowe et al., 2016). In addition, quantification of tau PET data requires rigorous processing, adequate co-registration of PET and structural imaging data and access to structural MRI for each subject, which may limit widespread use of this method in a clinical setting.

Study	**ROI**	**SUVR threshold**	**Partial volume correction (PVC)**
Jack et al. (2017)	Temporal meta-ROI[a]	**1.20 – 1.23** (cognitively impaired vs young controls)	No

		1.33 (cognitively impaired vs age-matched controls)	
Maass et al. (2017)	Temporal meta-ROI[a]	**1.27** (cohort 1) **1.20** (cohort 2)	No
Mishra et al. (2017)	Bilateral whole cortex ROI	**1.25** (whole cerebellum) **1.22** (cerebellar cortex)	Yes
Ossenkoppele et al. (2018)	Temporal meta-ROI[a]	**1.34** (Mean+2SD of controls) **1.27** (Younden Index)	No
Mattsson et al. (2018)	Braak I-V[b]	**1.37**	Yes
Jack et al. (2019)	Temporal meta-ROI[a]	**1.25**	No
Mattsson-Carlgren, Leuzy, et al. (2020)	Inferior temporal cortex	**1.29**	No
Lowe et al. (2020)[†]	Temporal meta-ROI[a]	**1.29**	No

Table 2. – Summary of published temporal meta-ROI SUVR thresholds for T-status determination

[a] *temporal meta-ROI: entorhinal, amygdala, parahippocampal, fusiform, inferior temporal, middle temporal*

[b] *Braak I-V: same as above + posterior cingulate, caudal anterior cingulate, rostral anterior cingulate, precuneus, inferior parietal, superior parietal, insula, supramarginal, lingual, superior temporal, medial orbitofrontal, rostral middle frontal, lateral orbitofrontal, caudal middle frontal, superior frontal and lateral occipital*

[†] *published after thesis article in Chapter 2*

While quantitative PET analysis is often used in conjunction with or instead of visual interpretation(Schwarz, 2021), visual interpretation of tau PET has multiple potential advantages over SUVR quantification alone, including assessment of topography of binding and detection of significant focal signal. However, a widely accepted standard for interpretation is currently lacking. Fleisher et al. (2020) recently proposed a clinically applicable SUVR-independent visual rating system consisting of 3 qualitatively defined FTP binding categories based on expected pattern in AD: 1- negative (no increased activity in neocortex, or activity restricted to the mesial temporal, anterolateral temporal and/or frontal regions) ; 2- moderate FTP AD pattern (uptake in the posterolateral temporal or occipital region); 3- advanced FTP AD pattern (uptake in the parietal or precuneus region or increased activity in the frontal region with uptake in posterolateral temporal, parietal or occipital region). This visual rating algorithm was validated in

a cohort of patients with autopsy data available and showed high accuracy for detection of Braak stage V-VI neurofibrillary tangles and high Alzheimer's disease neuropathological changes (ADNC). Inter-rater agreement (5 raters) was also high (κ=0.80). A similar visual rating algorithm has recently been proposed by Sonni et al. (2020), which was validated in two different cohorts and shown to be reliable, with high sensitivity and specificity for identifying patients with AD. In this proposed system, FTP binding pattern is assigned 4 possible categories: 1- negative (no significant binding outside expected background and off-target signal); 2- mild temporal binding (mild to moderate binding restricted to the medial temporal lobe and fusiform gyrus); 3- AD-like binding (binding extending beyond the medial temporal lobe/fusiform gyrus, consistent with Braak stage IV or greater); 4- non-AD-like (binding with atypical distribution, not following expected Braak staging for AD, for example subcortical or white matter signal). Authors reported a good inter-rater agreement (2 raters) for this visual rating system (κ=0.73), high correlation with cortical FTP SUVR ($r=0.71$, $p<0.001$), and association with clinical diagnosis and amyloid-status. Although this visual rating scheme is similar to that of Fleisher and colleagues, the inclusion of a mild temporal binding category may offer increased sensitivity for detection of earlier Braak stages. Given the recent FDA approval of FTP for clinical use in the United States, visual interpretation is likely to gain importance in the near future.

Complementary to PET biomarkers, CSF-based analyses of phospho-Tau (PTau181) have been well validated and are commonly used in the clinical and research setting given their relatively low cost and ease of accessibility compared to PET imaging. However, it has been proposed that analytical methodology, especially the type of assay, can considerably influence measures of PTau181 concentrations(Blennow & Zetterberg, 2018; Hansson et al., 2018; Palmqvist et al., 2019). For example, the widely used ELISA assay may lead to as much as 15% variability for biomarker quantification across laboratories(Grothe et al., 2021; Mattsson et al., 2013). The recently developed Elecsys® Phospho-Tau (181P) CSF assay (Roche Diagnostics International Ltd, Rotkreuz, Switzerland) is a fully automated electrochemiluminescence immunoassay which offers the advantage of increased reproducibility across multiple sites compared to other available assays such as ELISA-based assays(Dakterzada et al., 2021; Hansson et al., 2018; Lifke et al., 2019). Recently published data also suggest very high accuracy of Elecsys-derived CSF biomarkers *in vivo*

for detection of AD neuropathology at subsequent autopsy (Grothe et al., 2021; Mattsson-Carlgren et al., In press.), with an area under the curve of 0.88 for PTau181 in detection of Braak tau stages(Grothe et al., 2021) and an area under the curve of 0.96 for PTau181/Aβ42 in identifying intermediate-to-high ADNC(Mattsson-Carlgren et al., In press.).

1.4.3.2 Concordance between fluid and imaging biomarkers of T-status

Previous work has compared neuroimaging and CSF classification of amyloid and shown high concordance between biomarker status(Blennow et al., 2015; Doecke et al., 2020; Fagan et al., 2006; Jung et al., 2020; Lee et al., 2020; Willemse et al., 2021). In contrast, reports on agreement between CSF and PET-based biomarkers of tau pathology have shown highly variable results, with only modest correlation between both measures (r ranging from 0.29 to 0.75), and variable agreement on T-status ranging from 50 to 87%, as summarized in Table 3.

Study	PET tracer & threshold	CSF assay & threshold	Population	Correlation	% agreement
Chhatwal et al. (2016)	FTP Total cortical SUVR (no cutpoint)	ELISA Innotest (no cutpoint)	N=31 CN	**r= 0.48** (p<0.05)	n/a
Gordon et al. (2016)	FTP Inferior temporal lobe SUVR (no cutpoint)	ELISA Innotest (no cutpoint)	N= 52 CN and cognitively impaired	**r= 0.46** p<0.001	n/a
Brier et al. (2016)	FTP Mean cortical SUVR (no cutpoint)	ELISA Innotest (no cutpoint)	N=46 CN and mild AD	**r= 0.29** p=0.089	n/a
Mattsson et al. (2017)	FTP Braak I-V SUVR (cutpoint: 1.41-PVC)	ELISA Innotest (pTau cutpoint: 81 ng/L)	N= 73 CN, MCI and AD	β= 0.00567 p<0.01 (in AD only)	**70%**

La Joie et al. (2018)	FTP Mean cortical SUVR (cutpoint: 1.49)	ELISA Innotest (pTau cutpoint: 24 ng/L)	N=53 Mixed AD and non-AD	**r= 0.75** (p<0.05)	**87%**
Leuzy, Cicognola, et al. (2019)	[^{18}F]THK5317 Multiple cutpoints	ELISA Innotest (pTau cutpoint: 80 pg/mL)	N=14 (MCI and AD)	n/a	**50%**
Zhao et al. (2019)	FTP Global cortical SUVR (no cutpoint)	ELISA Innotest (no cutpoint)	N=115 CN, MCI and AD	**β= 4.74** p<0.01 (in AD only)	n/a
Mattsson-Carlgren, Andersson, et al. (2020)	FTP Inferior temporal cortex SUVR (1.31 -PVC)	Meso Scale Discovery (pTau cutpoint: 152.6 ng/L)	N=131 CN, MCI and AD	n/a	**74%**
Mattsson-Carlgren, Leuzy, et al. (2020)	FTP Inferior temporal cortex SUVR (1.29) Braak V-VI (1.32)	ELISA Innotest and Euroimmun (pTau cutpoint: 60.2 ng/L)	N=490 CN, MCI and AD	Inferior temporal cortex: **r=0.710** p<0.001 Braak V-VI: **r=0.594** p<0.001	**77%** **65%**
Meyer et al. (2020)	FTP Temporal meta-ROI SUVR (cutpoint 1.37)	Elecsys (pTau cutpoint: 26.64 pg/mL)	N=322 (CU, MCI and AD)	**r=0.51** p<.001	**75%**
Okafor et al. (2020)	FTP Global cortical SUVR (no cutpoint)	ELISA Innotest (no cutpoint)	N=29 MCI	**r=0.42** p=0.04	n/a
McSweeney et al. (2020)	FTP 8 ROIs (no cutpoint)	ELISA Innotest (no cutpoint)	N=74 CN	**r=0.55** p<0.001 (entorhinal ROI)	n/a

Wolters et al. (2020)	FTP Entorhinal cortex SUVR	ELISA Innotest (pTau cutpoint: 52 pg/mL)	N=78 CN, MCI and AD	**β=0.50** p≤0.01	n/a
Kreisl et al. (2021)†	[^{18}F]MK-6240 Braak regions (I to VI) (no cutpoint)	ELISA Innotest (no cutpoint)	N=21 CN, mixed AD and non-AD	**r=0.39** p=0.08 (for Braak II)	n/a
Guo et al. (2021)†	FTP Temporal meta-ROI SUVR (cutpoint 1.37)	Elecsys (pTau cutpoint: 26.64 pg/mL)	N=245 CN and MCI	(main analyses focused on plasma/PET and plasma/CSF)	**80%** (on N=20 with plasma, CSF and PET)
Boerwinkle et al. (2021) †	FTP composite ROI SUVR (amygdala, entorhinal cor-tex, inferior temporal cortex, and lateral occipital cortex) (cutpoint 1.22)	Elecsys (no cutpoint)	N=371 CN, MCI and AN	**r=0.369** p<0.05	n/a

Table 3. - Summary of concordance in biomarkers of T-status

Only studies reporting percent agreement and/or correlation between CSF pTau and tau PET are shown.

† *published after thesis article in Chapter 2*

As can be noted in Table 3, such variable concordance can be explained in part by the impact of methodology and technical factors, including wide variability between studies on thresholds for T-status for both CSF and PET measures, as well as use of different radiotracers, ROIs and CSF assays. Furthermore, comparative analysis of tau PET with the novel Elecsys® Phospho-Tau (181P) CSF assay described above is scarce(Boerwinkle et al., 2021; Guo et al., 2021; Meyer et al., 2020). Finally, studies have focused so far on comparing quantitative measures of tau PET with CSF, but no study has directly compared them to visual read.

1.5 Objectives

The objectives of this study were to assess concordance of T-status and correlation between different fluid and imaging biomarkers of tau in a cohort of patients with a wide range of neurodegenerative conditions and cognitively normal individuals issued from three independent cohorts. In particular, we aimed to:

1- Assess concordance of binary T-status obtained by FTP visual assessment, SUVR quantification and CSF PTau181
2- Compare sensitivity and specificity of each modality for distinguishing amyloid-positive patients with MCI and dementia due to AD from other clinical groups.

Note: The results of this study were published in the European Journal of Nuclear Medicine and Molecular Imaging, presented in its entirety in the following section. The first author of the article and author of the present thesis was responsible for project design, data collection and analysis, interpretation of findings, drafting and revision of the manuscript. Co-authors were involved as collaborators in all stages.

