^{18}F-APN-1607: A Promising PET Tracer for Tauopathies of All Isoform Repeat Types

Brad Navia, MD, PhD

Chief Medical Officer

Aprinoia Therapeutics

APRINOIA

Disclosures

APRINOIA

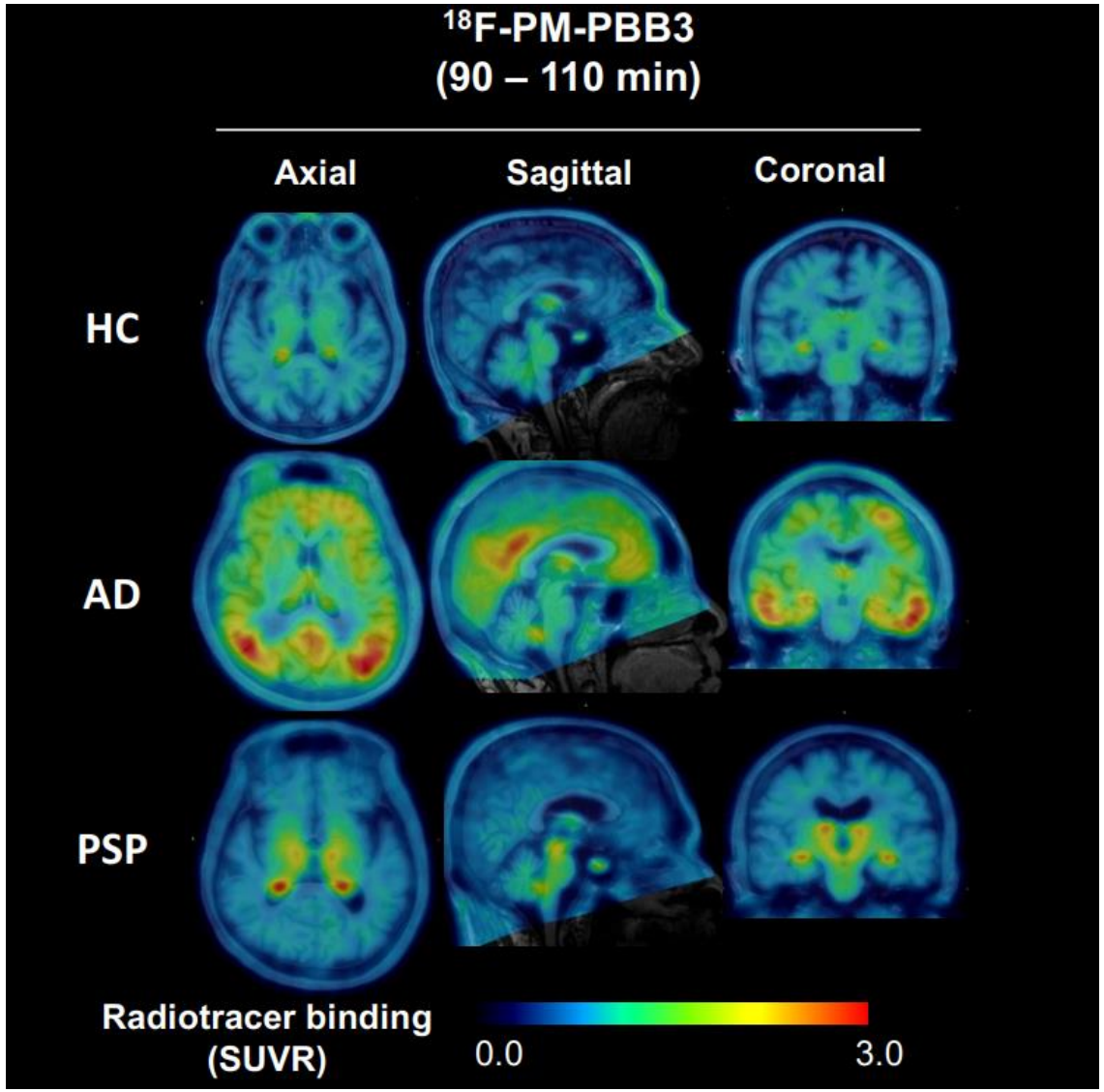
- Employee and a share holder of Aprinoia Therapeutics

APN-1607: A First- in- Class 3R/4R Tau Tracer

APRINOIA

- Background
  - ^{18}F-APN-1607 also known as APN-1607, ^{18}F-PM-PBB3, Florzolotau (INN)
- Nonclinical and binding profiles
- Clinical data and pathological correlations
  - Alzheimer's Disease (AD)
  - Progressive Supranuclear palsy (PSP)
  - Corticobasal Syndrome (CBS)
  - Frontal Temporal Dementia (FTD) and Pick's Disease (PiD)
  - Traumatic Brain Injury/CTE
- Conclusion
  - APN-1607 may provide a useful PET tau tracer for the diagnosis of a broad range of 3R and 4R Tauopathies

APN-1607: A Promising PET Tracer for Tauopathies of All IsoformTypes



APN-1607: A First- in- Class 3R/4R Tau Tracer

APRINOIA

- Only one tau PET tracer approved- Tauvid for the diagnosis of AD
- Several second-generation tau tracers are in development
- The development of a 4R tau tracer remains a significant unmet need
  - Early reliable diagnosis and differentiation from other disorders
  - Patient selection for therapeutic trials and monitoring for treatment response
- Makoto Higuchi and colleagues, QST, Japan developed ^{18}F-APN-1607 (APN-1607, Florzolotau)
  - World-wide license granted to APRINOIA Therapeutics
  - Large body of data supports APN-1607 as a first-in-class 3R/4R tau tracer

APN-1607: A First- in- Class 3R/4R Tau Tracer

APRINOIA

Challenges with Current PET Tracers[1]

^{18}F-flortaucipir (Tauvid®, Lilly)
- FDA-approved in 2020

- Off-target binding (MAO-B)
- Poor early detection of AD
- Limited use in non-AD tauopathies

^{18}F-PI-2620 (Life Molecular Imaging)

^{18}F-RO-948 (Roche)

- Reduced off-target binding, but limitations remain due to similar chemistry as Tauvid®

^{18}F-MK-6240 (Merck)

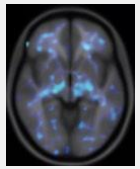
^{18}F-PI-2620 (Life Molecular Imaging)*

- Being investigated for 4R tauopathies, however data is inconsistent

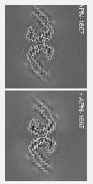
Useful in AD

^{18}F-APN-1607*

- Clinically administered in >3000 subjects; Phase 3 in China and Phase 2 in the US
- **Selectivc**, No MAO-A/B binding



- Binds to **4R tau**, so it can be used in preclinical models, e.g., **rTg4510 mouse model**



- Only tau tracer with **CryoEM structure** of APN-1607 bound to AD tau available, allowing further structure-based drug design[2]
- Tau tracer with **wide utility** in AD and many non-AD tauopathies, including PSP, CBS, bvFTD, PNFA, & Pick's

useful in all tauopathies

* Published data in PSP

1 Jie et al. FDA-Approved PET Tracer for Imaging Tau Pathology in Alzheimer's Disease. Pharmaceuticals 2021, 14, 110.

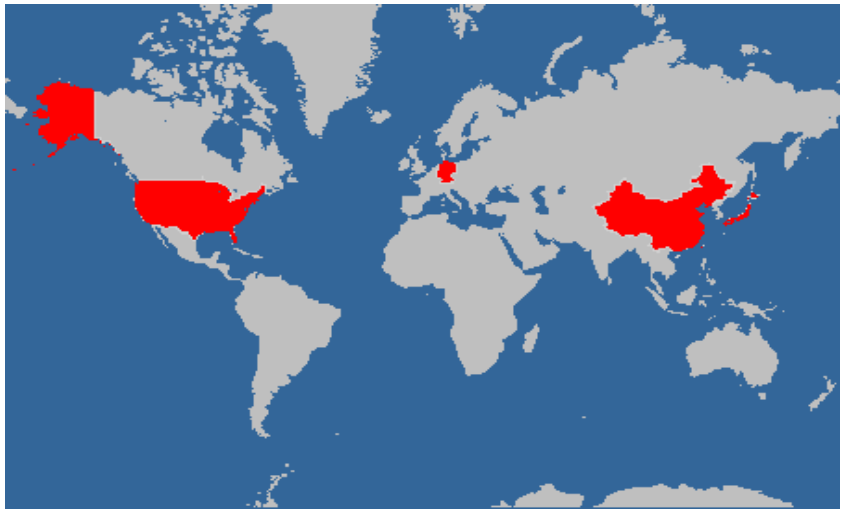
2 Shi, Y., et al. Cryo-EM structures of tau filaments from Alzheimer's disease with PET ligand APN-1607. Acta Neuropathol 141, 697–708 (2021).

*APN-1607 is light sensitive, <500nm; requires special lighting conditions

APN-1607: Current Development Status

APRINOIA

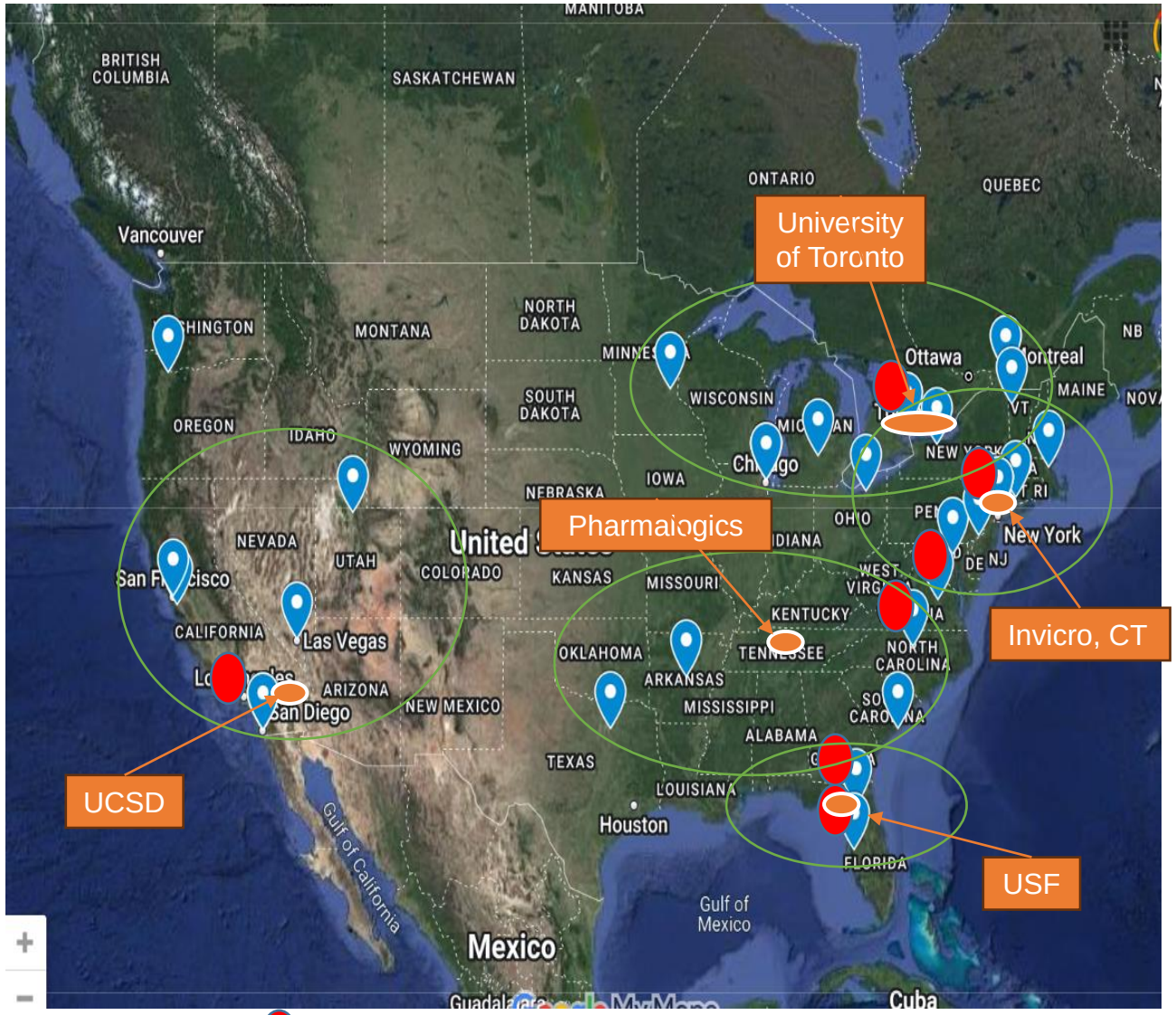
- >3000 individuals have been scanned to date at 15 sites in several countries.
  - Diverse diagnoses:
    - AD spectrum
    - 4R tauopathies (esp. PSP and variants); CBS; also various types of FTD, PiD (3R)
    - CTE
  - Cross-sectional and longitudinal studies
- Sponsored studies:
  - Phase 1 studies in US: favorable dosimetry and test/retest data
  - Phase 2 study in AD (US, Taiwan, Japan)
  - Single Pivotal Phase 3 study in AD (China) for approval
  - PI-initiated studies in Taiwan, Japan, China and Germany; planned in US
  - Single global Phase 3 in PSP planned in US, Canada, EU (UK, Germany), Japan, Taiwan
- PSP: Orphan disorder designation (US)

