SUPPLEMENTARY MATERIAL

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

European Journal of Nuclear Medicine and Molecular Imaging

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)*

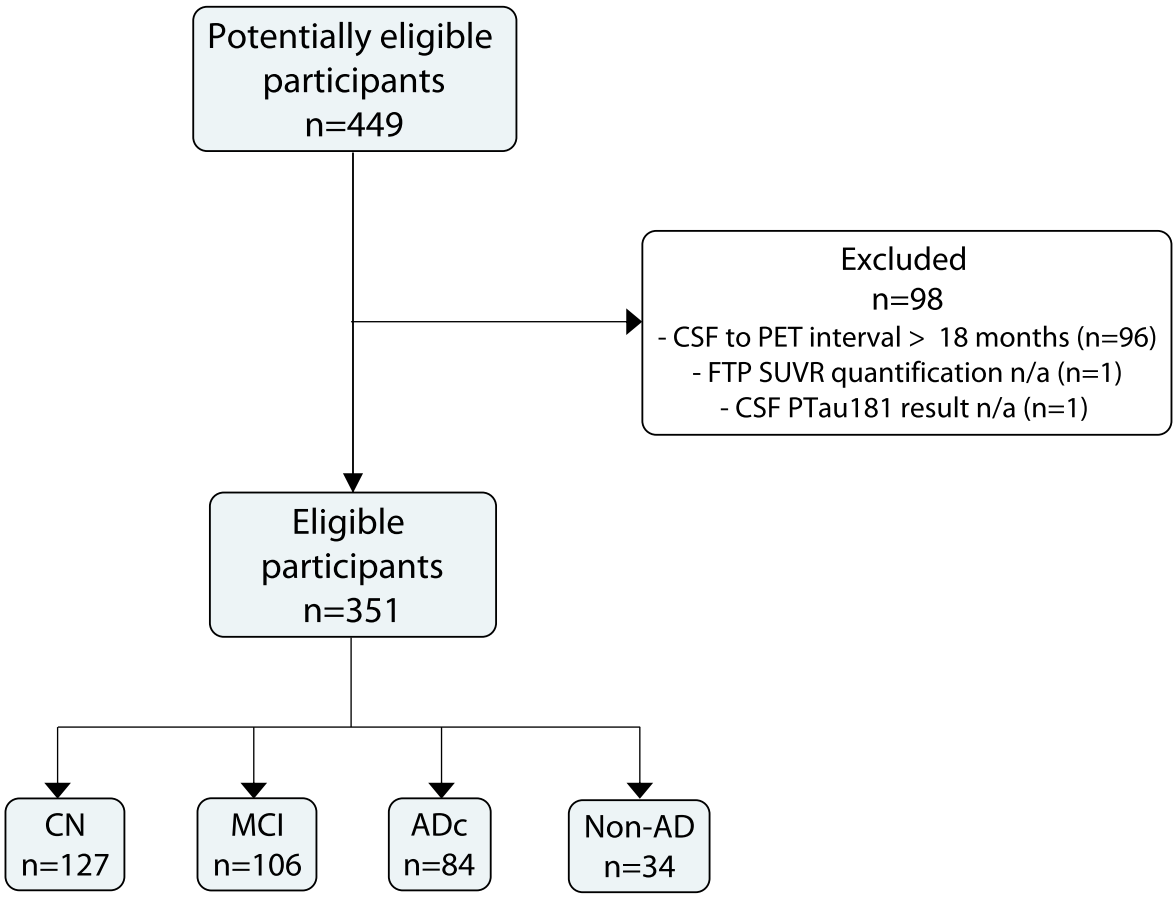
[a] *Memory and Aging Center, Dept. of Neurology, University of California San Francisco, San Francisco, CA, US*
[b] *Lawrence Berkeley National Laboratory, Berkeley, CA, US*
[c] *Roche Diagnostics GmbH, Penzberg, Germany*
[d] *Clinical Memory Research Unit, Lund University, Lund, Sweden*
[e] *Helen 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*

Corresponding author: provost.karine@gmail.com

	ADNI (n=179)	UCSF ADRC (n=98)	BioFINDER (n=74)
Age	72.3 ± 8.1	62.8 ± 8.5	75.6 ± 4.7
Sex (M, %)	76 (42%)	48 (49%)	32 (43%)
Education	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, AD_c: Alzheimer's disease dementia, non-AD_c: non-AD disorders