Section 2 – Article published in European Journal of Nuclear Medicine and Molecular Imaging

Comparing ATN-T designation by tau PET visual reads, tau PET quantification, and CSF PTau181 across three cohorts

Karine Provost[a], Leonardo Iaccarino[a], David N. Soleimani-Meigooni[a,b], Suzanne Baker[b], Lauren Edwards[a], Udo Eichenlaub[c], Oskar Hansson[d], William Jagust[b,e], Mustafa Janabi[b], Renaud La Joie[a], Orit Lesman-Segev[a], Taylor J. Mellinger[a], Bruce L. Miller[a], Rik Ossenkoppele[d,f], Julie Pham[a], Ruben Smith[d], Ida Sonni[b,g] Amelia Strom[a], Niklas Mattsson-Carlgren[d,h,i] , Gil D. Rabinovici[a,b,e,j]

For the Alzheimer's Disease Neuroimaging Initiative (ADNI)*

[a] *Memory and Aging Center, Dept. of Neurology, University of California San Francisco, San Francisco, CA, US*

[b] *Lawrence Berkeley National Laboratory, Berkeley, CA, US*

[c] *Roche Diagnostics GmbH, Penzberg, Germany*

[d] *Clinical Memory Research Unit, Lund University, Lund, Sweden*

[e] *Helen Wills Neuroscience Institute, UC Berkeley, Berkeley, CA, US*

[f] *Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, the Netherlands*

[g] *Ahmanson Translational Theranostics Division, Department of Molecular and Medical Pharmacology, UC Los Angeles, Los Angeles, CA, US*

[h] *Department of Neurology, Skåne University Hospital, Lund, Sweden*

[i] *Wallenberg Centre for Molecular Medicine, Lund University, Lund, Sweden*

[j] *Dept. of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA, US*

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Corresponding author:

Karine Provost, M.D.

University of California San Francisco, Memory and Aging Center

675 Nelson Rising Lane, Suite 190, San Francisco, California, USA, 94143

Fax: +1(415)353-8292

2.1 Abstract

Purpose: To compare rates of tau biomarker positivity (T-status) per the 2018 Alzheimer's Disease (AD) Research Framework derived from [^{18}F]flortaucipir (FTP) PET visual assessment, FTP quantification, and cerebrospinal fluid (CSF) phosphorylated Tau-181 (PTau181).

Methods: We included 351 subjects with varying clinical diagnoses from three cohorts with available FTP PET and CSF PTau181 within 18 months. T-status was derived from: (1) FTP visual assessment by two blinded raters; (2) FTP standardized uptake value ratio (SUVR) quantification from a temporal meta-ROI (threshold: SUVR ≥ 1.27); (3) Elecsys® Phospho-Tau (181P) CSF (Roche Diagnostics) concentrations (threshold: PTau181 ≥ 24.5 pg/ml).

Results: FTP visual reads yielded the highest rates of T+, while T+ by SUVR increased progressively from cognitively normal (CN) through mild cognitive impairment (MCI) and AD dementia. T+ designation by CSF PTau181 was intermediate between FTP visual reads and SUVR values in CN, similar to SUVR in MCI, and lower in AD dementia. Concordance in T-status between modality pairs ranged from 68% to 76% and varied by clinical diagnosis, being highest in patients with AD dementia. In discriminating Aβ+ MCI and AD subjects from healthy controls and non-AD participants, FTP visual assessment was most sensitive (0.96) but least specific (0.60). Specificity was highest with FTP SUVR (0.91) with sensitivity of 0.89. Sensitivity (0.73) and specificity (0.72) were balanced for PTau181.

Conclusion: The choice of tau biomarker may differ by disease stage and research goals that seek to maximize sensitivity or specificity. Visual interpretations of tau PET enhance sensitivity compared to quantification alone, particularly in early disease stages.

Keywords: Tau, PET, Flortaucipir, Alzheimer's disease, biomarkers, CSF

2.2 Introduction

Alzheimer's disease (AD) clinical research has been transformed by the advent of in vivo biomarkers for amyloid-beta (Aβ) and tau; the proteins that form the plaques and tangles that define AD neuropathology (Lowe et al., 2016; Marquie et al., 2015; Olsson et al., 2016; Scholl et al., 2019). Correct identification of biomarker status is important for screening participants and for outcome evaluation in clinical trials of novel disease-modifying therapies (Blennow & Zetterberg, 2018; Cummings, 2019). The AT(N) research framework (Jack et al., 2016) proposes binary classification of all individuals as positive or negative for amyloid, tau and neurodegeneration, allowing interchangeable use of cerebrospinal fluid (CSF) or imaging measures. While previous work has compared neuroimaging and CSF classification of amyloid and neurodegeneration, few studies have compared fluid and imaging definitions of T-status (Brier et al., 2016; Chhatwal et al., 2016; Gordon et al., 2016; La Joie et al., 2018; Leuzy, Chiotis, et al., 2019; Mattsson et al., 2017; Mattsson et al., 2018; Meyer et al., 2020; Zhao et al., 2019).

Tau positron emission tomography (PET) is frequently analyzed using semi-quantitative metrics such as the standardized uptake value ratio (SUVR), commonly considering a region of interest (ROI) consisting of brain regions involved early in disease course, such as a temporal lobe region-of-interest (meta-ROI) (Jack et al., 2017; Maass et al., 2017; Ossenkoppele et al., 2018). Independent studies have indicated different meta-ROI SUVR thresholds for positivity, typically ranging between SUVR 1.2-1.4 (Jack et al., 2019; Jack et al., 2017; Maass et al., 2017; Meyer et al., 2020; Ossenkoppele et al., 2018). The accuracy of semi-quantitative metrics, however, can be affected by multiple determinants, including partial volume, threshold effects and spillover from off-target areas (Baker et al., 2019; Lowe et al., 2016). Quantification of tau PET data also requires access to structural magnetic resonance imaging (MRI) and adequate co-registration.

In contrast to SUVR quantification, visual interpretation of tau PET allows for assessment of topography of binding and may lead to detection of significant focal signal. However, a widely accepted standard for interpretation is currently lacking. A visual rating algorithm has been recently proposed by Fleisher et al., with high accuracy for detection of Braak stage V-VI neurofibrillary tangles and high Alzheimer's disease neuropathological changes (ADNC) at

autopsy using [^{18}F]flortaucipir (FTP) (Fleisher et al., 2020). Visual interpretation of FTP PET is likely to gain importance given the recent Food and Drug Administration approval of this tracer for clinical use in the United States.

CSF-based analyses of phospho-Tau (PTau181) have been well validated and are commonly used (Blennow et al., 2010). However, it has been proposed that analytical methodology, including type of assay, can considerably influence measures of PTau181 concentrations (Blennow & Zetterberg, 2018; Hansson et al., 2018; Palmqvist et al., 2019). The Elecsys® Phospho-Tau (181P) CSF assay (Roche Diagnostics International Ltd, Rotkreuz, Switzerland) is a fully automated electrochemiluminescence immunoassay with increased reproducibility across multiple sites compared to other available assays (Hansson et al., 2018; Lifke et al., 2019). The literature on comparative analysis of this assay with tau PET is limited (Mattsson-Carlgren, Andersson, et al., 2020; Meyer et al., 2020).

In contrast to amyloid biomarkers for which CSF and PET show high concordance (Blennow et al., 2015; Doecke et al., 2020; Fagan et al., 2006; Oh et al., 2017), agreement between PET and CSF-based biomarkers of tau pathology are highly variable, ranging from 50% to 87%, and show only modest correlation (r=0.29 to 0.75) (Brier et al., 2016; Chhatwal et al., 2016; Gordon et al., 2016; La Joie et al., 2018; Leuzy, Chiotis, et al., 2019; Mattsson et al., 2017; Mattsson et al., 2018; Mattsson-Carlgren, Andersson, et al., 2020; Mattsson-Carlgren, Leuzy, et al., 2020; Meyer et al., 2020; Okafor et al., 2020; Wolters et al., 2020; Zhao et al., 2019), largely impacted by methodology and technical factors. The objectives of this study were to perform cross-validation of different biomarkers of tau in a cohort of patients with neurodegenerative conditions. In particular, we aimed to firstly assess concordance of binary T-status obtained by FTP visual assessment, SUVR quantification and CSF PTau181; and secondly to compare sensitivity and specificity of each modality for distinguishing amyloid-positive patients with mild cognitive impairment (MCI) and dementia due to AD from other clinical groups.

2.3 Methods

2.3.1 Study population

The cohort consisted of a convenience sample of 351 participants enrolled in research studies at the University of California San Francisco Alzheimer's Disease Research Center (UCSF ADRC, n=98), the Alzheimer's Disease Neuroimaging Initiative (ADNI, n=179) and the Swedish BioFINDER study (n=74). The participants spanned a wide range of clinical diagnoses (Supplementary Table 1), had undergone FTP PET between June 2014 and May 2019, had structural MRI available, and had undergone lumbar puncture within 18 months from the PET scan with available PTau181 Elecsys measurements (Supplementary Figure 1).

Clinical diagnoses were made blinded to biomarker results, based on established criteria; participants were either cognitively unimpaired or assigned a diagnosis of MCI (Albert et al., 2011), probable AD dementia (McKhann et al., 2011) (herein referred to as AD clinical diagnosis: AD_c), or non-AD disorders (behavioral variant frontotemporal dementia (Rascovsky et al., 2011), semantic or non-fluent variant primary progressive aphasia (Gorno-Tempini et al., 2011), corticobasal syndrome (Armstrong et al., 2013), progressive supranuclear palsy (Hoglinger et al., 2017; Litvan et al., 1996), dementia with Lewy bodies (McKeith et al., 2017) or vascular dementia (Roman et al., 1993)). Amyloid status was determined by PET or CSF, details can be found in Supplementary Table 2.

Some data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

Written informed consent was obtained from all participants or their surrogates. The study was approved by local institutional review boards for human research.

2.3.2 FTP PET acquisition & processing

FTP PET acquisition and processing has been described in detail elsewhere (Maass et al., 2017; Ossenkoppele et al., 2018) (Supplementary Table 2). In brief, participants underwent FTP brain PET following injection of ~370 MBq at 80-100 min post-injection (UCSF and BioFINDER) or 75-105 min post-injection (ADNI). PET data was reconstructed using an iterative method with attenuation correction. Subjects also underwent MRI, which was used for PET processing only. FTP PET regional SUVR data was extracted in native space after co-registration to T1-weighted MRI with SPM12 and cortical parcellation with FreeSurfer (version 5.3, https://surfer.nmr.mgh.harvard.edu/). Reference region for FTP-PET was the inferior cerebellar gray matter(Baker et al., 2017). Non-partial volume corrected data were used.

2.3.3 CSF analysis

CSF samples were collected following lumbar puncture and processed using established protocols (Supplementary Table 2). Samples were stored in polypropylene tubes at -60°C or below until biomarker analysis. All samples were analyzed with the fully automated electrochemiluminescence immunoassay Elecsys Phospho-Tau (181P) CSF on a cobas e 601 analyzer (Roche Diagnostics International Ltd, Rotkreuz, Switzerland). Samples from UCSF and BioFINDER cohorts were analyzed at the Clinical Neurochemistry Laboratory, University of Gothenburg, Sweden, and samples from ADNI were analyzed at the University of Pennsylvania biomarker core laboratory (Bittner et al., 2016; Hansson et al., 2018).

2.3.4 T-status definition

2.3.4.1 T-status based on visual assessment of FTP PET scans

Anonymized images were independently assessed by two raters (one nuclear medicine physician, K.P. and one behavioral neurologist, D.S.M., both with experience in interpreting brain PET scans). Raters were blinded to all clinical information, amyloid status, CSF results and SUVR quantification values. In addition, intensity normalized SUVR images were multiplied by a random factor to ensure blinding to SUVR values during interpretation. Images were viewed on MRIcron (https://www.nitrc.org/projects/mricron) using the NIH color scale. Raters manually thresholded

images to adjust contrast so that inferior cerebellar gray matter appeared as pale green to light blue (roughly equivalent to an upper threshold of 2.2-2.5 SUVR). A total of 47 scans (randomly sampled) were duplicated and were read twice by each rater to assess intra-rater reliability.

Visual assessment was based on *a priori* criteria (Figure 1), previously described (Sonni et al., *under review).* Images were assigned T+ status if there was an AD-like pattern of binding (i.e. moderate-to-intense signal in the parieto-temporal cortex, following typical Braak and Braak distribution)(Braak & Braak, 1991; Schwarz et al., 2016) or if there was significant, confluent binding restricted to the temporal lobes. A T- status was assigned if the FTP was within normal limits (including within the expected range of off-target binding for this tracer(Baker et al., 2019; Lowe et al., 2016)) or was suggestive of a non-AD pattern of binding (for example, extensive binding in the frontal white matter). This visual interpretation scheme is similar although not identical to the approach described by Fleisher et al. that received FDA regulatory approval(Fleisher et al., 2020).