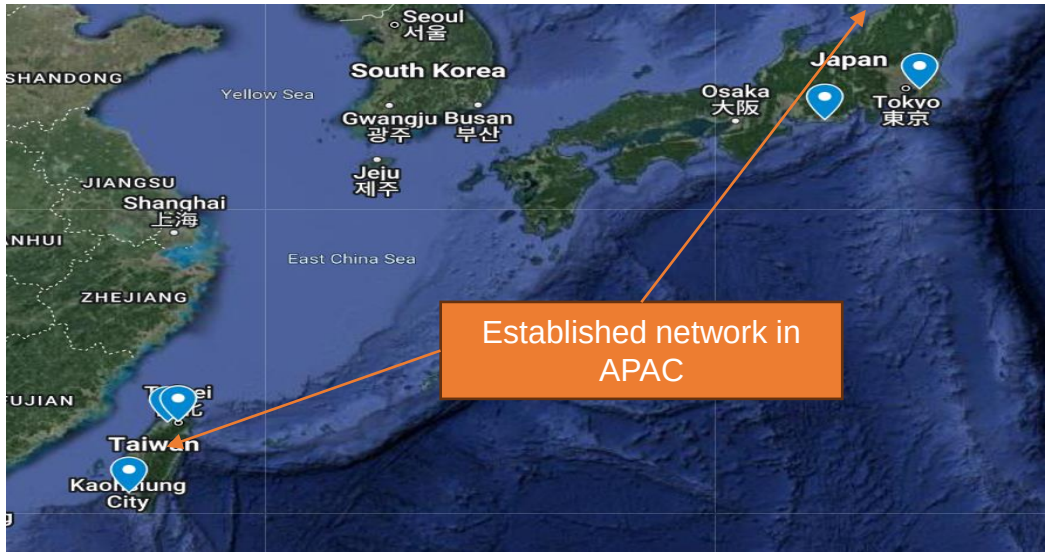


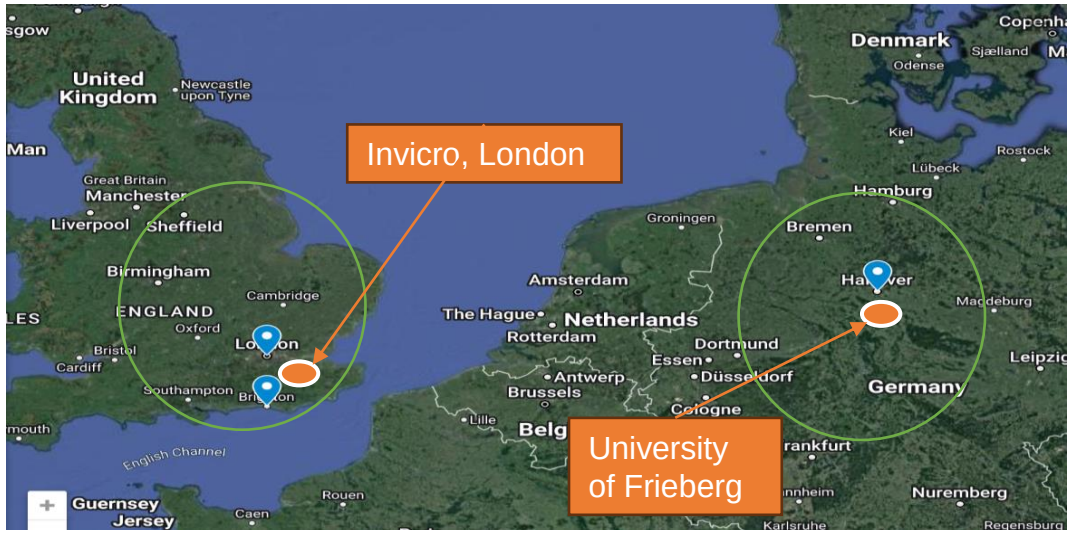
Diagnosis	N
Cognitively intact	460
MCI	388
AD	673
PSP	471
FTD	141
CBS	70
PD	73
MSA	45
VCI/VaD	80
Other	392

APN-1607 PSP Phase 3: Planned CMO Network and Clinical Site Distribution

APRINOIA

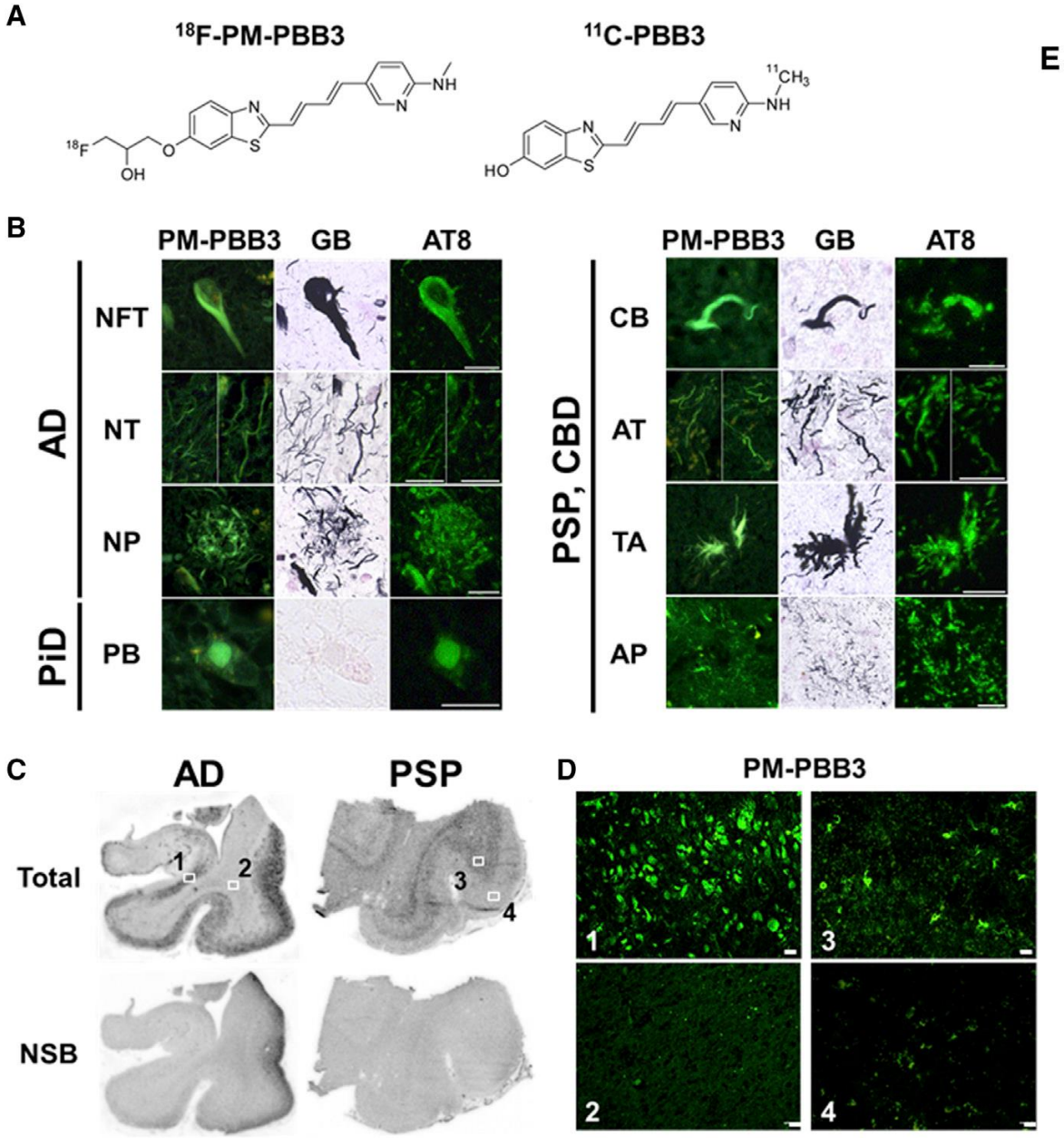


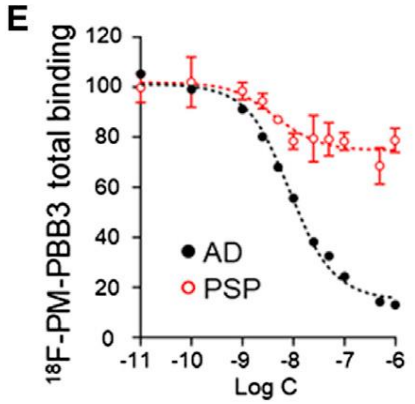




APN-1607: Nonclinical Profile

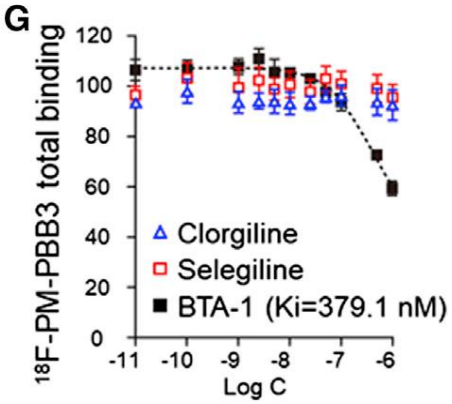
APRINOIA





F

	Kd (nM)	B max (pmol/g)	BP
AD			
PM-PBB3	7.6	5743	752.7
PBB3	6.4	3934	614.7
PSP			
PM-PBB3	3.4	688.2	199.9
PBB3 *	4.8	589.7	122.5



Tagai 2020

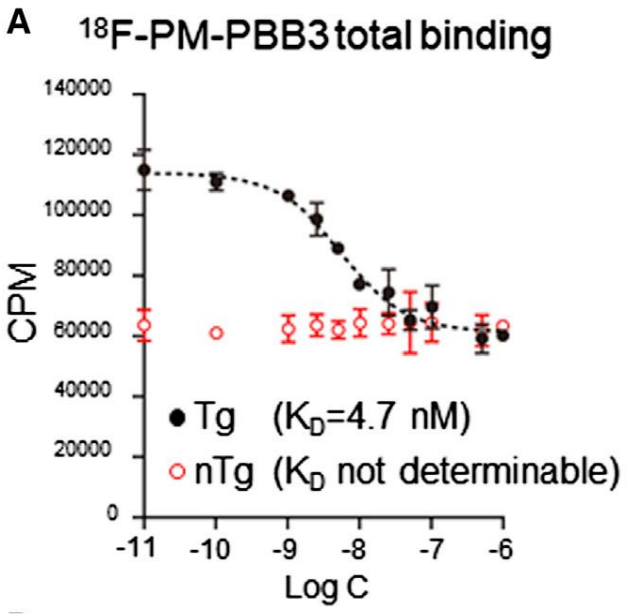
Postmortem tauopathy brain tissue

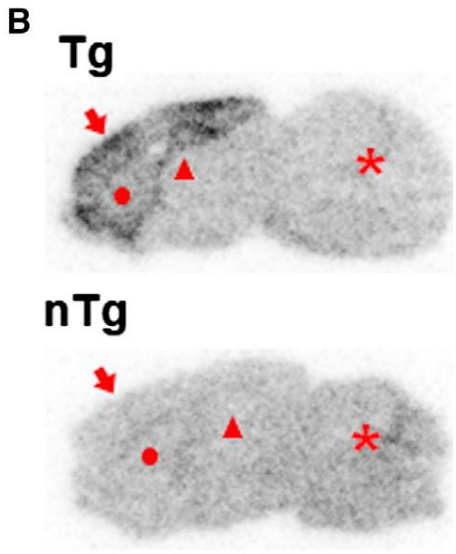
- Labels aggregated tau in disease-specific structures (nM affinity in AD, PSP, CBD)
- Kinetics illuminated by 2-photon microscopy
- No significant binding to protein panel in vitro
- No binding to MAO A/B by competition assays