Supplementary Figure 1. Study design

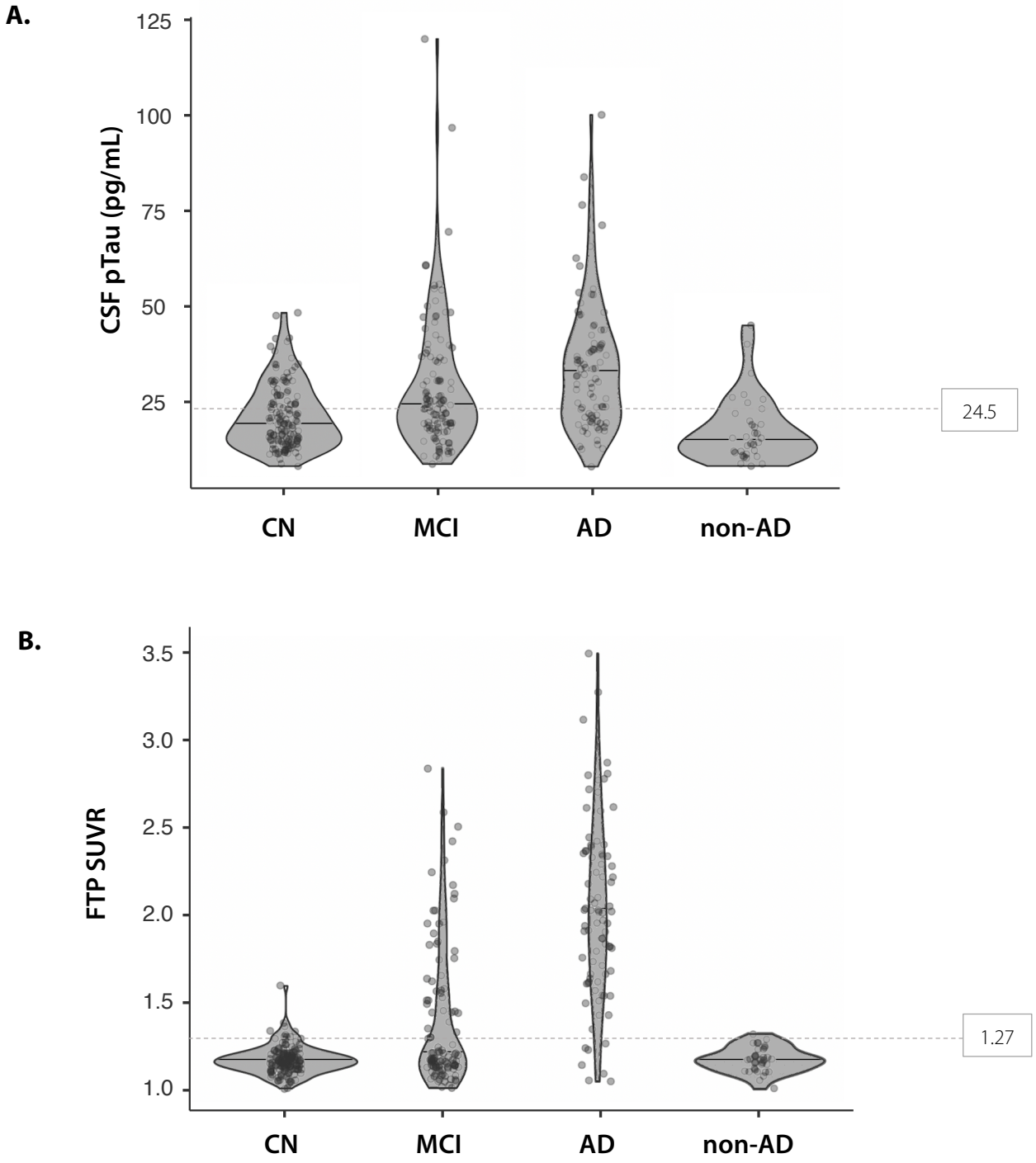
CN: cognitively normal, MCI: mild cognitive impairment, AD: Alzheimer's disease dementia, non-AD$_c$: non-Alzheimer's disease disorders, n/a: not available

	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)