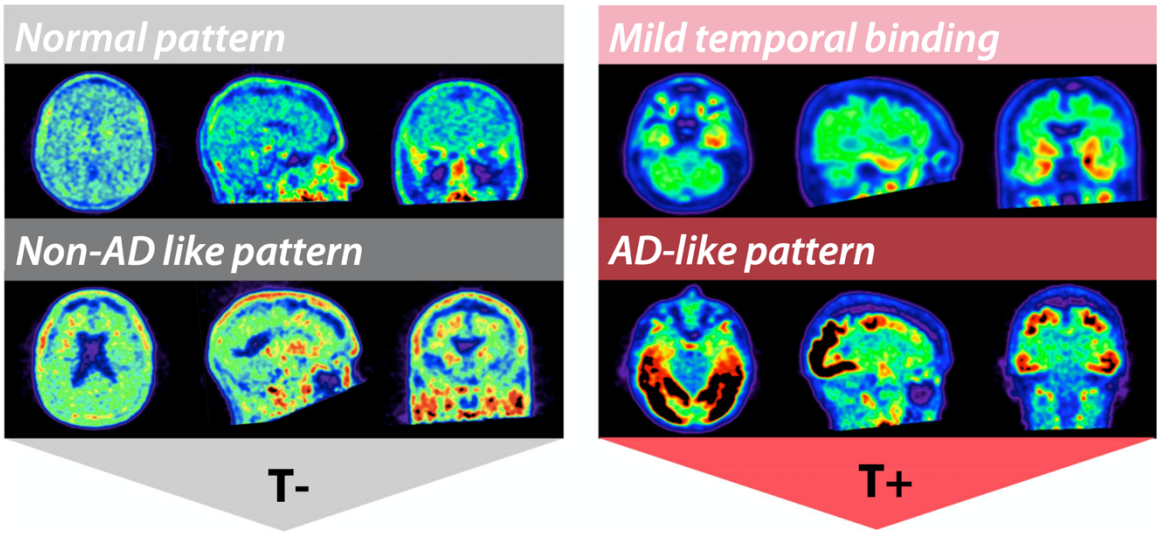

Figure 1. - Rating scheme for visual assessment of FTP pattern of binding to define T-status.

Normal pattern of binding and non-AD-like pattern (for example, mild-to-moderate signal in the frontal white matter) were assigned T-status. Classic AD-like pattern following Braak and Braak distribution extending beyond the temporal lobes, and mild temporal binding (confluent binding restricted to the temporal lobes) were assigned T+ status

In case of discordance in T-status between the two raters, consensus was obtained from a third independent rater (radiologist O.L.S. or neurologist R.S. with experience in interpreting FTP PET), blinded to all clinical information and to the interpretation of the other two raters. In such cases, the majority (two out of three) T-status was used.

2.3.4.2 T-status based on FTP SUVR quantification

A bilateral weighted average SUVR from a composite temporal meta-ROI (amygdala, entorhinal, fusiform, parahippocampal, inferior temporal and middle temporal regions) was calculated based on Freesurfer-parcellated regions as previously published(Jack et al., 2017; Maass et al., 2017; Ossenkoppele et al., 2018). A scan with a meta-ROI SUVR value >1.27 was considered T+, based on previously published data in an independent cohort from Gangnam Severance Hospital in Seoul, South Korea (threshold defined comparing Aβ+AD vs controls)(Ossenkoppele et al., 2018).

2.3.4.3 T-status based on CSF PTau181

For binary T-status based on CSF PTau181, we derived a cutoff from an independent ADNI cohort with available results on the Elecsys Phospho-Tau (181P) assay. This was done by estimating a threshold comparing Aβ+AD subjects (n=183) vs. controls (independent of amyloid status, n=404) with a Receiver Operating Characteristic analysis, mirroring the methodology of the previously published threshold used for the temporal meta-ROI SUVR(Ossenkoppele et al., 2018). Using Youden Index, a cutoff value of 24.5 pg/mL was found (sensitivity 0.70, specificity 0.84, area under the curve 0.83 (95%CI 0.80-0.87)).

2.3.4.4 Statistical analyses

For visual assessment of FTP, analysis of intra- and inter-rater agreement was performed using Cohen's kappa statistic. To evaluate concordance between PET-based and CSF-based T-status, overall percent agreement (OPA) was used. For evaluation of diagnostic performance by modality, accuracy in the study sample is provided, along with estimated area-under-the-curve (AUC, calculated as sensitivity + specificity/2), to provide a metric that is not biased by the prevalence estimate in the sample. Between groups comparison were performed using Kruskall-

Wallis H test for continuous variables and X^2 for nominal variables. Statistical significance was considered for p<0.05. Statistical analyses were performed using SPSS (version 25, IBM, Armonk, NY).

2.4 Results

Patient characteristics can be found in Table 4[1]. The cohort consisted of 127 cognitively normal (CN) participants, 106 MCI subjects, 84 AD_c patients and 34 patients with non-AD disorders. There was a statistically significant difference in age, sex, education, MMSE and rate of Aβ positivity between diagnostic groups. The distribution of CSF PTau181 and FTP SUVR by clinical diagnosis can be found in Supplementary Figure 2.

	CN ($n = 127$)	MCI ($n = 106$)	AD_c ($n = 84$)	Non-AD ($n = 34$)	p value
Age	73.9 ± 6.8	71.7 ± 9.0	66.1 ± 9.2	65.3 ± 9.7	$p \leq .001^{\dagger}$
Sex (M, %)	45 (35%)	47 (44%)	44 (52%)	20 (59%)	$p = .03$
Education	14.9 ± 3.8	15.8 ± 3.0	15.5 ± 3.5	17.4 ± 4.2	$p = .004^{\dagger\dagger}$
MMSE	29.2 ± 1.0	27.0 ± 2.7	20.9 ± 4.8	25.2 ± 6.3	$p < .001^{\dagger\dagger\dagger}$
Amyloid status (Aβ+, %)	48 (38%)	61 (58%)	81 (96%)	6 (18%)	$p < .001$
Provenance	UCSF ADRC 0 ADNI 80 BioFINDER 47	UCSF ADRC 15 ADNI 83 BioFINDER 8	UCSF ADRC 50 ADNI 16 BioFINDER 18	UCSF ADRC 33 ADNI 0 BioFINDER 1	

Table 4. - Patient characteristics.

Mean ± SD is indicated for continuous variables. CN cognitively normal, MCI mild cognitive impairment, ADc Alzheimer's disease dementia, non-ADc non-AD disorders (including patients with clinical diagnoses of behavioral variant frontotemporal dementia, non-fluent variant primary progressive aphasia, progressive supranuclear palsy, corticobasal syndrome, dementia with Lewy bodies, and one subject with chronic traumatic encephalopathy)

† Significant for all pairwise comparisons except CN vs MCI (p = .26) and AD vs non-AD (p = 1.00)

[1] Table numbers have been modified from the original article to match order of thesis manuscript

†† Pairwise comparisons significant only between CN and non-AD (p = .002)

††† Significant for all pairwise comparisons except MCI vs non-AD (p = 1.00)

2.4.1 Reliability of FTP visual assessment

Using the visual rating scheme for determination of binary T-status on FTP, intra-rater reliability (n=47) for rater 1 was κ=0.87 (95%CI 0.73-1.00) and for rater 2 was κ=0.78 (95%CI 0.59-0.96). Overall percent agreement (n=351) was 84%, with 57 cases requiring consensus read from the third rater (Supplementary Figure 3). Inter-rater reliability in the overall sample was κ=0.64 (95%CI 0.56-0.72), and κ=0.79 (95%CI 0.40-1.00) for scans of participants with AD_c.

2.4.2 T-status by modality and clinical diagnosis

Overall, FTP visual reads yielded the highest rates of T+ (Figure 2). This was true across clinical diagnoses, and for Aβ+ and Aβ- participants, with the exception of Aβ- non-AD dementia. T+ as defined by SUVR increased progressively from CN to MCI to AD_c and showed the lowest rates of T+ in Aβ- participants. T+ designation by CSF PTau181 was intermediate between FTP visual reads and SUVR values in CN, similar to SUVR in MCI, and lower in AD_c. CSF PTau181 generally yielded lower rates of T+ than FTP visual reads in Aβ- participants, and yielded zero T+ designations in the Aβ- AD_c category (likely clinical misdiagnosis of AD).

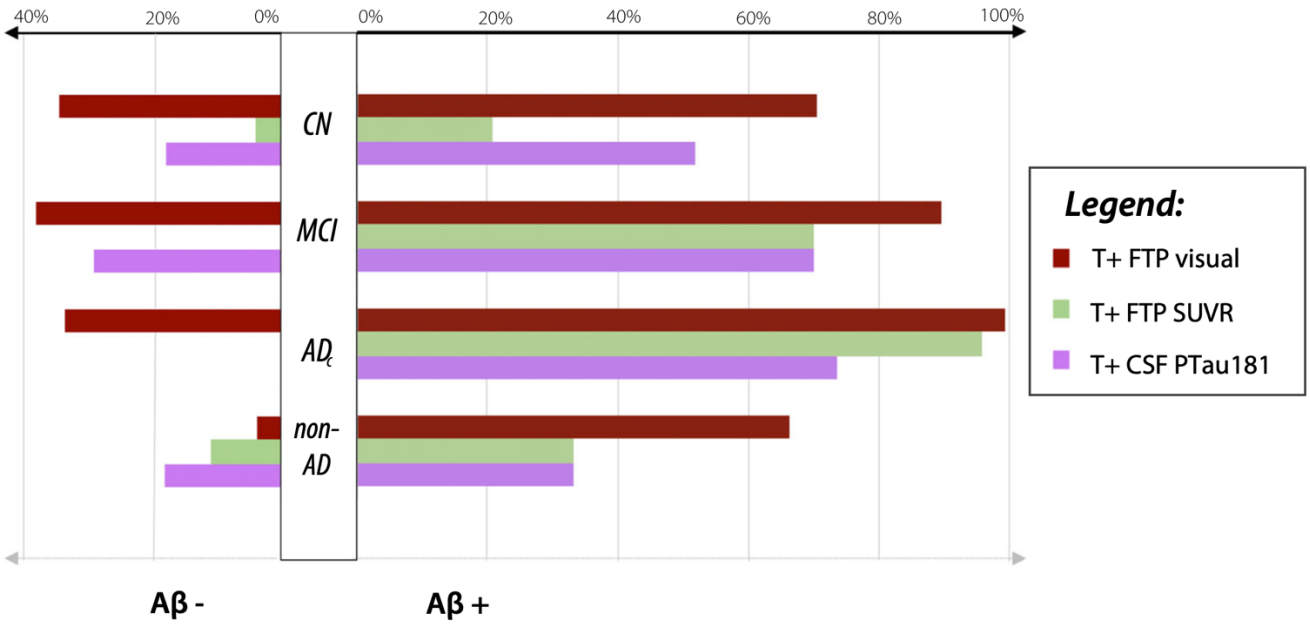

Figure 2. - Percentage of T+ by modality, clinical diagnosis, and amyloid status.

CN, cognitively normal; MCI, mild cognitive impairment; ADc, Alzheimer's disease dementia; non-AD, non-AD disorders

2.4.3 Concordance in T-status between modalities

Figure 3 shows four representative cases with discordance in T-status between at least one modality pair. These examples illustrate the potential advantage of integrating visual assessment of tau PET, which in early cases could detect subtle increased binding in a classic AD-pattern, or significant binding outside of the target ROI, which were missed by SUVR quantification (first, second and fourth rows in Figure 3). The third case (Aβ-) illustrates false-positive near-threshold SUVR quantification, with non-AD binding pattern upon visual assessment (predominant binding in the frontal white matter), as we know that FTP may show subtle increased signal in cases with non-AD pathology (Josephs et al., 2016; Tsai et al., 2019; Utianski et al., 2018).