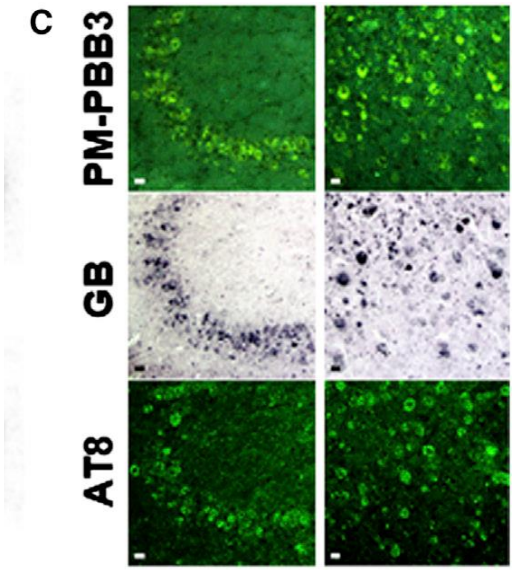
Tagai, et al; Neuron 2021

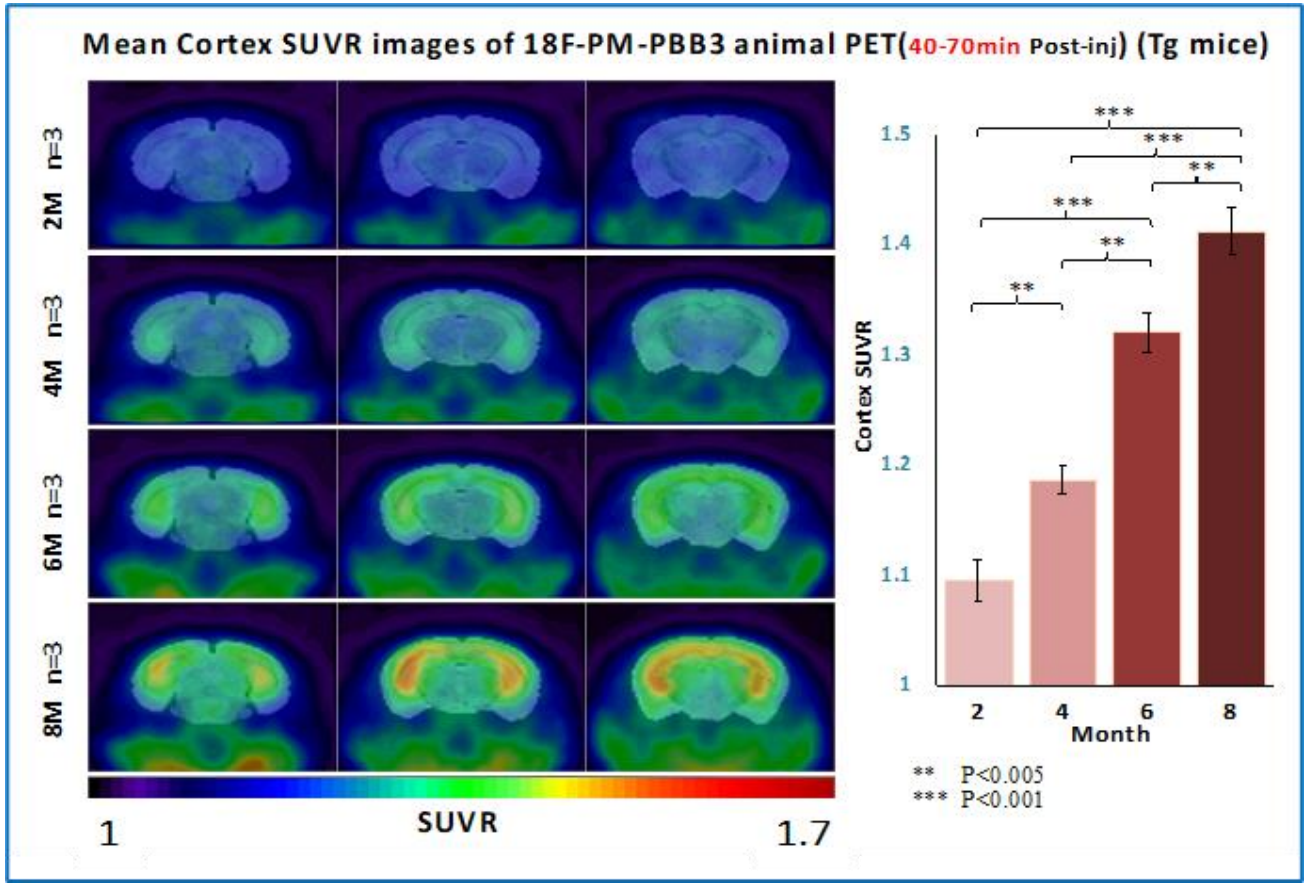
APN-1607: Nonclinical Profile : rTg4510 (4R Tau)

APRINOIA









(Weng 2020; data on file)

rTg4510 mouse

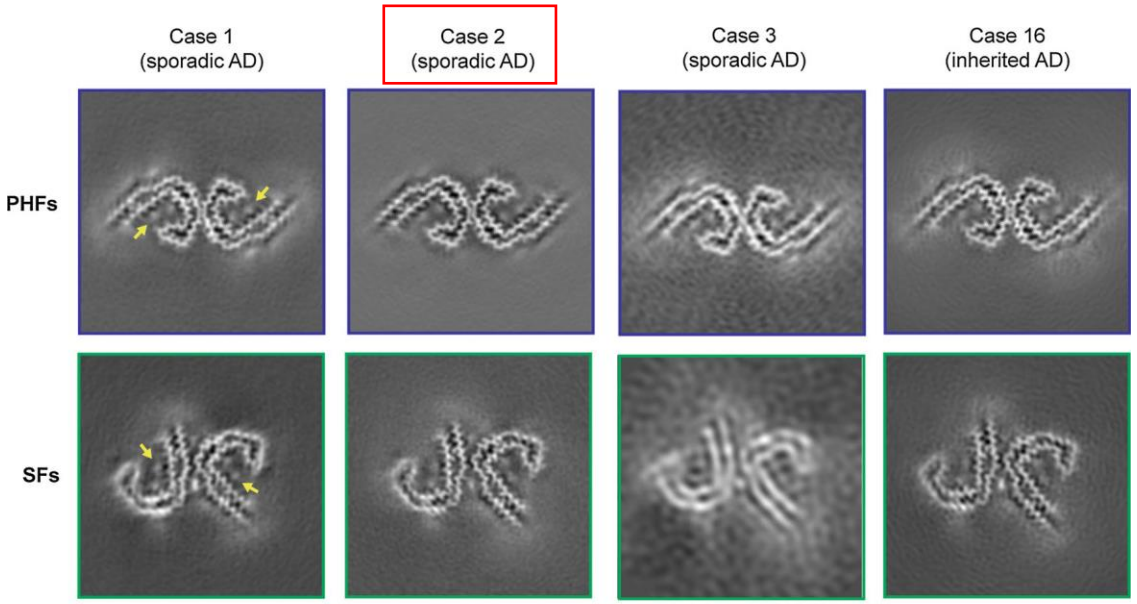
- No binding in nTg; detects 4R tau aggregates in Tg, with linear age-related signal increase
- Useful for therapeutics development

Tagai,et al; Neuron, 2021

APN-1607: Cryo-EM Identifies Binding in AD Tau folds

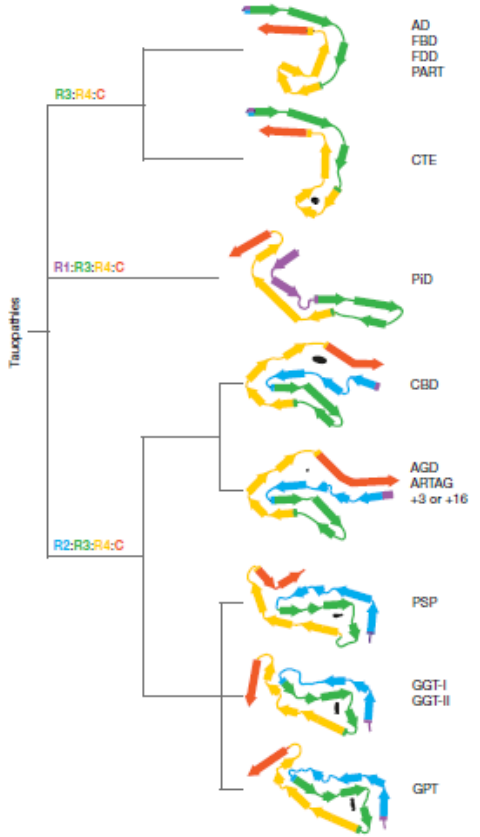
APRINOIA

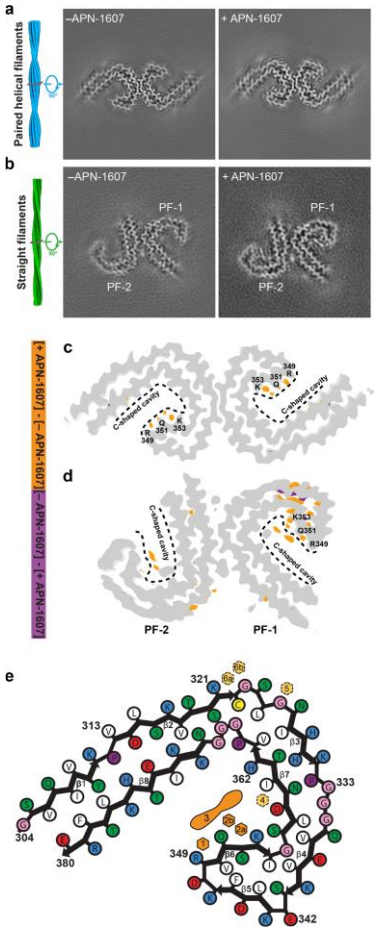
- Cryo-EM to determine the binding sites of the Alzheimer tau folds in PHF and SF
- Two major sites in the β-helix of PHFs and SFs and a third major site in the C-shaped cavity of SFs.
- Binding sites 1 and 2 have Q351 in common, which adopts an extended conformation