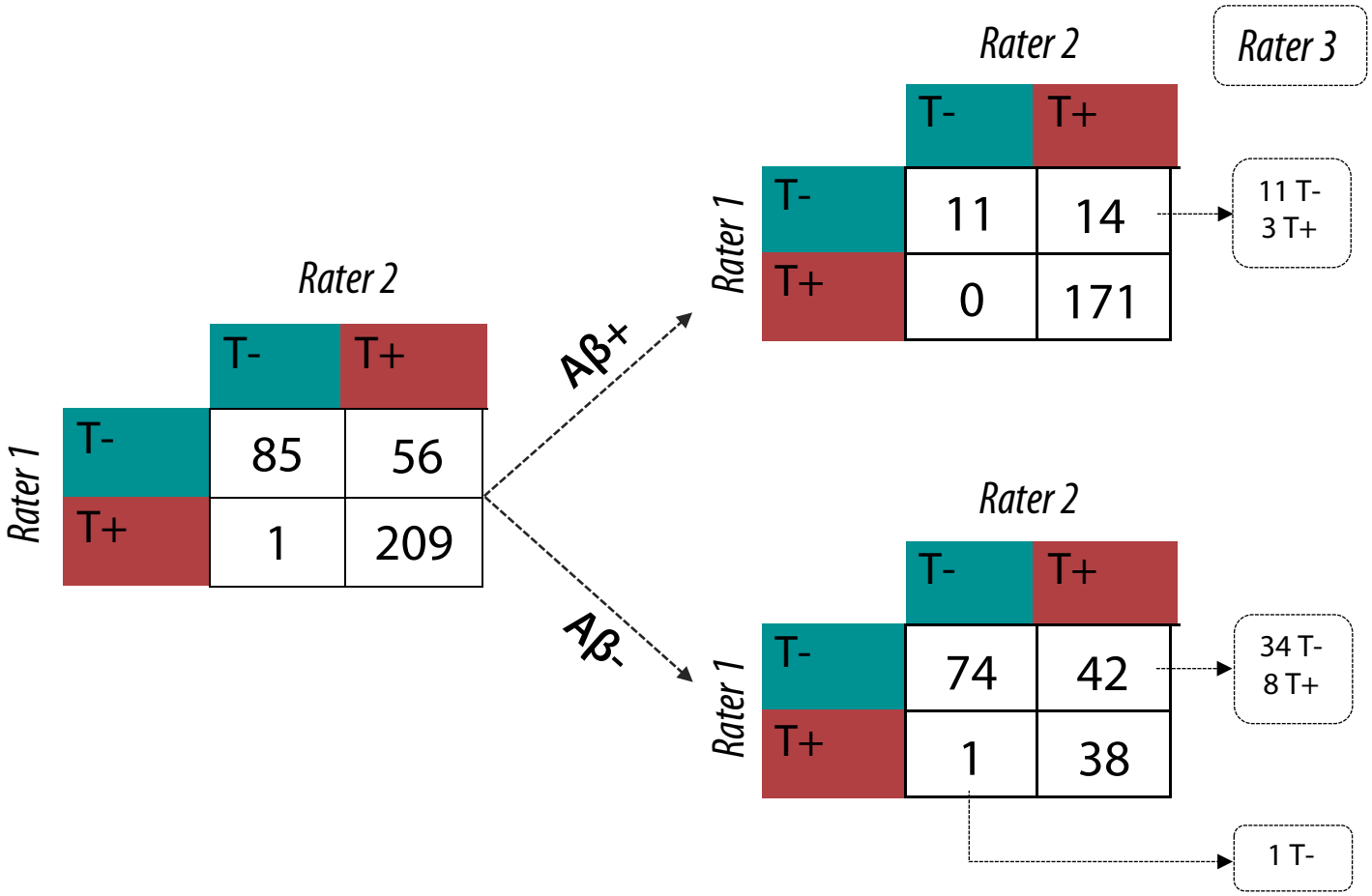
Supplementary Table 2. Detailed methods for determination of amyloid status, imaging parameters and CSF collection for each cohort

REFERENCES

1. Ossenkoppele R, Schonhaut DR, Scholl M, Lockhart SN, Ayakta N, Baker SL, et al. Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. Brain. 2016;139:1551-67. doi:10.1093/brain/aww027.
2. Joshi AD, Pontecorvo MJ, Clark CM, et al. Florbetapir F18 Study Investigators. Performance characteristics of amyloid PET with florbetapir F18 in patients with alzheimer's disease and cognitively normal subjects. *J Nucl Med*. 2012;53(3):378-384.
3. Clark CM, Schneider JA, Bedell BJ, et al. AV45-A07 Study Group. Use of florbetapir-PET for imaging beta-amyloid pathology. *JAMA*. 2011;305 (3):275-283. doi:10.1001/jama.2010.2008
4. Ossenkoppele R, Rabinovici GD, Smith R, Cho H, Scholl M, Strandberg O, et al. Discriminative Accuracy of [18F]flortaucipir Positron Emission Tomography for Alzheimer Disease vs Other Neurodegenerative Disorders. JAMA. 2018;320:1151-62.
5. Blennow K, Hampel H, Weiner M, Zetterberg H. Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. Nat Rev Neurol. 2010;6:131-44. doi:10.1038/nrneurol.2010.4.