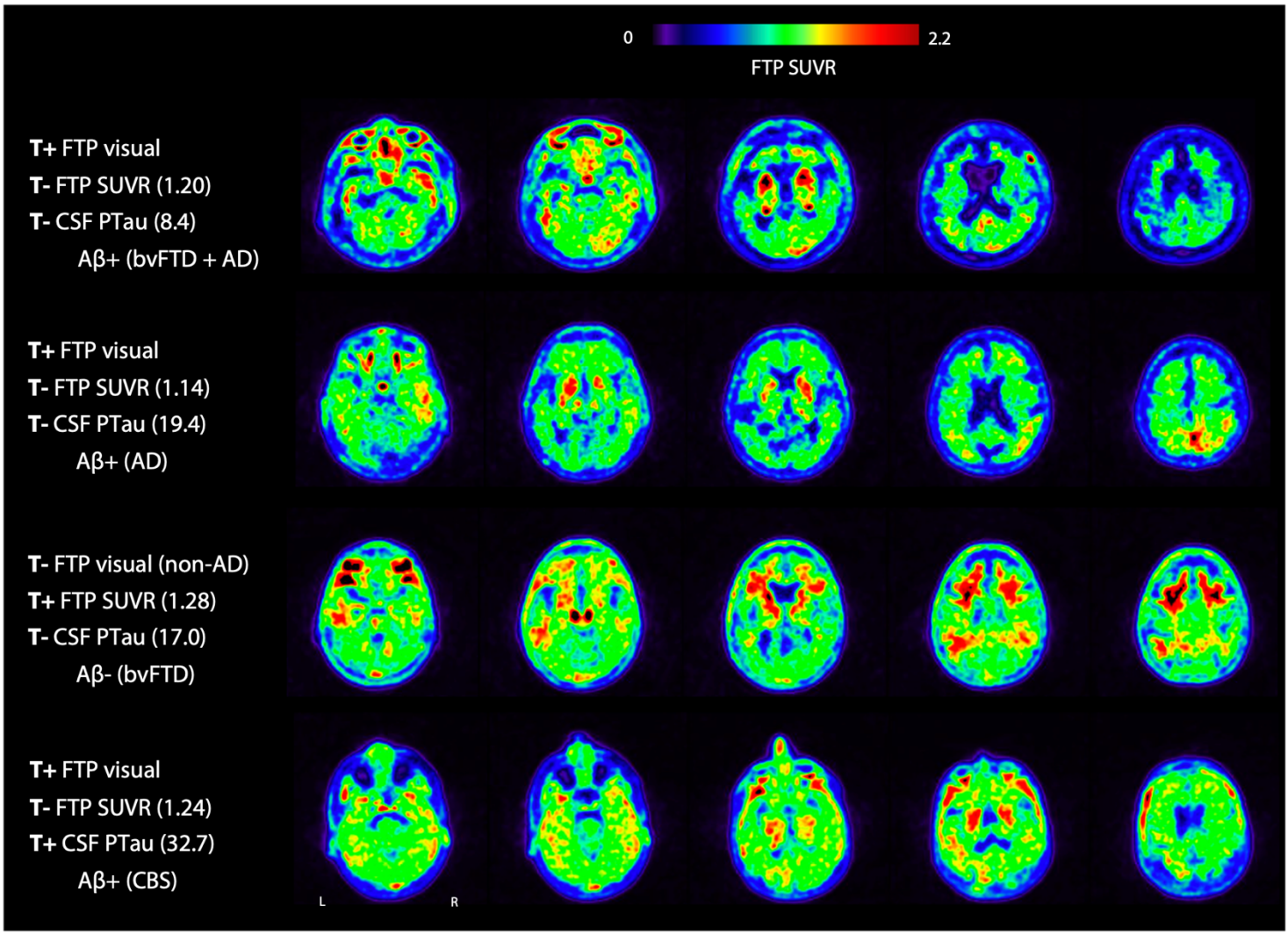

Figure 3. - Examples of discordant T-status between FTP visual assessment, SUVR quantification, and CSF PTau181.

Selected axial slices of FTP are shown. Amyloid status is based on PET. Clinical diagnosis is indicated in parentheses. bvFTD, behavioral variant frontotemporal dementia; CBS, corticobasal syndrome

T-status was concordant between all three modalities in 206 participants (59%). Overall percent agreement between modality pairs ranged from 68% to 76% in the whole cohort, with lowest overall agreement between FTP visual read and CSF PTau181 (Figure 4). FTP SUVR and CSF PTau181 showed consistently high agreement in CN, MCI and ADc, whereas agreement between

FTP SUVR and visual reads increased with clinical impairment and was nearly perfect (95%) in ADc. In non-AD dementia, concordance was lowest between FTP SUVR and CSF pTau181.

Figure 4. - Inter-modality overall percent agreement between modalities by clinical diagnosis.

CN, cognitively normal; MCI, mild cognitive impairment; ADc, Alzheimer's disease dementia; non-AD, non-AD disorders

There was a significant positive correlation between continuous measures of CSF PTau181 and FTP SUVR (r= 0.61, p< .001; Figure 5). Nearly all patients who were T+ on FTP SUVR were also T+ on visual assessment, while half of the patients who were T+ on CSF PTau181 and T- on FTP SUVR quantification were T+ on visual assessment (Figure 5, top left quadrant). Details of positive and negative percent agreement between modalities can be found in Supplementary Table 3.

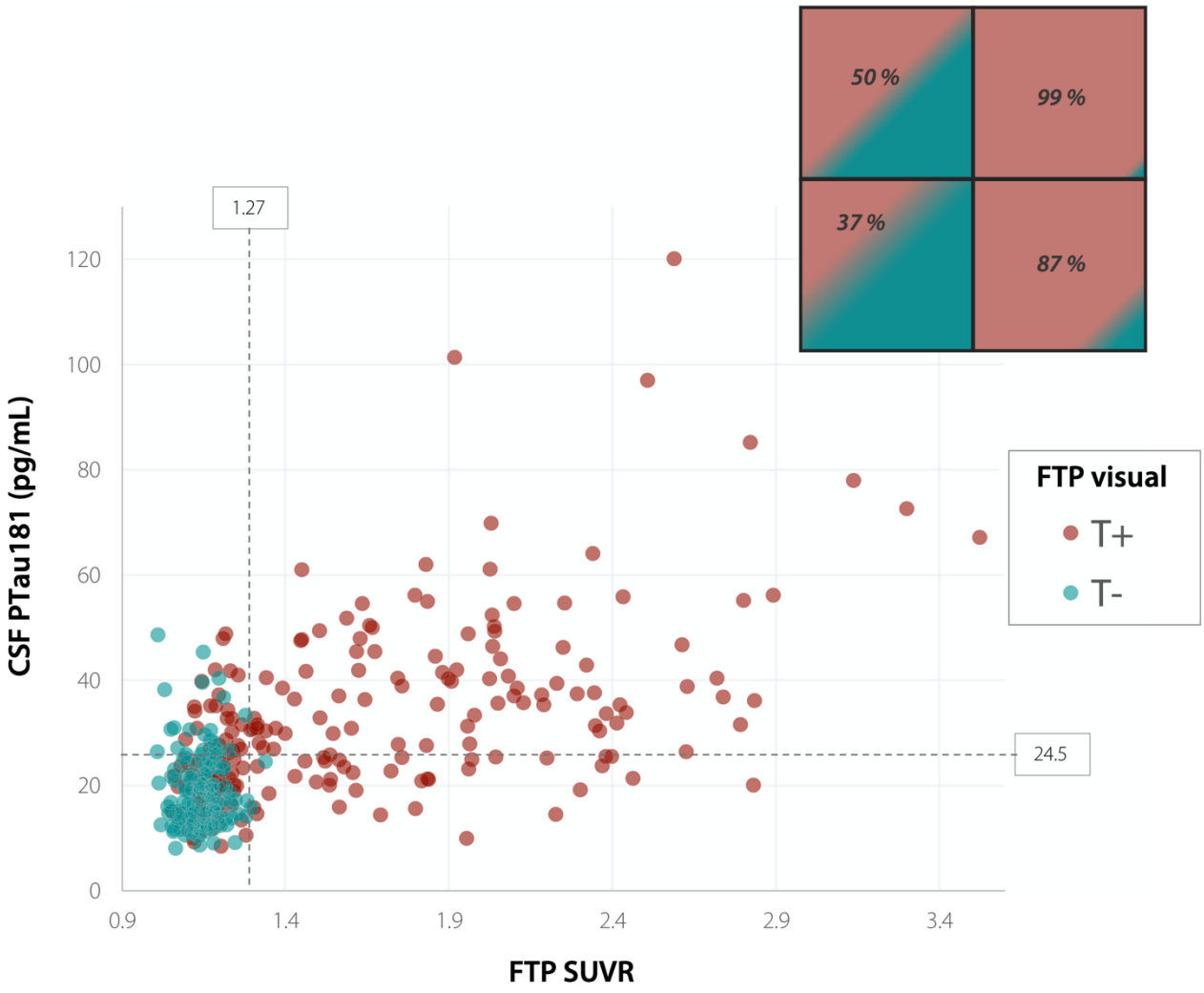

Figure 5. - Scatter plot of CSF PTau181 and FTP SUVR values in T+ and T− patients by FTP visual assessment.

Dotted lines show threshold of positivity for CSF PTau181 and FTP temporal meta-ROI SUVR. Insert in the top right corner shows percentage of T+ cases by visual assessment for each quadrant of the scatterplot

2.4.4 Factors associated with a discordance in T-status

When comparing patients with concordant T-status across all three modalities to patients with discordance in at least one modality pair (Table 5), patients with a discordance in T-status were significantly older, were more likely to be male, and had intermediate rates of Aβ positivity, mean

CSF PTau181 and FTP SUVR values. CN Aβ+ participants were disproportionally represented in this group (67%) and were nearly always T+ on CSF and/or FTP visual assessment, while negative on SUVR quantification. 27% of Aβ+ AD_c patients were also found in this category, nearly all of whom were positive on both measures of tau PET but negative on CSF PTau181.

	Concordant T− ($n = 99$)	Concordant T+ ($n = 107$)	Discordant T status ($n = 145$)	p value*
Age	68.1 ± 8.3	68.4 ± 9.3	73.7 ± 8.5	$p < .001^{\dagger}$
Sex (M, %)	39 (39%)	39 (36%)	78 (54%)	$p = .01$
Education	15.6 ± 3.9	15.4 ± 3.3	15.5 ± 3.6	$p = .83$
MMSE	28.3 ± 2.5	23.2 ± 5.0	26.9 ± 4.6	$p < .001^{\dagger}$
Amyloid status (Aβ+, %)	14 (14%)	106 (99%)	76 (52%)	$p < .001$
CSF PTau181 (pg/mL)	16.1 ± 4.2	42.4 ± 16.6	23.2 ± 8.5	$p < .001$
FTP SUVR	1.14 ± 0.1	1.97 ± 0.5	1.28 ± 0.3	$p < .001$
Diagnosis (% Aβ+)	52 CN (15%) 23 MCI (17%) 2 AD_c (0%) 22 non–AD (9%)	9 CN (89%) 38 MCI (100%) 59 AD_c (100%) 1 non-AD (100%)	66 CN (48%) 45 MCI (42%) 23 AD_c (96%) 11 non-AD (27%)	$p < .001$

Table 5. - Comparison of subjects with concordant T-status across all modalities and subjects with discordant T-status in at least one modality pair.

Mean ± SD is shown for continuous variables.

**p values shown for Kruskal-Wallis H test for continuous variables, and x2 for nominal variables*

† Bonferroni-corrected p values for pairwise comparisons are all < .001 except; T− vs discordant T for age (p = 1.0), and T− vs discordant T for MMSE (p = .06)

In subjects who had a discordant T-status in at least one modality pair, the mean CSF PTau181 and FTP SUVR values were very close to the cutoff used for binary classification. For visual assessment of FTP, cases requiring consensus from a third rater tended to have lower values of both CSF PTau181 (mean 20.7 pg/L) and FTP SUVR (mean 1.15) (Supplementary Figure 4).

Focusing on patients with clinical diagnosis of AD (n=84), there was no significant difference in global cognition (MMSE) between participants who were CSF T+ (~71%) and T- (~29%) (p= .40,

Supplementary Table 4). Average FTP SUVR was higher in T+ CSF patients compared to T- ($p<0.001$).

2.4.5 Sensitivity and specificity of T-status for Aβ+ MCI/AD$_c$ by modality

To determine sensitivity and specificity of T-status obtained with each modality, we contrasted Aβ+ cognitively impaired participants (MCI or AD$_c$) with all other subjects. Sensitivity was highest with FTP visual assessment (0.96, 95%CI 0.91-0.98), while specificity was highest with FTP SUVR quantification (0.91, 95%CI 0.87-0.95). CSF PTau181 had 0.73 sensitivity (95%CI 0.64-0.80) and 0.72 specificity (95%CI 0.65-0.78; Table 6). Overall accuracy was highest with FTP SUVR quantification (0.89, 95%CI 0.85-0.92, AUC 0.88), followed by FTP visual assessment (0.74, 95%CI 0.69-0.79, AUC 0.78) and CSF PTau181 (0.72, 95%CI 0.67-0.77, AUC 0.73).