Falcon 2018

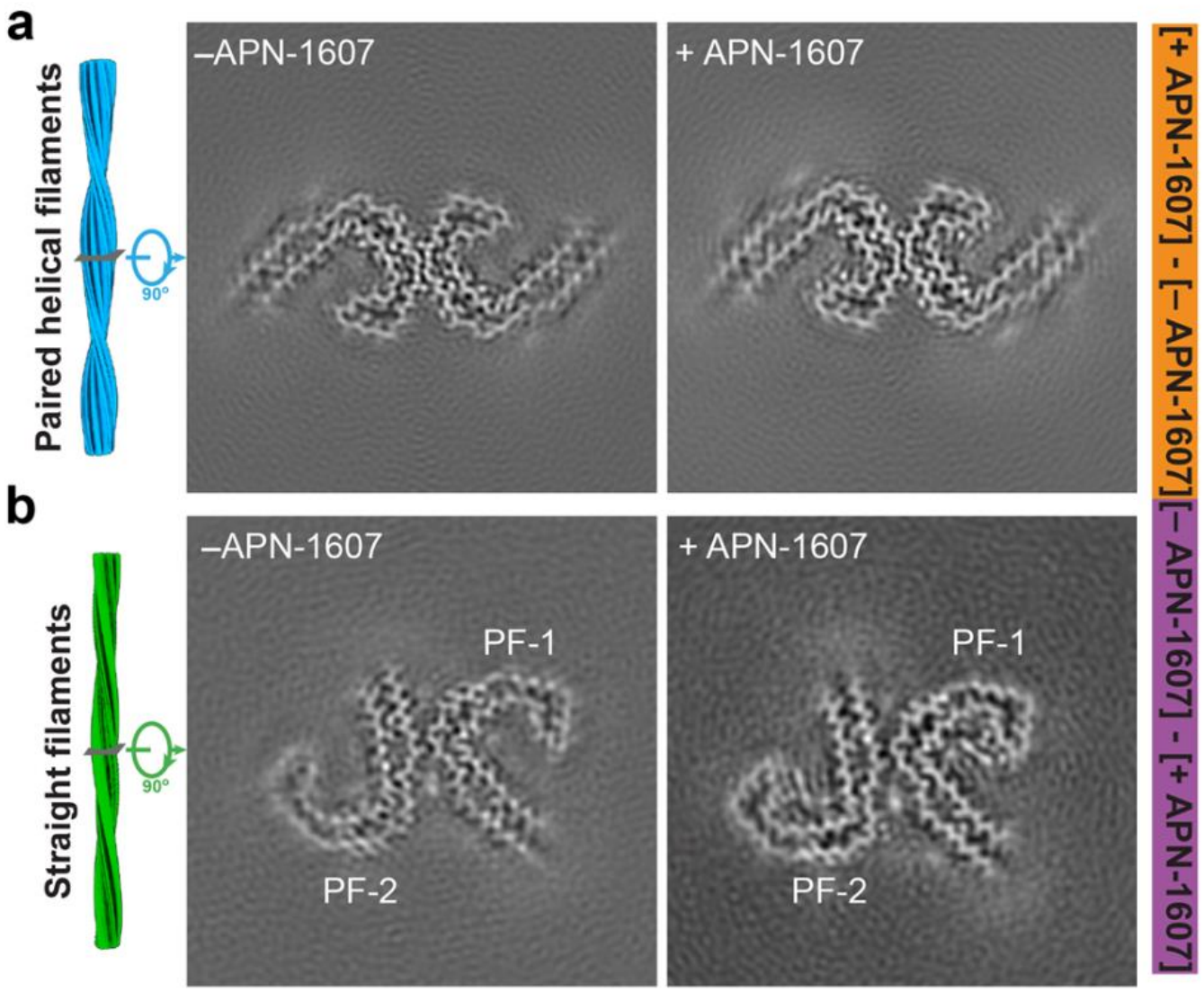
Shi et al; Acta Neuropath ,2021

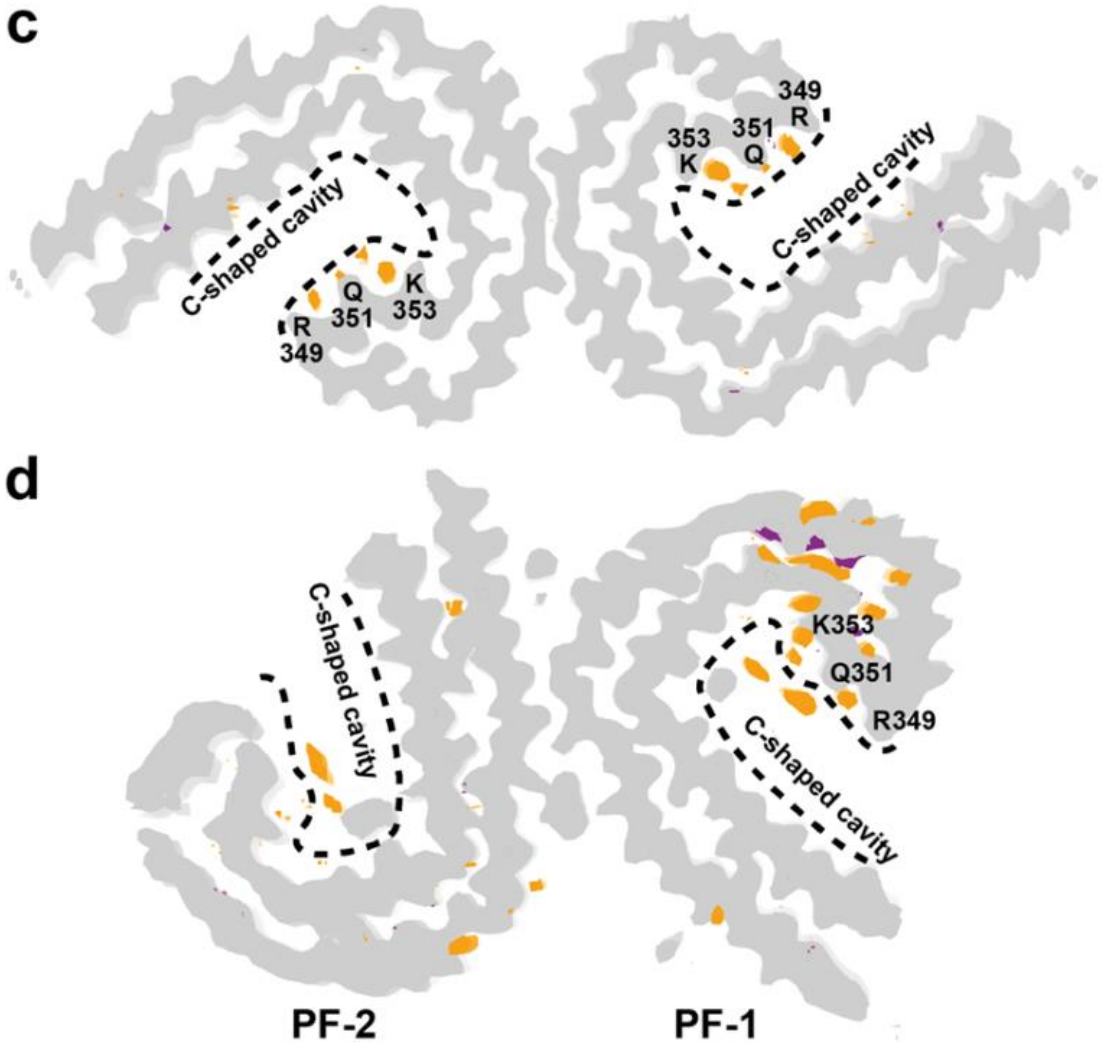




Cryo-EM identifies Binding Sites in AD Tau Folds

APRINOIA





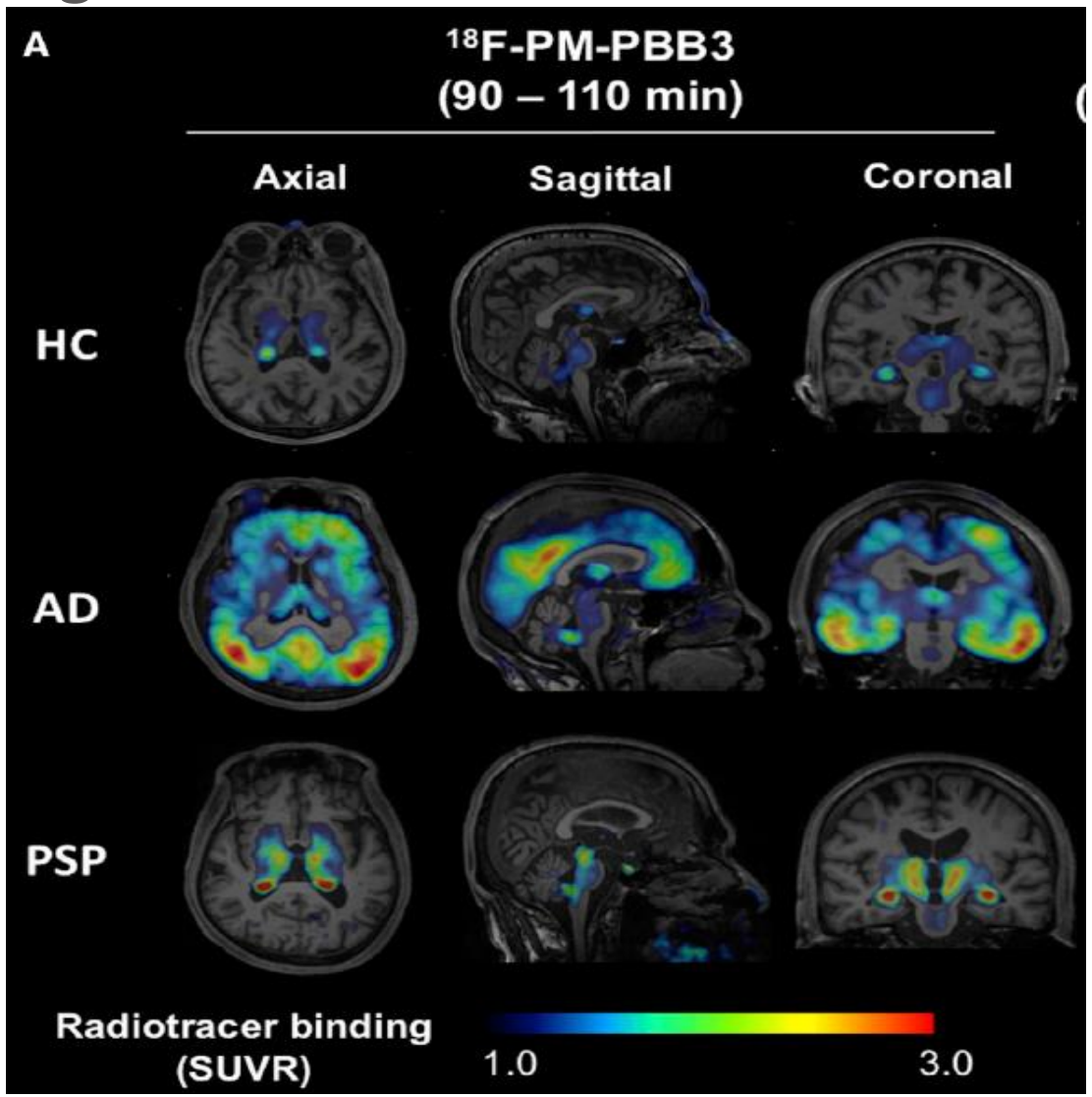
APN-1607: Cryo-EM Identifies Binding in AD Tau folds

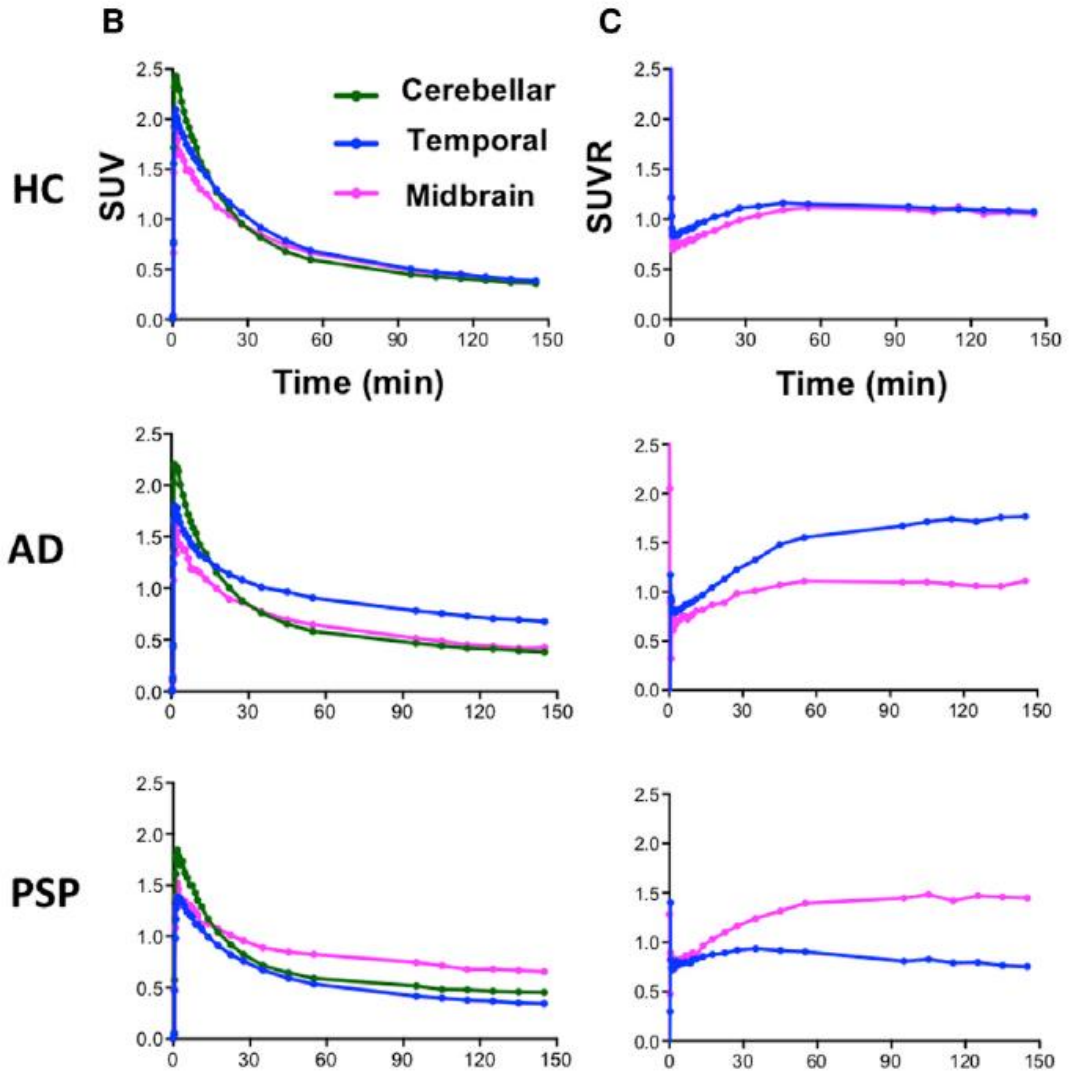
APRINOIA

- In homogenate binding assays of tissue from the same case, 6 nM ^{3}H-APN-1607 bound sarkosyl insoluble tau with high specificity (87% signal/noise ratio) and 16-fold greater than in non-demented control brain(Data from Nancy Stratman, Biogen)
- Cryo-EM structures of tau filaments from PCA and PART identical to AD
- Fluorescent 1607 labeled tau inclusions in brain tissue sections from these cases, suggesting APN1607 may provide a useful PET ligand for PCA and PART as well as AD
- However, if APN1607 also binds to brain regions from patients with PSP, CBD, FTD and CTE but the tau filaments differ among these disorders, how does one explain APN 1607 binding in these different disorders?
- it remains to be determined if other tau PET ligands bind in the same grooves of Alzheimer tau, why APN1607 is a better ligand for 4R tau
- CryoEM could provide further insight into SAR that could lead to better PET tau ligands