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

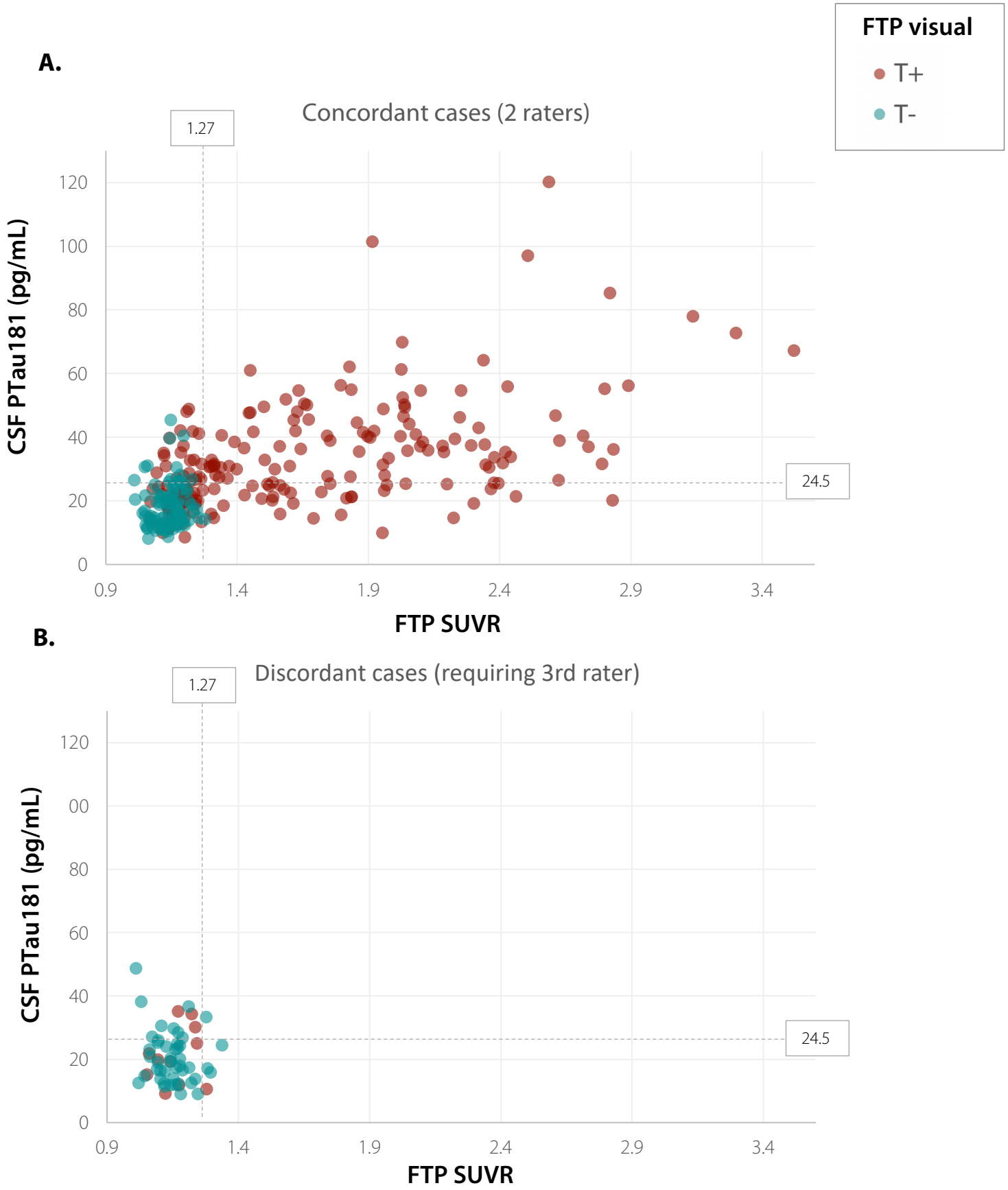


Supplementary Figure 3. Assigned T-status on FTP visual assessment by amyloid status for both raters (n=351)

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

	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. 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)

	CSF PTau181 T+ (n=60)	CSF PTau181 T- (n=24)	p value
Age	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

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,