	FTP visual assessment	FTP SUVR quantification	CSF PTau181
Gold standard: clinical ($n = 351$)			
Sensitivity	0.96 (0.91–0.98)	0.85 (0.78–0.91)	0.73 (0.64–0.80)
Specificity	0.60 (0.53–0.67)	0.91 (0.87–0.95)	0.72 (0.65–0.78)
Gold standard: Aβ status ($n = 351$)			
Sensitivity	0.89 (0.84–0.93)	0.68 (0.60–0.74)	0.66 (0.59–0.73)
Specificity	0.70 (0.62–0.77)	0.96 (0.92–0.99)	0.79 (0.72–0.85)
Gold standard: pathology ($n = 11$)			
Sensitivity	1.00 (0.54–1.00)	0.83 (0.36–1.00)	0.50 (0.12–0.88)
Specificity	1.00 (0.48–1.00)	0.80 (0.28–0.99)	0.80 (0.28–0.99)

Table 6. - Sensitivity and specificity by modality

Multiple gold standard for evaluation of sensitivity and specificity were used; first, clinical gold standard (i.e., detection of Aβ + MCI and AD patients vs all other subjects), second, amyloid status alone (Aβ + vs Aβ−), and lastly, pathology in a small subsample (using moderate-to-high ADNC as gold standard). 95% CI values for sensitivity and specificity are shown in parentheses

When discriminating Aβ+ vs Aβ- subjects regardless of clinical diagnosis or stage, overall accuracy was similar for FTP visual assessment and SUVR quantification (0.81, 95%CI 0.76-0.85, AUC 0.80

and 0.80, 95%CI 0.76-0.84, AUC 0.82 respectively), with nominally higher sensitivity for visual assessment (0.89, 95%CI 0.84-0.93), and higher specificity for SUVR quantification (0.96, 95%CI 0.92-0.99). CSF PTau181 showed intermediate sensitivity and specificity (0.66, 95%CI 0.59-0.73 and 0.79, 95%CI 0.72-0.85, overall accuracy 0.72, 95%CI 0.67-0.77, AUC 0.73). In early clinical disease stages (Aβ+ CN and MCI participants), FTP visual assessment yielded highest sensitivity (71% and 90% respectively), compared with 21% and 70% for FTP SUVR quantification and 52% and 70% for CSF PTau181.

Autopsy was available in a subsample of 11 participants from the UCSF ADRC cohort (mean age at time of PET 63.9 years, mean PET to autopsy interval 2.7 years). Of the 11 patients, four had AD both clinically and at autopsy, five patients had non-AD disorders at autopsy and the remaining two patients had mixed AD and non-AD pathology (Supplementary Table 5). Using intermediate-to-high ADNC (Montine et al., 2012) as a gold standard, the highest overall accuracy was with FTP visual assessment (1.00, 95%CI 0.72-1.00, AUC 1.00), followed by FTP SUVR quantification (0.82, 95%CI 0.48-0.98, AUC 0.82), and CSF PTau181 (0.64, 95%CI 0.31-0.89, AUC 0.65). Using pathological neurofibrillary tangle Braak stage ≥IV as a gold standard increased accuracy for CSF PTau181 (FTP visual assessment: 0.91, 95%CI 0.59-1.00, FTP SUVR quantification: 0.73, 95%CI 0.39-0.94, CSF PTau181: 0.73, 95%CI 0.39-0.94). Using a composite measure of CSF PTau181 and amyloid (PTau181/Aβ42 ratio >0.028 (Hansson et al., 2018)) also improved accuracy for detecting pathological Braak stage IV or higher (0.91, 95%CI 0.59-1.00).

2.5 Discussion

We compared CSF PTau181, visual assessment and SUVR quantification of FTP to define T-status in a large sample of controls and patients with neurodegenerative diseases accrued via three distinct cohort studies. Overall, we found concordance between all three modalities in 59% of participants. T-status designation varied by both modality and disease stage. FTP visual reads showed the highest sensitivity but generally lower specificity, with many Aβ- cases designated as T+, especially in CN subjects. FTP SUVR showed highest specificity, but sensitivity was low in Aβ+ CN, increasing progressively in MCI and dementia. Using our cutoff value, CSF PTau181 showed

good specificity across disease stages, with high sensitivity in Aβ+ CN but reaching a relative plateau in Aβ+ MCI. Overall, our results support an emerging recognition that T-status is dependent on both the biomarker used (CSF versus PET) and the method of measurement. Each modality and method has strengths and weaknesses that should be considered in the design of studies employing tau biomarkers, and using a combination of biomarkers may be beneficial.

Although biomarkers of tau are used interchangeably in the AT(N) framework (Jack et al., 2016), CSF and PET do not necessarily reflect the same underlying pathological processes, and differences in the biological substrate of each modality could explain some of the discrepancies observed in our results. Specifically, CSF PTau181 may be measuring Aβ-induced changed in tau phosphorylation and secretion as measured in soluble species (Mattsson-Carlgren, Andersson, et al., 2020), while PET radiotracers bind to paired helical filaments of aggregated tau fibrils (Buerger et al., 2006). Additionally, FTP PET visual reads have been shown to reliably identify later stages of tau pathology (Braak stage V-VI)(Fleisher et al., 2020), and SUVR quantification may additionally allow detection of Braak stage IV (Lowe et al., 2016; Pontecorvo et al., 2020; Soleimani-Meigooni et al., 2020). CSF PTau181 has been proposed as an earlier marker of tau pathology (Mattsson-Carlgren, Andersson, et al., 2020), though correlations with autopsy studies are still pending.

Concordance of T-status derived from FTP visual assessment, SUVR quantification and CSF PTau181 was moderate, averaging around 70-75% between modality pairs in the whole cohort. This is in line with previously published results on the concordance between FTP SUVR quantification and CSF PTau181; for example, 83% in a cohort from UCSF using the INNO-BIA AlzBio3 CSF Ptau181 assay(La Joie et al., 2018), 65-77% in BioFINDER using (EUROIMMUN and INNOTEST)(Mattsson-Carlgren, Leuzy, et al., 2020), and 75% in a recent review of ADNI participants using the Elecsys Phospho-Tau (181P) assay (Meyer et al., 2020).

The rates of T+ and agreement between tau biomarkers varied by disease stage. It has been hypothesized that CSF PTau181 becomes positive before tau PET, and may actually decrease in late stages of AD (Fagan et al., 2014; La Joie et al., 2018; Leuzy, Cicognola, et al., 2019; Scholl et al., 2019; Toledo et al., 2013). In contrast, FTP tracks disease progression in a linear way along

disease course, which could explain discordance between the two biomarkers in advanced cases. Mattsson-Carlgren et al. found a higher percentage of T+ with CSF PTau181 compared to SUVR quantification in the inferior temporal cortex in cognitively unimpaired Aβ+ subjects(Mattsson-Carlgren, Leuzy, et al., 2020), and none had significant FTP signal in Braak regions V-VI(Mattsson-Carlgren, Andersson, et al., 2020). This could explain the disproportionate number of T+ cases by CSF PTau181 and/or FTP visual assessment compared to SUVR quantification, which possibly represent early stages of the disease and may be subthreshold for quantification. In contrast, the near perfect agreement in T+ assignment between FTP visual assessment and SUVR quantification found in patients with AD_c is not surprising, given the high level of signal that is generally observed in these individuals (Ossenkoppele et al., 2016; Scholl et al., 2017). The concordance with CSF PTau181 was lower, however, with around 29% AD_c patients being T- on CSF. Similarly, Mattsson et al. had found that 46% of patients with AD dementia and positive tau PET had negative CSF PTau181 (Mattsson et al., 2017), although with a different assay. The lower concordance with CSF PTau181 in this patient group could be explained by differences in dynamics and longitudinal change of each modality. In our cohort, however, the AD_c T- CSF patients did not have lower MMSE to suggest that they represent more advanced cases.

Our results show that FTP visual assessment is a reliable tool for defining T-status in persons with cognitive impairment. Intra- and inter-rater reliability values in our study were similar to previously described visual rating schemes by Sonni et al. (in press) and Fleisher et al.(Fleisher et al., 2020). Expertise and individual rater characteristics could certainly have influenced our results; for example, in this study reads by rater 1 were more specific, while reads by rater 2 were more sensitive. Obtaining consensus by a third rater in discordant cases, however, should limit rater effect. In addition, the pattern of mild temporal binding remains of unknown significance. While we considered it to be T+, possibly reflecting early AD pathology, other groups consider binding restricted to the medial and/or anterior temporal lobes as T- (Fleisher et al., 2020). The relatively high rate of T+ in Aβ- CN subjects in our study (34%) may therefore represent “over-reading” of mild temporal signal and/or noise. However, a higher proportion of Aβ+ CN (71%) were visually read as T+, suggesting that there may be some visually discernable biologically meaningful signal. Further studies with histopathological correlation in cognitively unimpaired

subjects would be needed to guide visual interpretation of mild temporal signal. Modifying our visual rating scheme to consider only advanced AD-like pattern of binding as T+ would likely increase specificity at the expense of sensitivity. Off-target binding, especially in the choroid plexus or at the base of the skull, may also lead to challenges in visual interpretation of the medial temporal lobe, which may limit specificity.

Our comparative accuracy analyses showed that sensitivity for detection of Aβ+ MCI or AD patients can be maximized with FTP visual assessment; however, this method yielded a higher number of T+ in Aβ- participants. Focusing on the 34 Aβ- subjects who were T+ on visual assessment alone, all but one were CN individuals or MCI, and the vast majority were from the ADNI cohort. Qualitatively, these subjects' scans all displayed a similar pattern of FTP binding, consisting of mild signal especially in the temporal lobes. It is known that tau pathology may accumulate in the absence of Aβ in primary age-related tauopathy (PART)(Crary et al., 2014). Other groups have also described increased FTP signal in cognitively unimpaired participants, predominantly in the medial temporal lobes (Lowe et al., 2018). It is possible that visual assessment of tau PET picks up mild elevation in FTP that is not specific to underlying AD pathology, including but not limited to PART. Limiting investigation with tau PET to those subjects that are cognitively impaired or Aβ+, in an attempt to limit false positive visual reads, might be appropriate.

Previous studies have reported higher sensitivity with CSF PTau181 than with FTP SUVR quantification (Meyer et al., 2020). Sensitivity and specificity values for each modality are influenced by the threshold used for binary classification. The cutoff value we used for FTP SUVR has been previously validated (Ossenkoppele et al., 2018) and is similar to those used in previous studies, with most thresholds for quantification of a temporal meta-ROI ranging from 1.2 to 1.4 SUVR (Jack et al., 2017; Maass et al., 2017; Mattsson-Carlgren, Leuzy, et al., 2020; Meyer et al., 2020; Ossenkoppele et al., 2018). Our CSF PTau181 cutoff was similar to previously published threshold with the Elecsys Phospho-Tau (181P) electrochemiluminescence immunoassay in a cohort of ADNI subjects (26.64 pg/mL), though using a different gold standard (Aβ- cognitively unimpaired controls vs Aβ+ AD subjects) (Meyer et al., 2020) and to a proposed cutoff value of 27 pg/mL to predict cognitive decline (Blennow et al., 2019). The threshold we used was also

similar to the 95th percentile of CSF PTau181 in CN Aβ- in the independent ADNI cohort from which our cutoff was derived (29.89 pg/mL, n=271). Given the distribution of CSF PTau181 and FTP SUVR values in patients with discordant T-status, we can hypothesize that near-threshold cases explain a significant proportion of disagreement between modalities. Differences in sensitivity of CSF PTau181 might also be attributed to cohort composition. For example, in the study by Meyer et al., there was a high number of cognitively unimpaired subjects (n=214) and few AD dementia patients (n=11). Finally, some authors have suggested using a ratio of PTau181 to Aβ42 (to detect Aβ+ subjects)(Hansson et al., 2018), which in our subsample of 11 patients with autopsy confirmed diagnosis, led to a higher accuracy of CSF PTau181 for detecting AD. However, we opted not to use this ratio for comparative analyses of T-status, since Aβ42 reflects underlying amyloid pathology and could not be directly compared to measures of tau PET alone.