APN -1607 in AD and PSP: Tau Topologies Visualized with High Contrast

APRINOIA

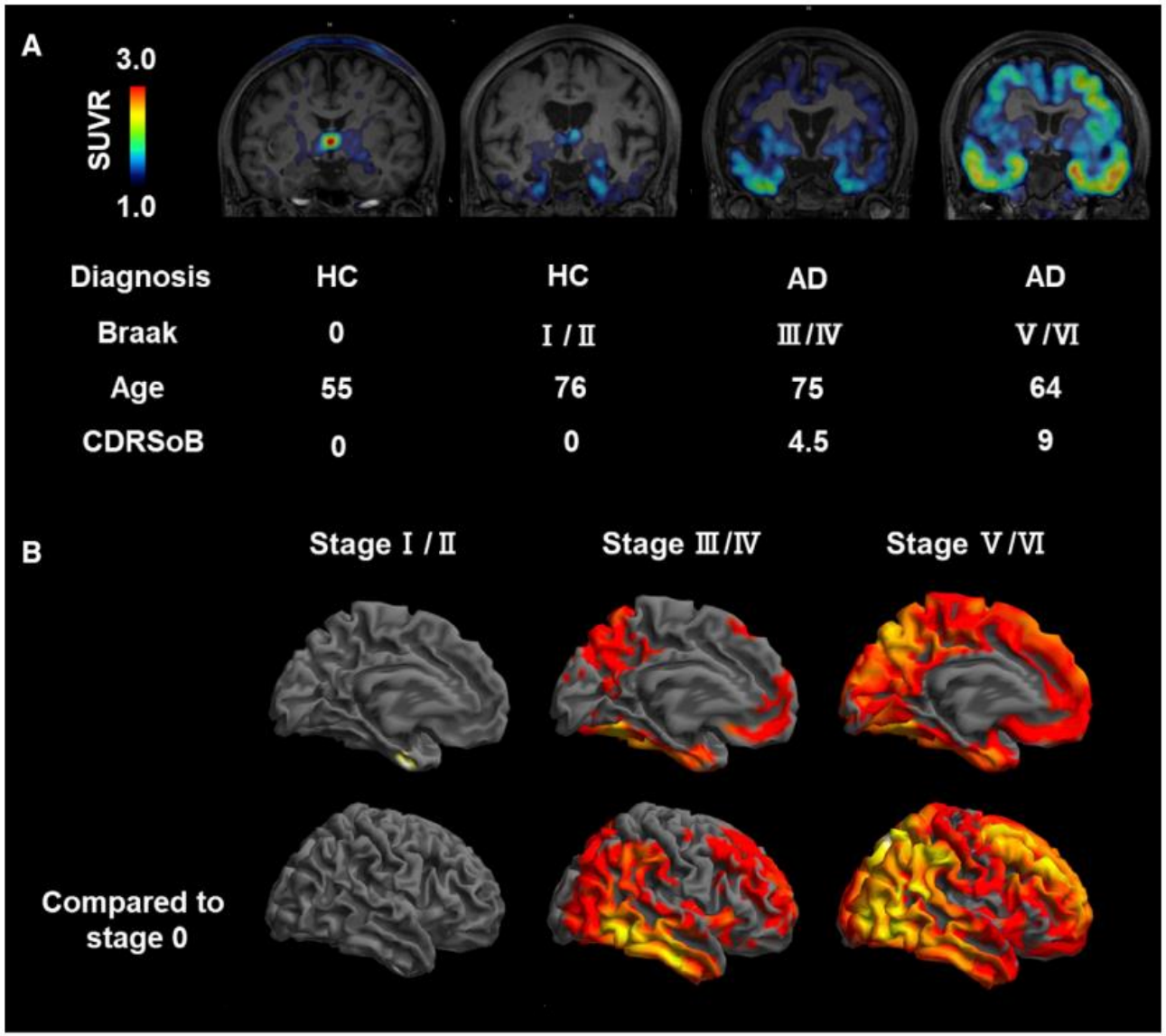


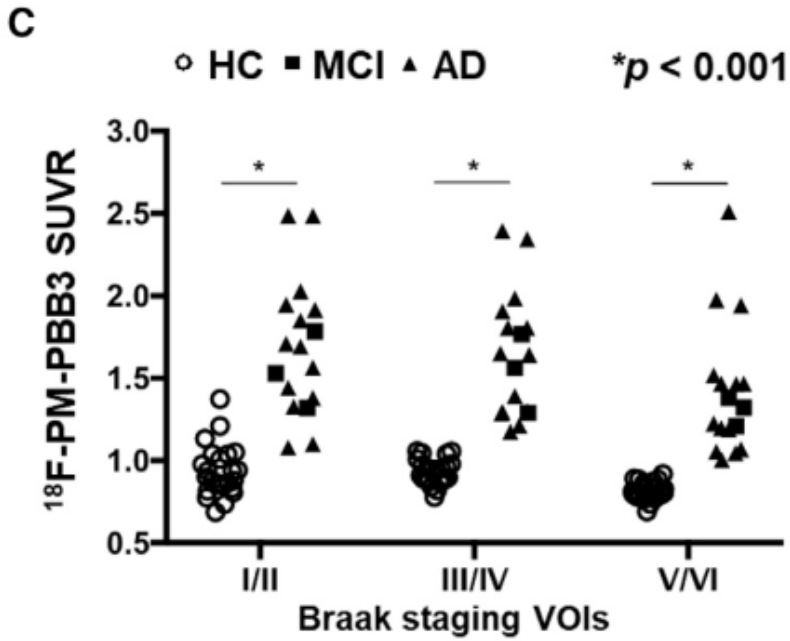


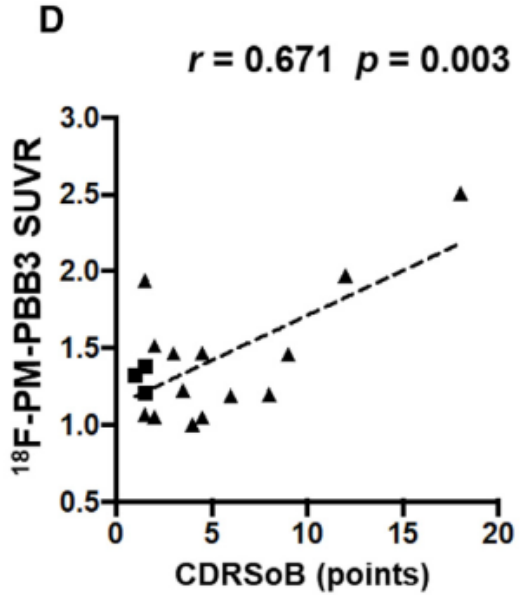
(Tagai, et al; Neuron, 2021)

APN-1607 in AD: Topology and Visualization of Spread

APRINOIA







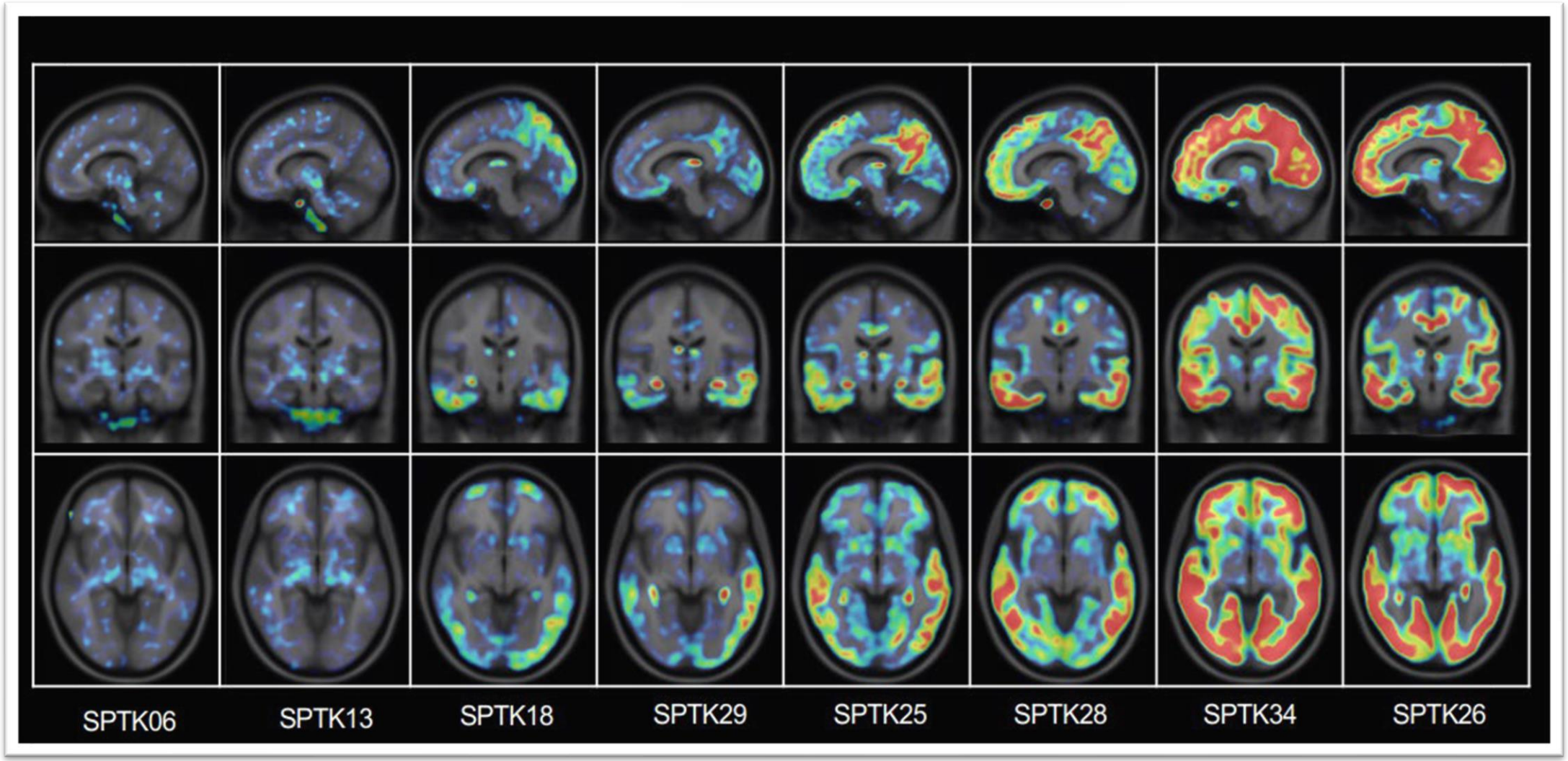
HC=23, MCI=3
AD=14

Tagai,et al; 2021

APN-1607 and Staging in Alzheimer's Disease

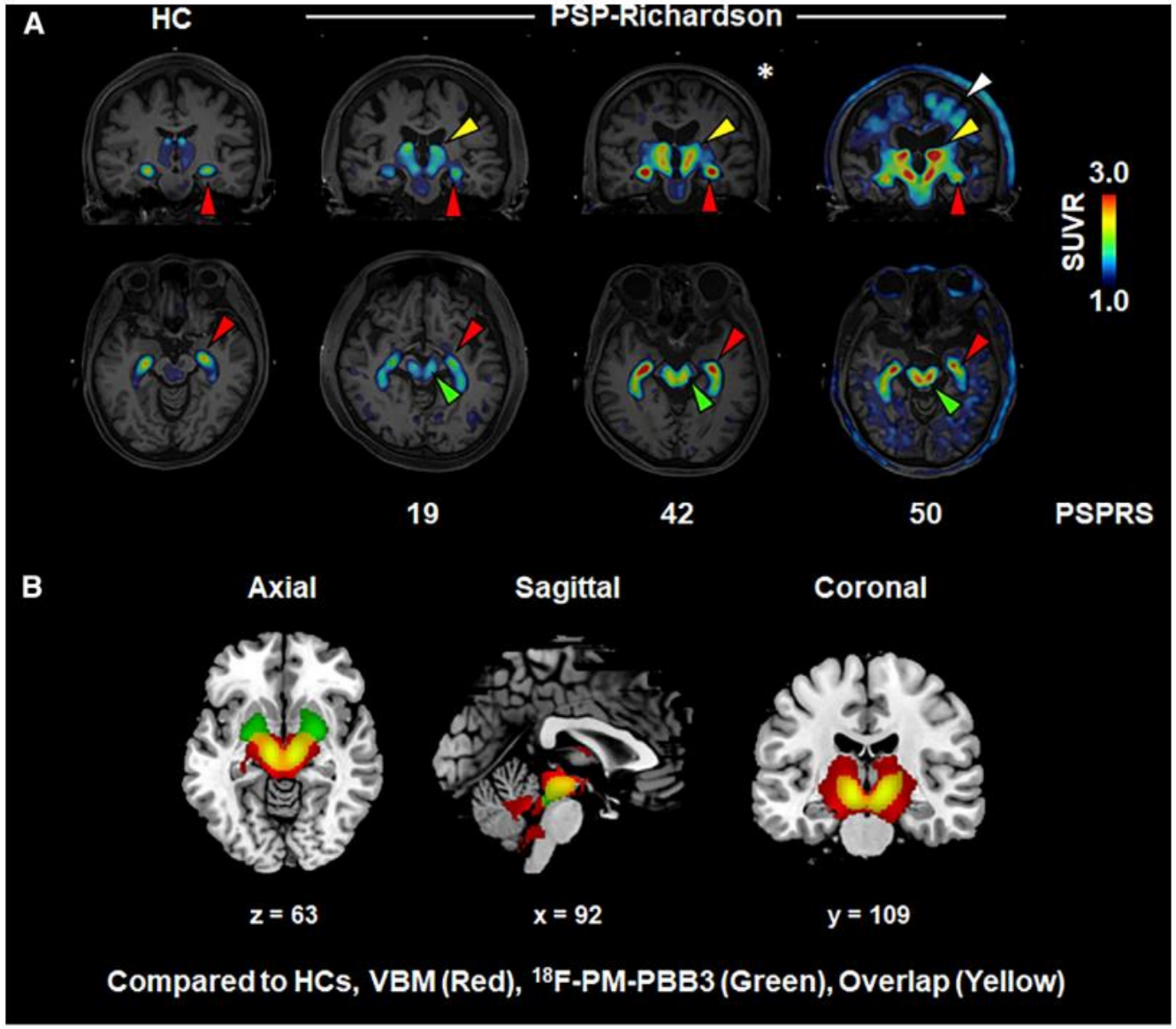
APRINOIA

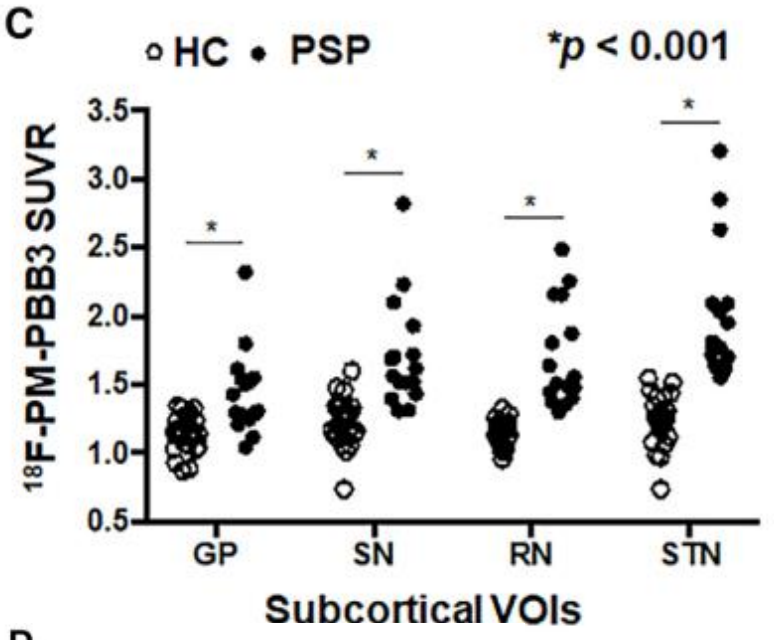
Normal	MCI	Early Alzheimer's	Advanced Alzheimer's

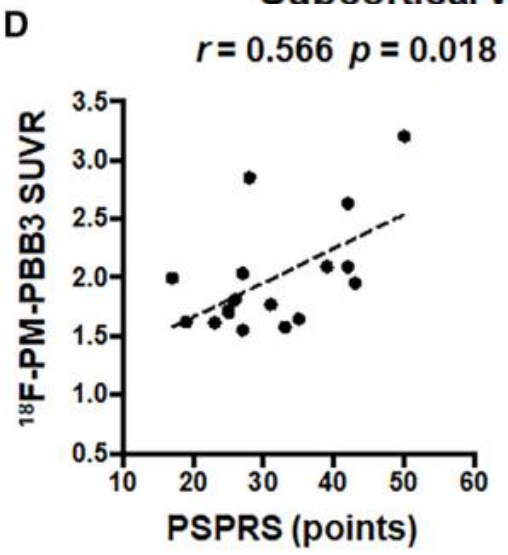


When should we intervene?