Recent advances have been reported in the development and validation of plasma assays for PTau181 and PTau217 (Barthelemy et al., 2020; Janelidze, Stomrud, et al., 2020; Karikari et al., 2020; Palmqvist et al., 2020; Thijssen et al., 2020). Plasma measures capture soluble phosphorylated tau species that have crossed the blood-brain barrier and correlate with CSF PTau concentrations and tau PET signal. Early data support the notion that plasma PTau follows the trajectory of CSF PTau, changing in the preclinical disease stage in association with Aβ, and reaching a relative plateau in the early symptomatic stage(Janelidze et al., 2018; Karikari et al., 2020; Lantero Rodriguez et al., 2020; O'Connor et al., 2020). Future work will determine how plasma measures of amyloid, tau and neurodegeneration compare to CSF and imaging markers in implementation of AT(N) classification in the AD Research Framework (Jack et al., 2016).

Major strengths of this study include the large number of subjects recruited from three different studies and spanning a wide range of neurodegenerative conditions, and the direct comparison of both visual and quantitative tau PET with CSF PTau measures. Furthermore, we had autopsy diagnosis available in a small sub-sample. Our study has several limitations. First, there were methodological differences between the three studies, notably in the composition of the cohorts, method of determination of amyloid status, and pre-analytic handling of CSF samples. Second, we used a visual interpretation method that was developed in-house – our method is similar but not identical to the method that has recently been validated, in particular regarding signal

restricted to the anterio-medial temporal lobes(Fleisher et al., 2020). Third, our results cannot be generalized to other tau PET tracers or CSF tau assays than the ones used in our study. Performance of both visual ratings and SUVR quantification of second-generation compounds such as MK-6240, JNJ-067 or RO-948(Leuzy, Chiotis, et al., 2019) may differ from FTP-PET. Similarly, CSF assays using different phosphorylation sites, for example PTau217 which has been shown to have high correlation with FTP(Janelidze, Stomrud, et al., 2020), may yield different estimates of accuracy and inter-modality concordance.

2.6 Conclusion

Biomarkers of tau, as listed in the AT(N) framework, are not interchangeable and show variable concordance depending on method of analysis and cohort. In our study, concordance of T-status derived from FTP visual assessment, SUVR quantification and CSF PTau181 varied across disease stage. An FTP visual read scheme that includes mild temporal binding maximizes sensitivity to early disease stage, including in preclinical AD, while SUVR quantification maximizes specificity. CSF PTau181 shows balanced sensitivity and specificity across the AD continuum. Each modality may offer a complementary role, and a combination of approaches may be ultimately beneficial. Recently published work has suggested measuring T as a continuous rather than binary variable may correlate better with prognosis(Mattsson-Carlgren, Leuzy, et al., 2020). Further work will be needed to compare FTP visual assessment and SUVR quantification to novel plasma biomarkers of phosphorylated tau (Karikari et al., 2020; Palmqvist et al., 2019; Thijssen et al., 2020).

Declarations

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Ethics approval: this study was performed in line with the principles of the Declaration of Helsinki. The study was approved by the University of California (San Francisco and Berkeley), Lawrence Berkeley National Laboratory (LBNL) and the Ethical Committee of Lund University, Sweden institutional review boards for human research. Each ADNI study site received approval from its institutional ethical standards committee on human experimentation.

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Section 3 – Discussion

We sought to examine concordance of T-status defined by CSF PTau181, visual assessment and SUVR quantification of FTP in a large sample of controls and patients with various neurodegenerative conditions, and compare sensitivity and specificity of each modality for diagnosing amyloid-positive symptomatic patients on the AD spectrum.

3.1 Concordance of T-status between biomarkers

Overall concordance between all three modalities was 59%, with between-pair concordance averaging around 70-75%. Although no previous study has directly compared FTP visual assessment to other biomarkers, our results on the agreement (76%) and correlation (r= 0.61) between FTP SUVR quantification and CSF PTau are in line with previously published results, as presented in Table 2 of the introduction. Indeed, studies with similar methodology and using the same CSF assay (Elecsys) showed results that were comparable to ours (75%, r=0.51 (Meyer et al., 2020); 80% (Guo et al., 2021); r=0.37 (Boerwinkle et al., 2021)). In our study, T-status designation varied not only by modality, but also by disease stage, with the lowest concordance found in CN and the highest in AD_c. This finding is not surprising, especially between different measures of tau PET, given the very high signal observed in patients at symptomatic stages of the disease(Ossenkoppele et al., 2016; Scholl et al., 2017).

Although it was initially suggested that fluid and imaging biomarkers of tau might be interchangeable in the AT(N) framework(Jack et al., 2016), there is mounting evidence that they indeed do not reflect the same underlying pathological processes. From a histological standpoint, tau tangles exist in three different maturity stages: pretangles (while tau starts to accumulate in the intracellular space of neurons), mature tangles (intracellular), and ghost tangles (at which point the neuronal body has dissolved and the protein is in the extracellular space)(Moloney et al., 2021). Since FTP binds to more mature forms of tangles, the level of tangle maturity in a subject's brain may influence observed tau PET signal (Lowe et al., 2016; Moloney et al., 2021). In contrast, it is thought that CSF measures of PTau reflect early changes in soluble tau phosphorylation and secretion that occur in response to accumulated Aβ(Mattsson-Carlgren,

Andersson, et al., 2020). These soluble species may represent tau at a different maturity stage, possibly before tangles become aggregated in the intracellular space(Bateman et al., 2012; Moloney et al., 2021). These differences in the biological substrates of CSF and PET may also explain the emerging evidence of temporal mismatch between the two modalities, with fluid biomarkers of tau becoming positive before imaging, and possibly decreasing in later stages of the disease(Fagan et al., 2014; La Joie et al., 2018; Leuzy, Cicognola, et al., 2019; Meyer et al., 2020; Moscoso et al., 2021; Scholl et al., 2019; Toledo et al., 2013). A recent study by Boerwinkle et al. (2021)has pinpointed a timeframe of 4 to 8 years where CSF positivity precedes tau PET. Furthermore, autopsy data suggests that tau PET is relatively insensitive to early Braak stages(Fleisher et al., 2020; Soleimani-Meigooni et al., 2020). Thus, CSF PTau has been proposed has a marker of disease "state", with a more variable temporal evolution, while tau PET reflects disease "stage", following a linear progression along disease course(Mattsson et al., 2017; Scholl et al., 2019). This may explain the variability of T+ agreement observed in our study by disease stage. In particular, individuals who were T+ on CSF but T- on PET seem to be far more frequent than the reverse, and may represent patients in earlier pathological stages of the disease, with insufficient levels of accumulated mature tau tangles to reach detection by PET. Other authors have also replicated these findings(Guo et al., 2021; Mattsson-Carlgren, Leuzy, et al., 2020). Similarly, AD patients that have reached the dementia stage had lower concordance with CSF PTau181 in our study, with 29% of patients that were T- on CSF. Mattsson et al. had also observed this discrepancy with 46% of AD dementia patients being tau PET positive, yet negative on CSF with the ELISA Innotest assay. Further large-scale longitudinal studies with serial measurements of CSF and PET measures would be needed to clarify the temporal dynamics of both biomarkers in later stages of the disease.

3.2 Comparative accuracy of biomarkers

3.2.1 FTP visual interpretation

Comparative analysis of sensitivity and specificity in our study revealed that sensitivity was highest with FTP visual reads (96%), with 100% accuracy compared to autopsy confirmed diagnosis in 11 patients. However, specificity was generally lower with this modality, with many Aβ- CN cases designated as T+. There are multiple possible contributing factors for this finding. First, raters' individual characteristics, training and expertise could certainly influence performance of FTP visual interpretation. Indeed, as illustrated in Supplementary Figure 3, rater 2 tended to "overcall" T+ scans, with the majority of those discordant cases being read as negative by the 3rd rater. However, both intra- and inter-rater reliability analyses in our study were comparable overall to previously published studies using similar visual rating schemes(Fleisher et al., 2020; Sonni et al., 2020). Further studies with a larger number of raters would be needed to better characterize the impact of individual rater sensitivity/specificity patterns.

Another plausible explanation for the lower specificity of FTP visual read observed in our study is the impact of mild temporal binding which we considered as T+. The visual rating scheme proposed by Fleisher et al. (2020) suggests restricting T+ interpretation to signal extending beyond the medial/anterior temporal lobes, which would have increased specificity at the expense of sensitivity in our study. Mild temporal signal on FTP remains of unknown significance for the moment. It may represent non-specific signal or noise, as suggested by the relatively high rate of T+ in Aβ- CN subjects in our study (34%), including possible misinterpretation due to adjacent sites of off-target binding in choroid plexi and the base of the skull. However, a higher proportion of Aβ+ CN (71%) were read as T+ in our study, suggesting that the signal might actually be biologically meaningful, possibly representing early AD tau pathology. A recent study by McSweeney et al. (2020) supports this hypothesis, showing that there is an association of FTP binding with amyloid-status, CSF pTau and CSF total tau in CN subjects with a family history of AD, even while the vast majority (91%) had temporal SUVR values that would be considered subthreshold on quantification. As stated by the authors, these findings suggest that subthreshold FTP signal should not be disregarded and may very well relate to an ongoing pathological process

occurring in the pre-clinical stage of the disease. Further studies with histopathological correlation in CN subjects would be needed to elucidate the true significance of mild temporal signal on visual assessment.

Finally, there is growing evidence that FTP binding is not specific to AD tau pathology, and significant binding may be observed in other neurodegenerative conditions, including tauopathies such as progressive supranuclear palsy and corticobasal degeneration, but also non-tau related proteinopathies(Bevan Jones et al., 2016; R. W. Bevan-Jones et al., 2018; W. R. Bevan-Jones et al., 2018; Ghirelli et al., 2020; Josephs et al., 2016; McMillan et al., 2016; Schonhaut et al., 2017; Soleimani-Meigooni et al., 2020; Tsai et al., 2019; Utianski et al., 2018). While in some cases, a distinct non-AD pattern of binding might be readily identified on visual assessment, it is possible that the distribution of signal may overlap with AD in other cases and lead to a false positive interpretation. In particular, subjects with MAPT mutations, c9orf72 mutations or semantic variant primary progressive aphasia showing intense FTP binding in the temporal lobe may be indistinguishable from AD and be identified as T+(Bevan Jones et al., 2016; R. W. Bevan-Jones et al., 2018; W. R. Bevan-Jones et al., 2018; Soleimani-Meigooni et al., 2020; Tsai et al., 2019). Similarly, primary age-related tauopathy (PART) manifests as mesial temporal tau accumulation in the absence of Aβ(Crary et al., 2014), and may be responsible for mild FTP binding in the temporal lobe in CN subjects observed in our study and reported by other groups(Das et al., 2019; Lowe et al., 2018; Weigand et al., 2020), including one patient with an autopsy-confirmed diagnosis of PART (Lowe et al., 2020). This entity remains somewhat controversial however, with some authors suggesting that A-T+ individuals may actually represent patients early on the AD pathological continuum(Weigand et al., 2020). Other reports have indicated significant FTP binding in dementia with Lewy bodies, hippocampal sclerosis, globular glial tauopathies, and patients with various subtypes of TAR DNA binding protein 43 (TDP-43)(Ferreira et al., 2020; Gomperts et al., 2016; Lowe et al., 2020; Soleimani-Meigooni et al., 2020). Finally, focal signal due to non-neurodegenerative lesions may occasionally be misleading, such as uptake in a meningioma, cavernous malformation, or infarct or hemorrhage, although usually the pattern of binding will be easily recognized upon visual assessment or upon correlation with anatomic imaging (Bruinsma et al., 2017; Lockhart et al., 2017).

3.2.2 FTP SUVR quantification

FTP SUVR showed the highest specificity of all three modalities (91%), at the expanse of lower sensitivity especially in preclinical stages of the disease such as Aβ+ CN. In keeping with our findings, multiple studies have suggested that FTP SUVR quantification reflects relatively high Braak stages and may miss mild elevations in FTP signal, especially when using higher thresholds of positivity(Lowe et al., 2020; McSweeney et al., 2020; Soleimani-Meigooni et al., 2020). Cutoff values remain largely arbitrary and cohort-dependent, and will certainly influence accuracy of this metric in determining T-status. Some authors have proposed using lower SUVR threshold values to better capture subjects in early pre-clinical stages of the disease, which may be especially important in selecting patients for anti-tau therapies (McSweeney et al., 2020).

Although it could be expected that using a quantitative measure alone may reduce specificity owing to FTP signal in non-AD pathologies or off-target binding as detailed in the previous section, only few patients had “false-positive” quantification results in our study, which were readily identified by visual assessment. This is probably due to the relatively low number of non-AD subjects with significant FTP signal in the temporal meta-ROI in our study, although this could theoretically be of importance if this method becomes widely used in the clinical setting.