APN-1607 in PSP and Correlation with Disease Severity







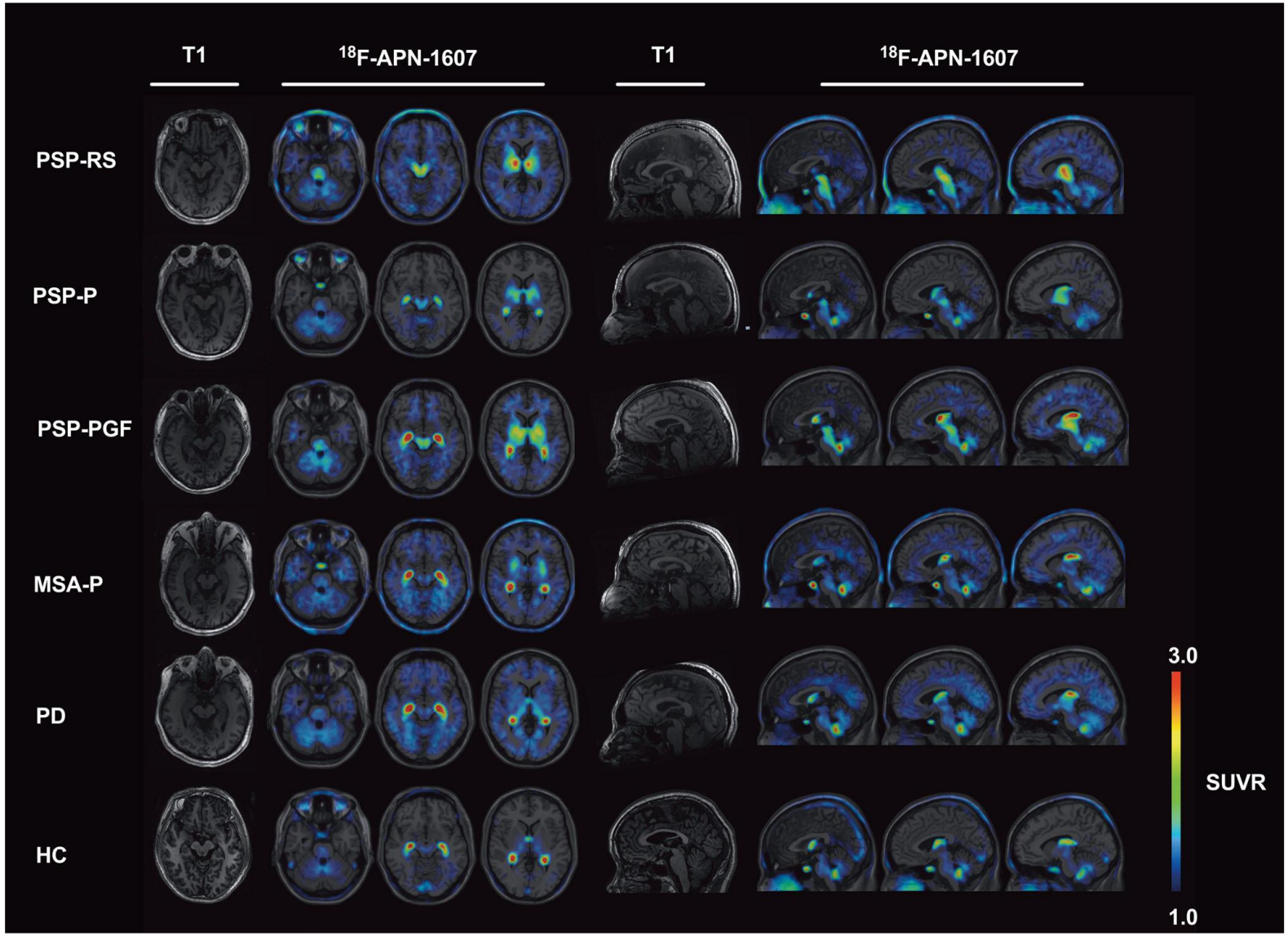
N= 16

Tagai,et al; 2021

APN-1607 in PSP and Correlation with Disease Severity

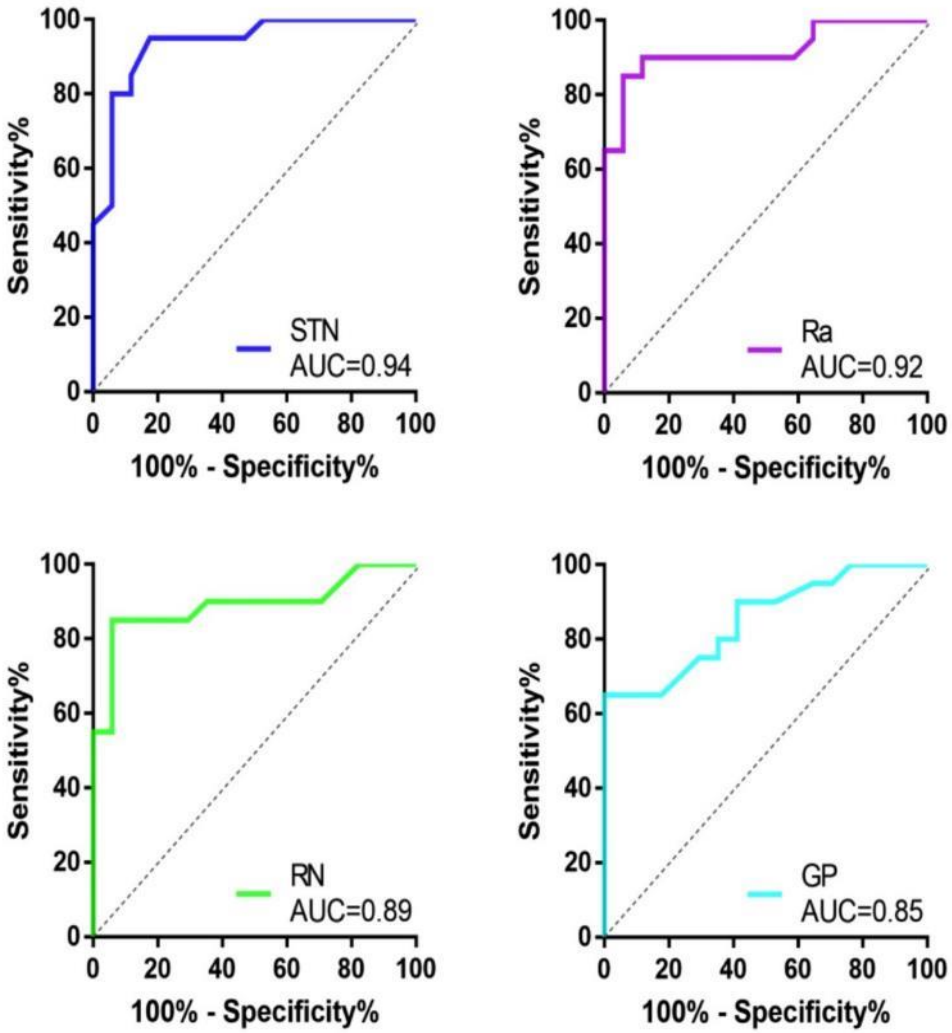
APRINOIA

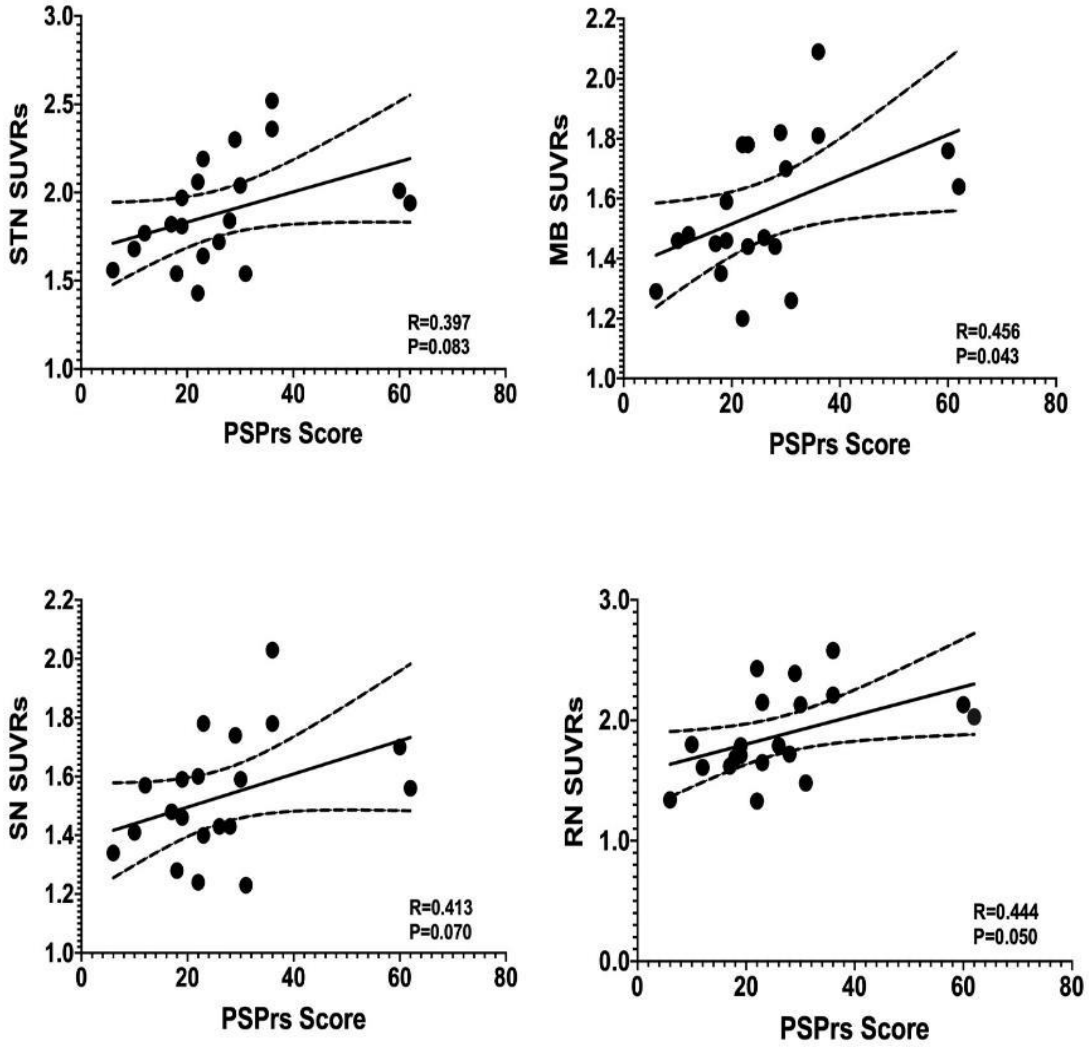
PSP=20,
{PSPRS=16)
MSA-P=7
PD=10
HC=13



(Li, et al; Mov Disorders, 2021)

APN-1607 in PSP and Correlation with Disease Severity

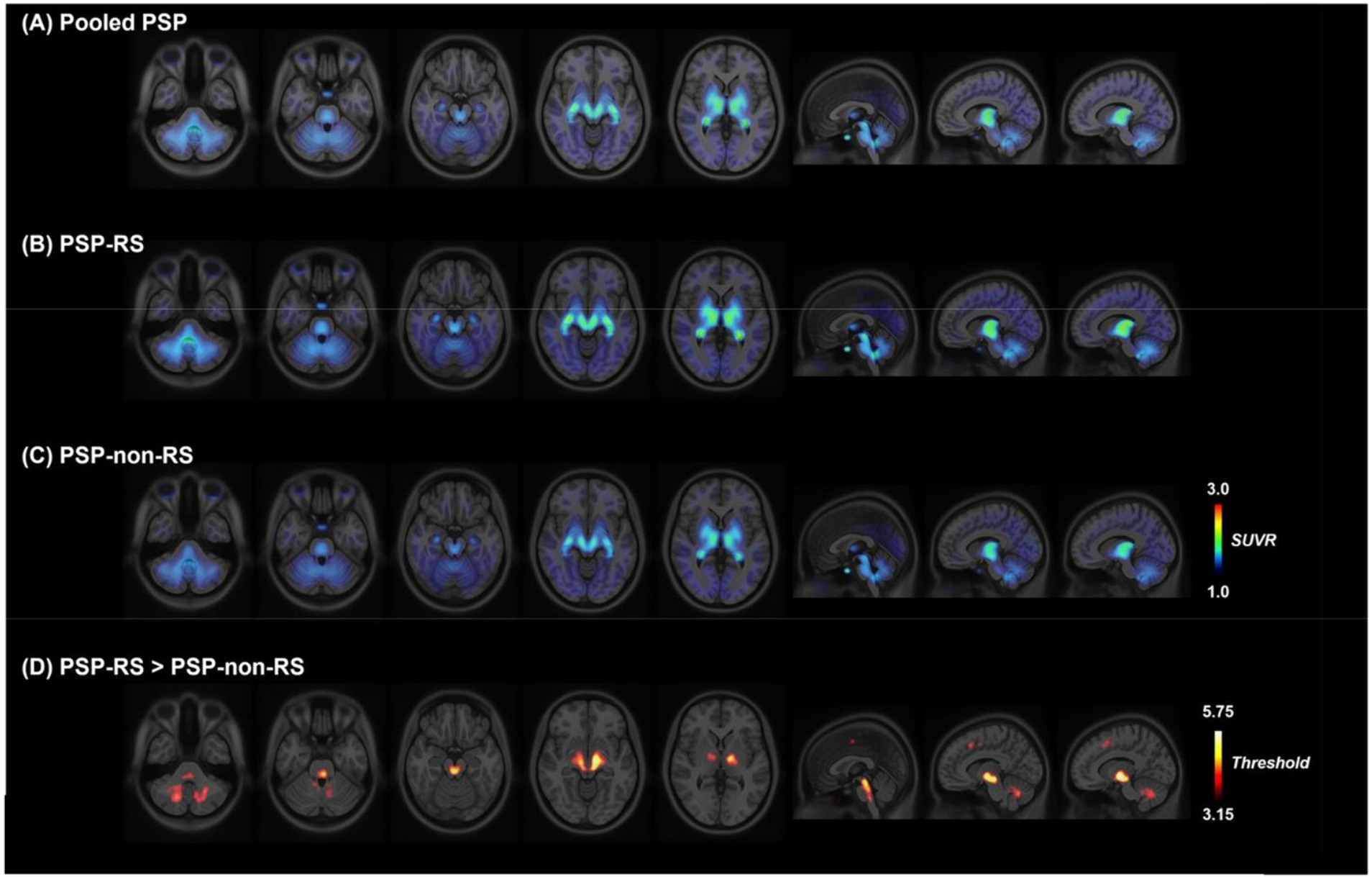




Li et al , 2021

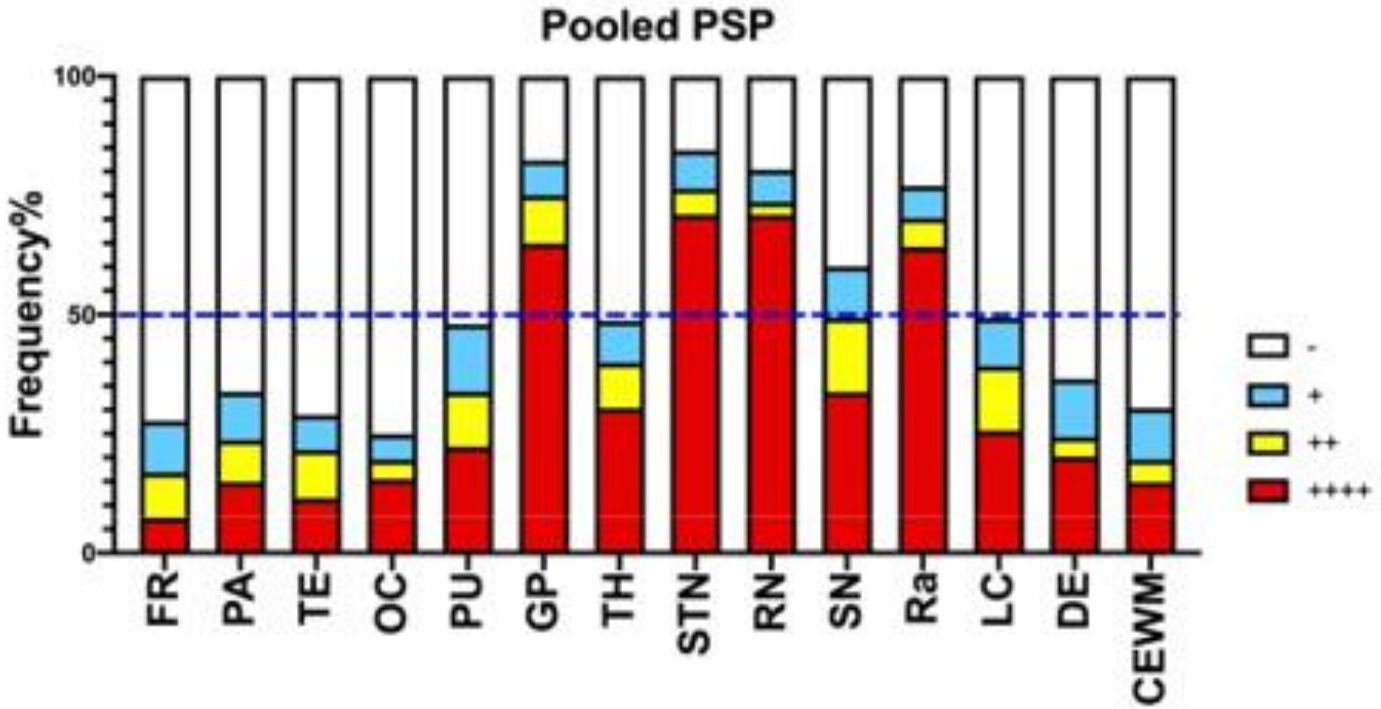
APN 1607 in PSP: Distribution, Dynamics and Pattern of Tau Pathology

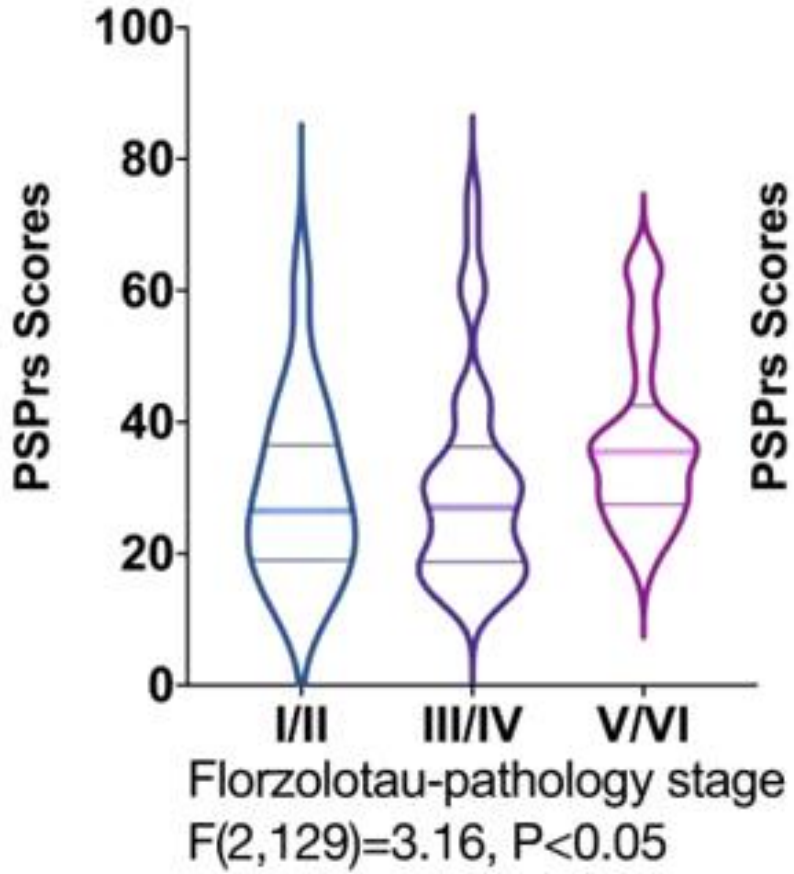
PSP=148
PSPRS=84
nonRS=64



Liu ,et al 2023

APN 1607 in PSP: Distribution, Dynamics and Pattern of Tau Pathology





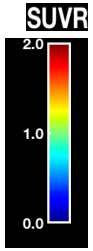
Cluster 1: red nucleus, subthalamic nucleus, raphe nuclei, and globus pallidus,
Cluster II: thalamus, locus coeruleus, substantia nigra and putamen;
Cluster III: dentate nucleus, cerebral white matter, and cortices

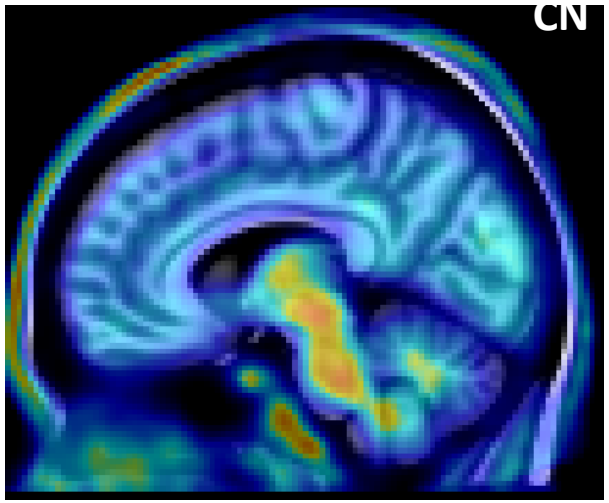
Liu, et al 2023

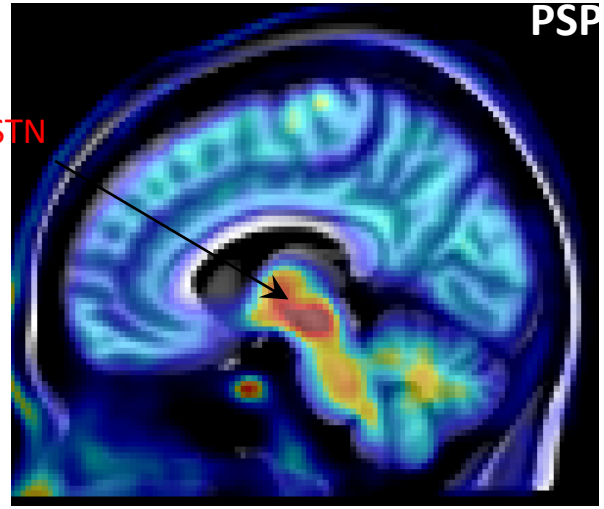
Findings and Conclusions

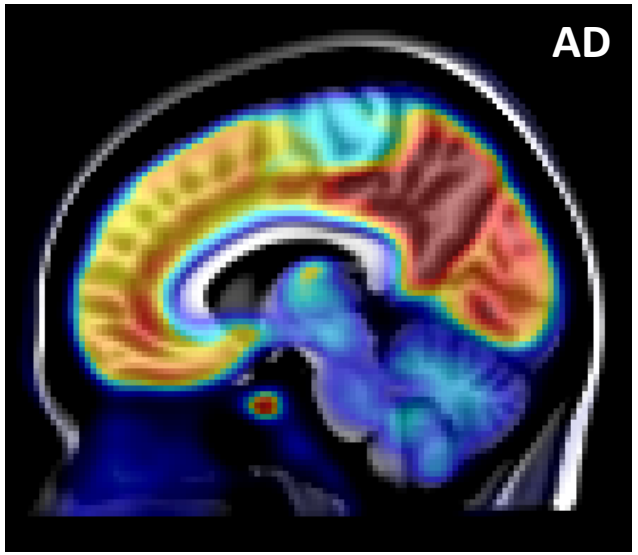
- APN1607 retention starts in subcortical regions.
- The advance of tau accumulation visualized by APN 1607 PET showed a significant correlation with clinical severity
- The distribution and dynamics of tau accumulation in PSP similar to the reconstructed maps of tau propagation in *postmortem* studies (Kovacs et al, Acta Neuropath, 2020)

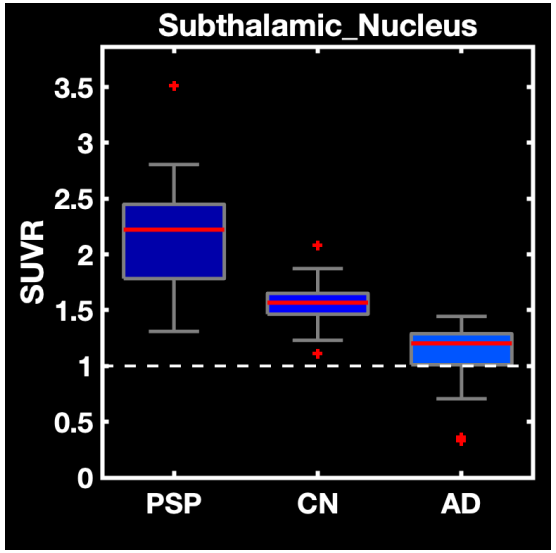
APN-1607 distinctive uptake patterns in AD and PSP