3.2.3 CSF PTau181

Using our cutoff value, CSF PTau showed high sensitivity in Aβ+ CN but reached a relative plateau in Aβ+ MCI cases, while specificity was good across diagnostic groups. Accuracy of CSF Ptau is most certainly influenced by the threshold value used to determine positivity. Since the Elecsys assay is relatively new, few studies have investigated optimal threshold values for diagnostic purposes in AD subjects, although most cutoffs proposed in the literature to date were similar to the one we used in our study (26.64 pg/mL (Guo et al., 2021; Meyer et al., 2020); 27 pg/mL (Blennow et al., 2019; Karikari et al., 2021). In contrast, Grothe et al. (2021) proposed a significantly lower threshold (19.3 pg/mL) which was optimized for distinguishing pathologically confirmed cases of AD dementia vs CN and non-AD subjects at autopsy. Using a lower threshold such as this one would have likely increased sensitivity in our cohort. The population, gold standard and outcome used to derive threshold values certainly influence accuracy of

quantitative metrics, and near-threshold cases may account for a significant proportion of disagreement between modalities.

3.3 Novel biomarkers and the evolving AT(N) framework

Biomarkers of tau are continuously evolving, and multiple novel targets have emerged in recent years. Considering PET imaging, new radiotracers targeting tau are in development (ex: [^{18}F]JNJ-64326067, [^{18}F]PI-2620, [^{18}F]MK-6240) and show promise for accurately identifying AD tau, with some potential advantages over available molecules such as FTP, including lower off-target binding(Baker et al., 2021; Beyer & Brendel, 2021; Mormino et al., 2021).

One of the most exciting developments in the field of AD research has been the emergence of assays for detection of PTau in plasma, which can be readily and non-invasively obtained through a simple blood draw. Plasma concentrations of PTau (PTau181, PTau217 or PTau231) reflect soluble species that have crossed the blood-brain barrier, and data to date suggests that this biomarker correlates with both CSF PTau and tau PET(Barthelemy et al., 2020; Guo et al., 2021; Janelidze et al., 2021; Janelidze, Mattsson, et al., 2020; Karikari et al., 2021; Karikari et al., 2020; Keshavan et al., 2021; Palmqvist et al., 2020; Suarez-Calvet et al., 2020; Thijssen et al., 2020). There is limited knowledge about the temporal dynamics of plasma biomarkers, but early evidence supports the notion that plasma biomarkers of tau follow the same trajectory as CSF biomarkers, becoming positive early in the disease process, likely before tau PET, and reaching a plateau in later stages(Janelidze et al., 2021; Janelidze et al., 2018; Karikari et al., 2020; Lantero Rodriguez et al., 2020; Moscoso et al., 2021; O'Connor et al., 2020). The concordance of these novel biomarkers with FTP imaging, especially with visual assessment algorithms given the recent approval for clinical use of tau PET, remains to be determined.

In addition to novel biomarkers of tau, evolving understanding of the multifactorial pathological disease mechanisms at play in AD have led to a recent proposal of a modified ATX(N) system(Hampel et al., 2021). As such, the fourth ‘X’ biomarker category includes fluid and imaging markers of various additional pathophysiological processes such as dysfunctions of synaptic

activity, blood-brain barrier and neuroinflammation. Additionally, a growing number of authors suggest that the A, T and N categories need not necessarily be used as binary indicators, but that continuous measures or inclusion of “intermediate” categories may be more informative, in an attempt to limit the arbitrary effect of thresholds (Hampel et al., 2021; Jack et al., 2016; Mattsson-Carlgren, Leuzy, et al., 2020). Others have also argued for distinguishing fluid and imaging biomarkers in the AT(N) framework, rather than using them interchangeably(Guo et al., 2021).

Section 4 – Conclusion

Fluid and imaging biomarkers of tau, as listed in the AT(N) framework, are not interchangeable, and concordance of T-status seems to depend on both method of analysis and disease stage. Each modality offers advantages that should be interpreted in light of its weaknesses and tailored to the specific goals of research studies employing these biomarkers. Fluid biomarkers are more readily accessible and less expensive and have the added advantage of allowing measurements of multiple molecular biomarkers in a single sample(Grothe et al., 2021). As such, the use of CSF or plasma may be favored as an initial screening tool, especially in large-scale or population-wide settings. PET imaging, however, offers invaluable insight into disease stage and topography of tau pathology, which may be of clinical importance for diagnosis and identification of specific disease phenotypes, as well as prognosis and prediction of future decline(Graff-Radford et al., 2021; La Joie et al., 2020). Using a combination of biomarkers, therefore, may be beneficial and optimize sensitivity/specificity for diagnosis of AD. Future research will need to focus on the concordance of novel biomarkers with PET imaging, and investigate optimal detection of early disease stages (for example mesial temporal lobe binding thresholds) for enrolling patients in trials of anti-tau pharmacotherapy.

Accurate diagnosis of AD will be of utmost importance in the near future to ensure judicious and cost-effective use of therapy, especially with the recent approval of an anti-amyloid antibody treatment (Aducanumab) in the United States by the FDA. Considering the high cost (56,000$US annually), controversial benefit and potential risk profile of this novel therapy, a biomarker-confirmed diagnosis of AD is likely to become the standard of practice in the clinical setting(Rabinovici, 2021).

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Supplementary material

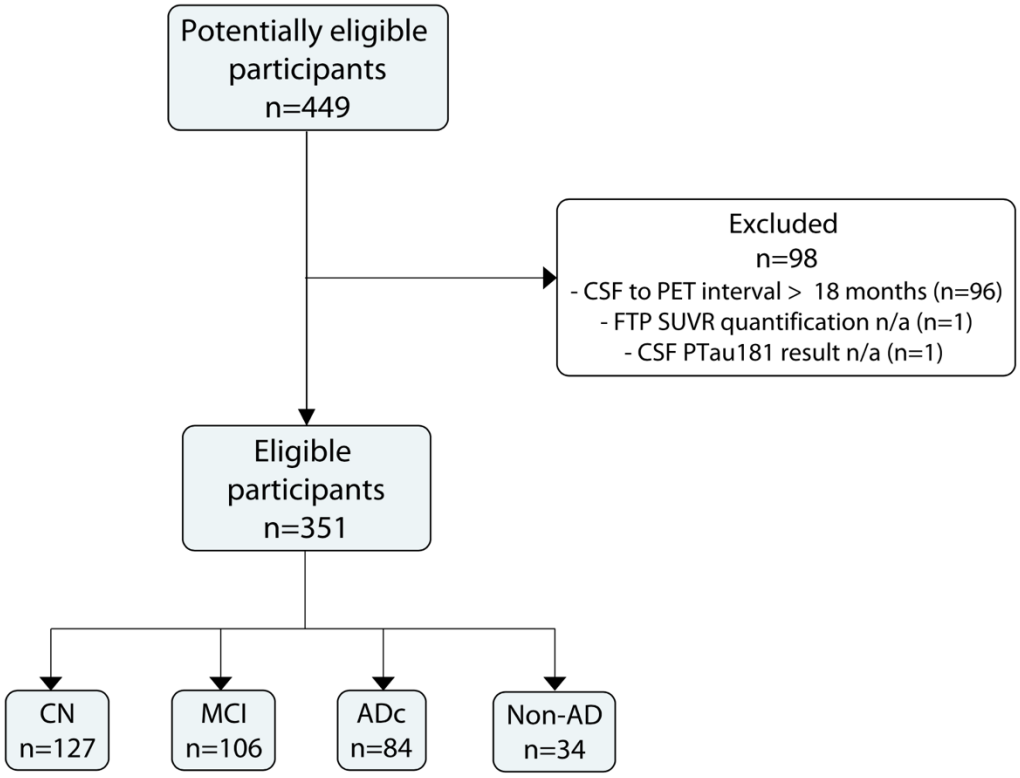
Supplementary Table 1.

	ADNI (n=179)	UCSF ADRC (n=98)	BioFINDER (n=74)
Age (y)	72.3 ± 8.1	62.8 ± 8.5	75.6 ± 4.7
Sex (M, %)	76 (42%)	48 (49%)	32 (43%)
Education (y)	16.3 ± 2.5	16.9 ± 3.7	12.0 ± 3.6
MMSE	27.7 ± 2.7	22.8 ± 6.2	26.9 ±
Amyloid status (Aβ+, %)	85 (47%)	64 (65%)	47 (64%)
Clinical diagnosis (%)			
CN	80 (45%)	0 (0%)	47 (64%)
MCI	83 (46%)	15 (15%)	8 (11%)
AD_c	16 (9%)	50 (51%)	18 (24%)
non-AD	0 (0%)	33 (34%)	1 (1%)

Supplementary Table 1. - Patient characteristics from the final cohort (n=351) by site.

Mean ± SD is shown for continuous variables. CN: cognitively normal, MCI: mild cognitive impairment, ADc: Alzheimer's disease dementia, non-ADc: non-AD disorders

Supplementary Figure 1.



Supplementary Figure 1. - Study design

CN: cognitively normal, MCI: mild cognitive impairment, AD: Alzheimer's disease dementia, non- ADc: non-Alzheimer's disease disorders, n/a: not available

Supplementary Table 2.

	UCSF ADRC	ADNI	BioFINDER
Determination of amyloid status	[^{11}C]PIB PET global neocortical SUVR > 1.21 (ref 1)	[^{18}F]florbetapir SUVR > 1.11 [^{18}F]florbetaben SUVR> 1.08 (ref 2,3)	[^{18}F]Flutemetamol PET global neocortical SUVR > 0.69 or CSF Aβ42 < 650 ng/L (ELISA Innotest) (ref 4)
MRI acquisition	3T Tim Trio or Prisma scanner (Siemens Medical Solutions)	3T scanners (multiple) (http://adni.loni.usc.edu/wp-content/themes/freshnews-dev-v2/documents/mri/ADNI3-MRI-protocols.pdf)	3T Tim Trio or Skyra scanner (Siemens Medical Solutions)
PET [^{18}F]flortaucipir acquisition	Biograph 6 Truepoint PET/CT (Siemens Medical Solutions) 80-100 min post injection	Multiple scanners (http://adni.loni.usc.edu/wp-content/uploads/2012/10/ADNI3_PET-Tech-Manual_V2.0_20161206.pdf) 75-105 min post injection	Discovery 690 PET/CT (GE Medical Systems) 80-100 min post injection
PET processing	Processed locally	Extracted SUVR values downloaded from adni.loni.usc.edu	Extracted SUVR values provided from Lund University
CSF collection	ADNI protocol (adni.loni.usc.edu)		Alzheimer's Association Flow Chart for CSF biomarkers (ref 5)

Supplementary Table 2. - Detailed methods for determination of amyloid status, imaging parameters and CSF collection for each cohort

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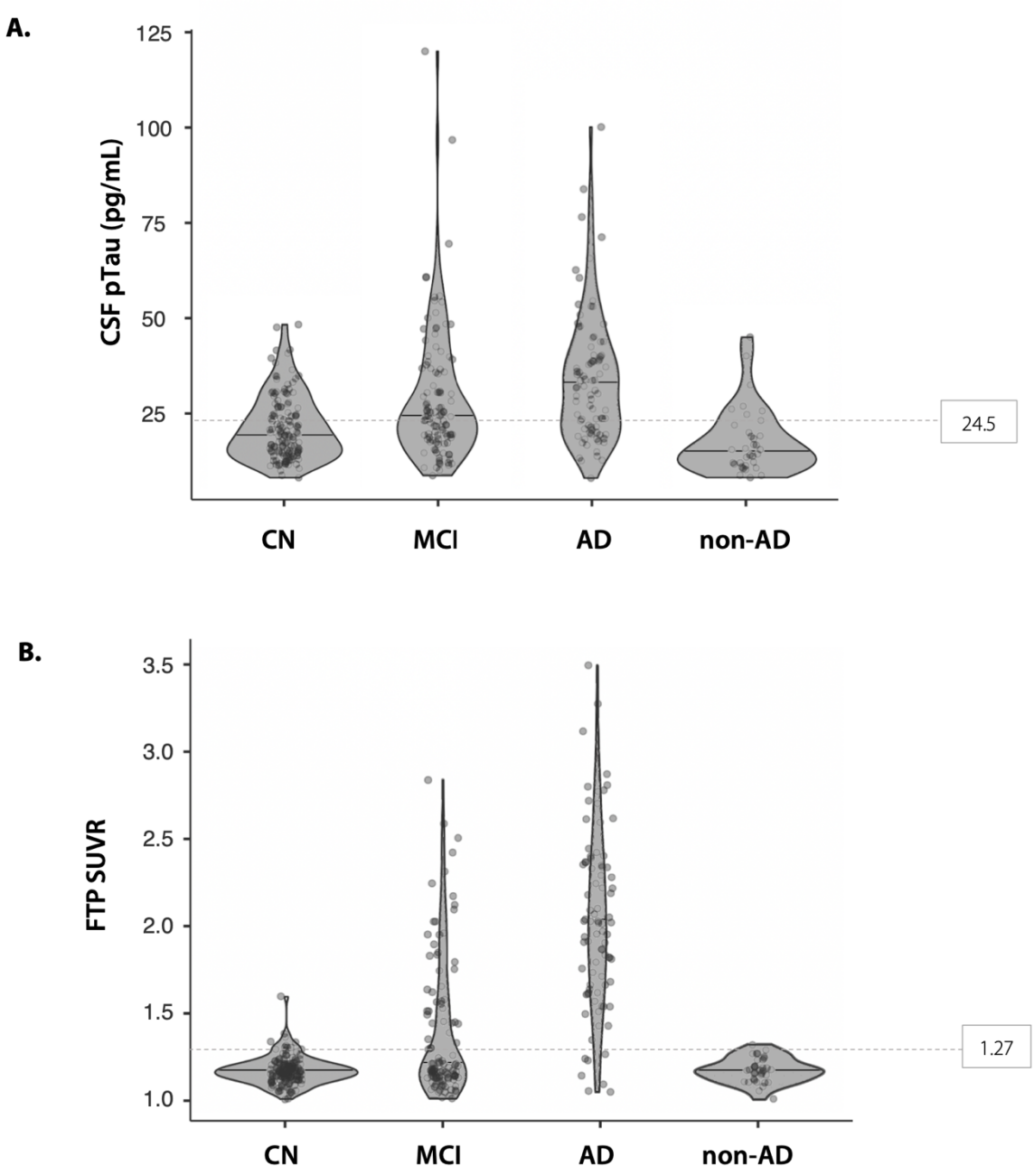
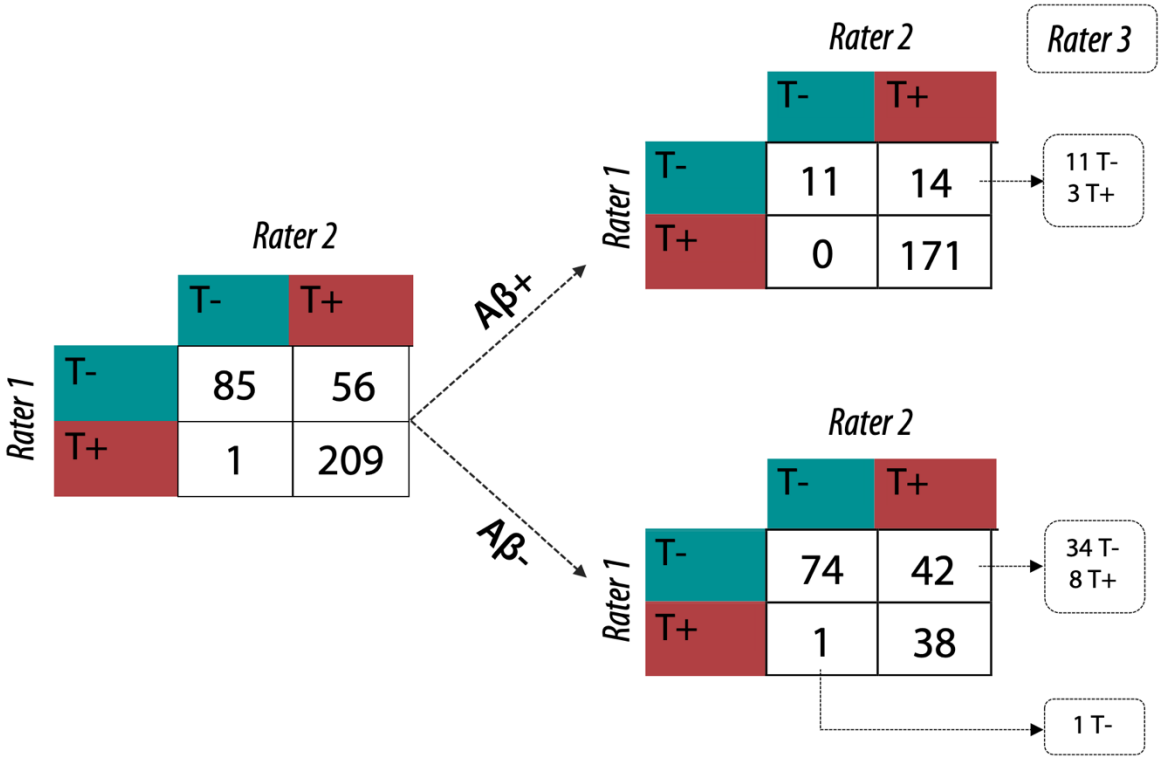
Supplementary Figure 2.



Supplementary Figure 2. - Violin plots of CSF PTau181 (A) and FTP SUVR (B) values by clinical clinical diagnosis

Supplementary Figure 3.



Supplementary Figure 3. - Assigned T-status on FTP visual assessment by amyloid status for both raters (n=351)

Consensus T-status from 3rd rater is shown in dotted bubbles for discordant cases (n=57)

Supplementary Table 3.

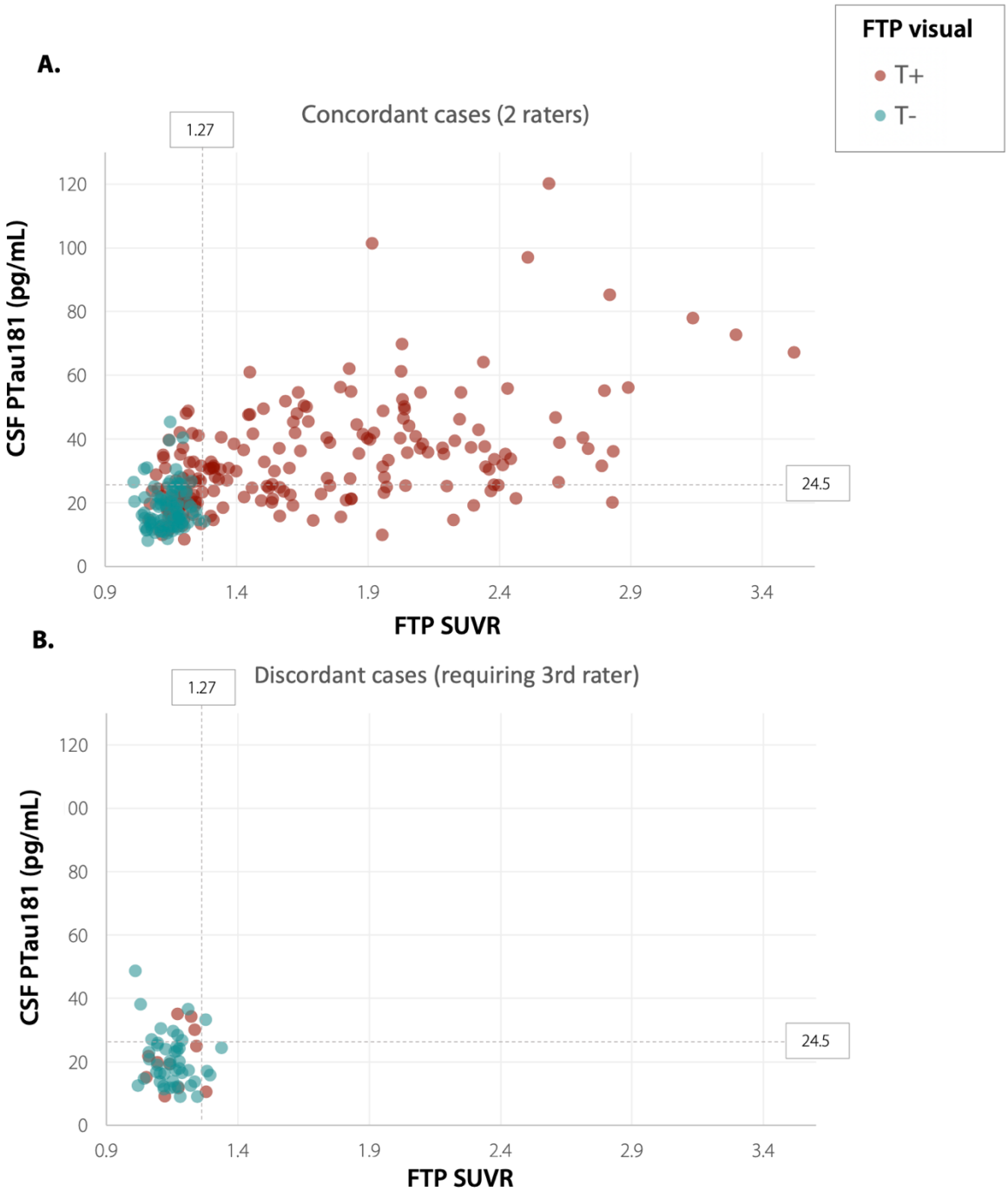
	FTP visual assessment	FTP SUVR quantification	CSF pTau
FTP visual assessment	-	PPA: 96% NPA: 59%	PPA: 83% NPA: 54%
FTP SUVR quantification	PPA: 61% NPA: 96%	-	PPA: 67% NPA: 84%
CSF pTau	PPA: 61% NPA: 79%	PPA: 78% NPA: 75%	-

Supplementary Table 3. Positive and negative percent agreement between modalities

PPA: positive percent agreement, NPA: negative percent agreement

Row names indicate the index test that was considered for these analyses (ex: CSF pTau vs FTP visual assessment: in 61% of cases when CSF pTau was positive, visual assessment was also positive).

Supplementary Figure 4.



Supplementary Figure 4. - *Distribution of CSF PTau181 and FTP SUVR in T+ and T- cases on visual assessment by consensus from two raters (A, n=295) versus three raters (B, n=56)*

Supplementary Table 4.

	CSF PTau181 T+ (n=60)	CSF PTau181 T- (n=24)	p value
Age (y)	65.4 ± 9.2	68.0 ± 9.1	p= .25
MMSE	20.3 ± 5.5	21.3 ± 4.6	p= .40
CSF PTau181 (pg/mL)	42.5 ± 15.4	19.4 ± 3.4	p< .001
FTP SUVR	2.16 ± 0.48	1.71 ± 0.47	p< .001

Supplementary Table 4. - Characteristics of patients with clinical diagnosis of AD (n=84, 81Aβ+), and T- or T+ status by CSF PTau181

Mean ± standard deviation are shown for continuous variables

Supplementary Table 5.

Subject	Clinical diagnosis	Pathological diagnosis	Thal phase (0-5)	Braak stage (0-6)	CSF PTau181 (pg/mL)	FTP SUVR	FTP visual
1	bvFTD	FTLD-tau (MAPT) & AD	5	4	8.4	1.20	positive
2	PSP	FTLD-tau (PSP) & AD	5	3	10.5	1.28	positive
3	PSP	FTLD-tau (PSP)	1	2	16.1	1.18	negative
4	PSP	FTLD-tau (CBD)	0	1	11.9	1.16	negative
5	AD	AD	5	6	37.6	2.35	positive
6	nfvPPA	FTLD-tau (PSP)	2	2	25.9	1.18	negative
7	bvFTD	AGD	0	3	11.5	1.06	negative
8	bvFTD	FTLD-tau (MAPT)	0	0	17.0	1.28	negative
9	AD	AD	5	6	55.1	2.80	positive
10	AD	AD	5	6	46.4	2.03	positive
11	AD	AD	5	6	19.1	2.30	positive

Supplementary Table 5. - Details of patient with autopsy confirmed diagnosis (n=11) in the UCSF ADRC cohort

bvFTD: behavioral variant fronto-temporal dementia, FTLD: fronto-temporal lobar degeneration, MAPT: microtubule associated protein tau, AD: Alzheimer's disease, PSP: progressive supranuclear palsy, CBD: corticobasal degeneration, nfvPPA: non-fluent variant primary progressive aphasia, AGD: argyrophilic grain disease