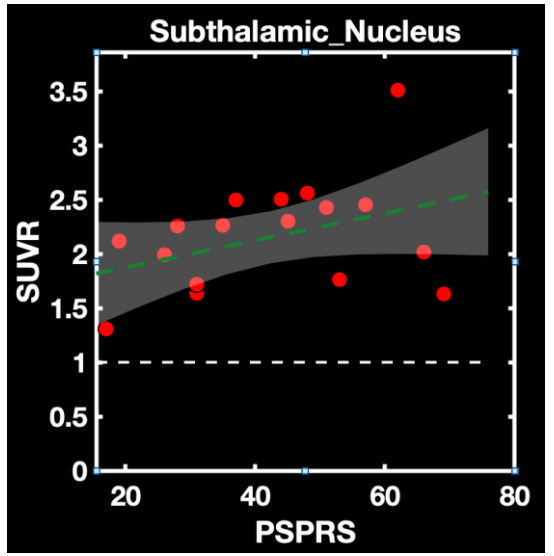












Cristian Salinas, Jonathan DuBois

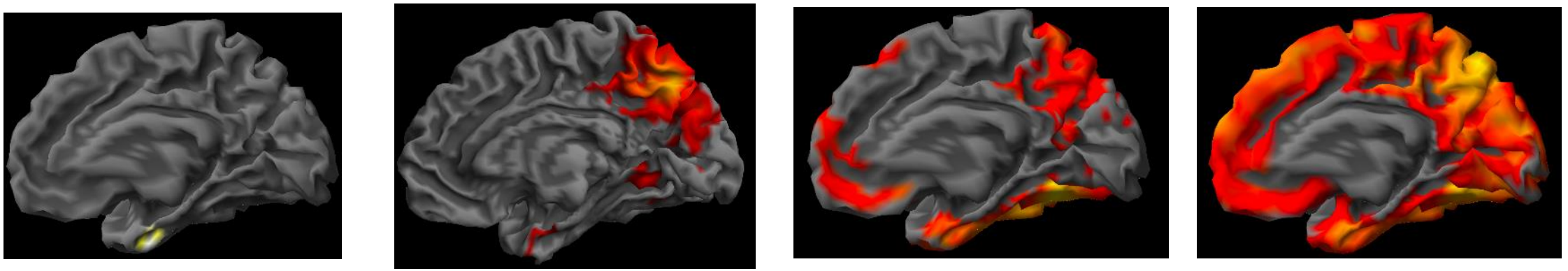
APN 1607 Can Track Disease Progression in AD and PSP

APRINOIA

Aging

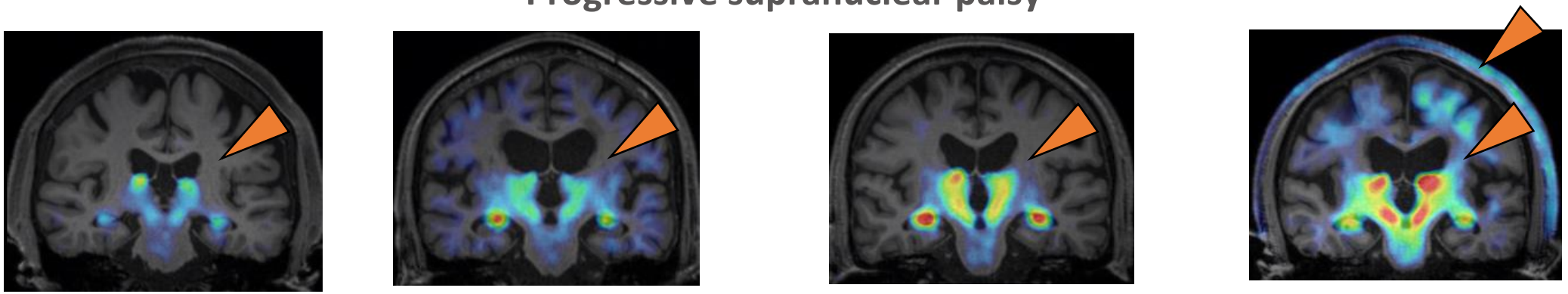
Mild cognitive impairment

Alzheimer dementia



Clinical severity

Progressive supranuclear palsy



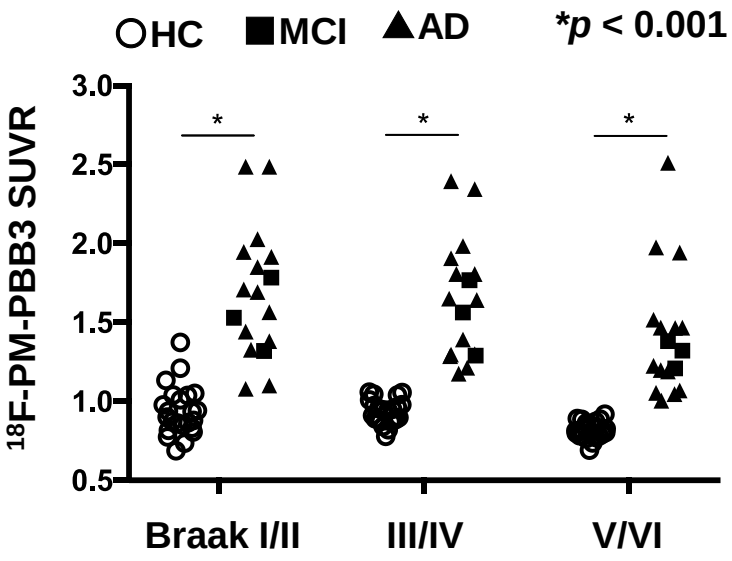
Clinical severity

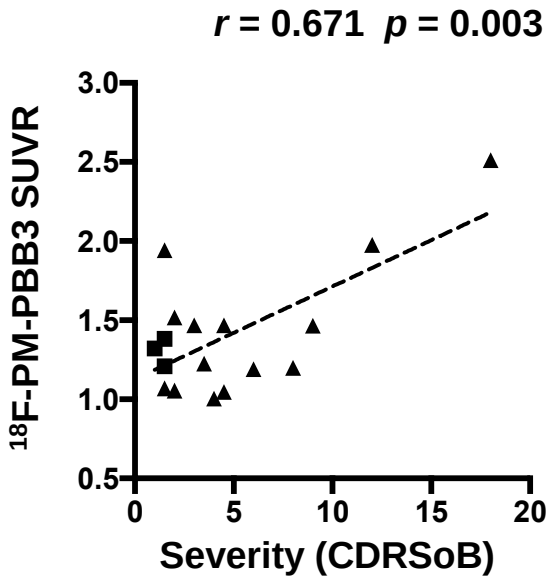
(Neuron 2021)

Diagnostic accuracy and utility for staging the disease

APRINOIA

AD



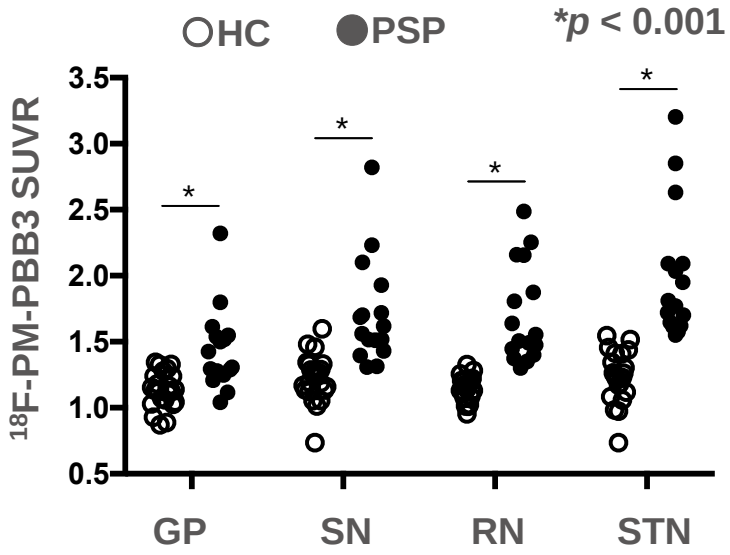


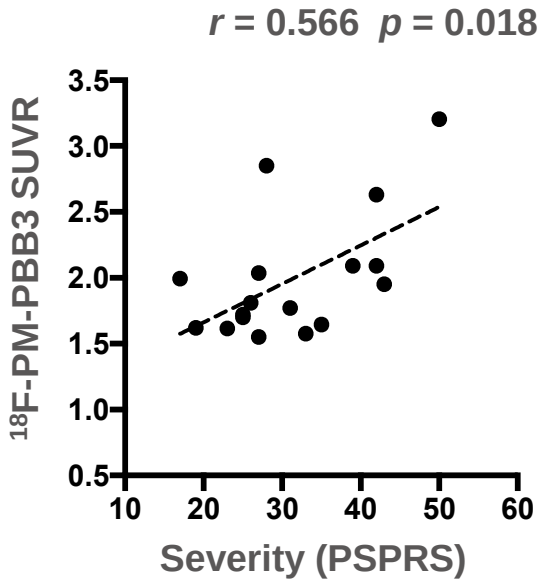
Sensitivity
Specificity
= 100%

(Braak III/IV & V/VI areas)

Close correlation between neoroctical SUVR and disease severity

PSP





Sensitivity
Specificity
~ 95%

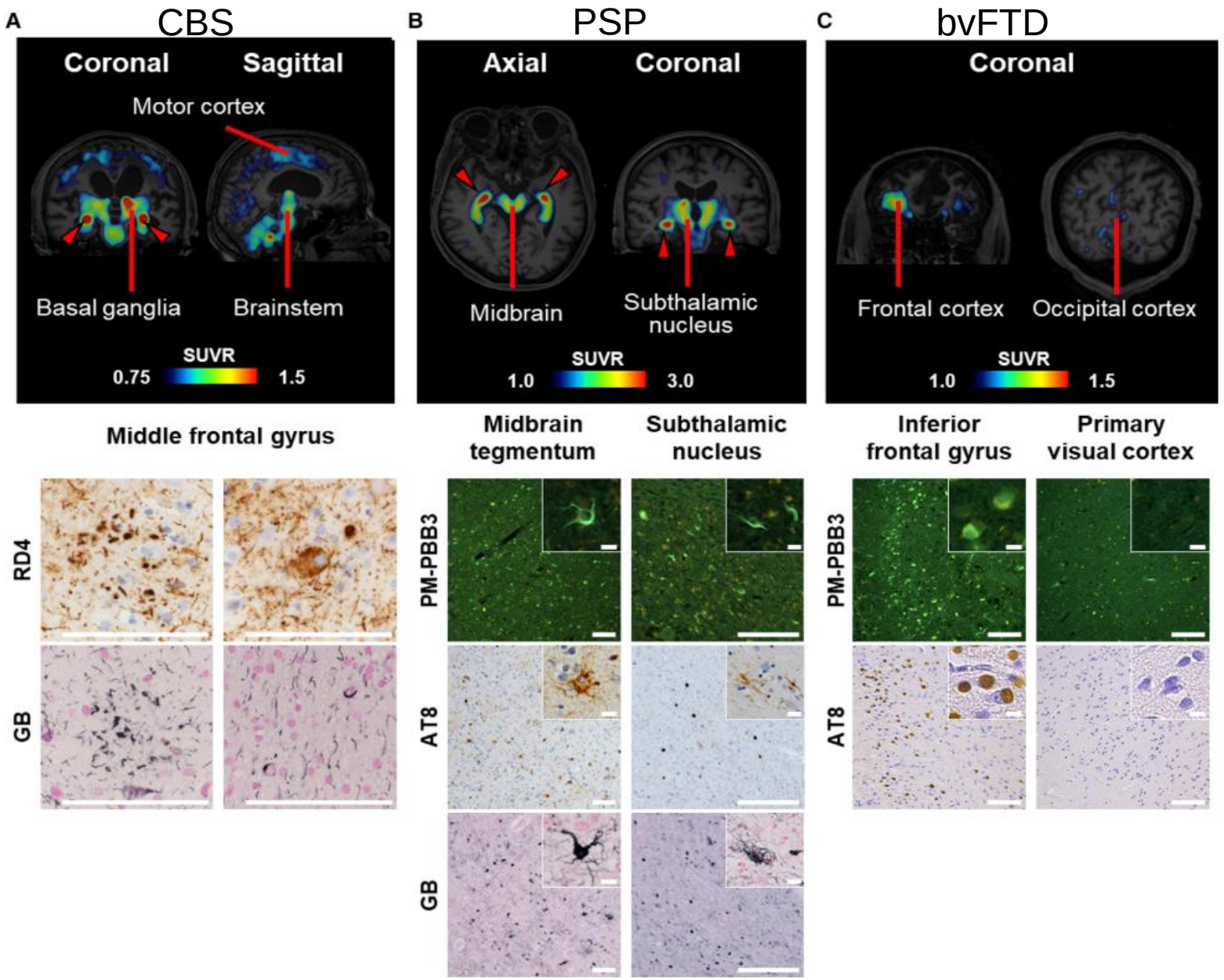
(subthalamic nucleus; STN)

Close correlation between STN SUVR and disease severity

(Neuron 2021)

APN-1607 in Pathology Confirmed Cases of CBS, PSP and PiD

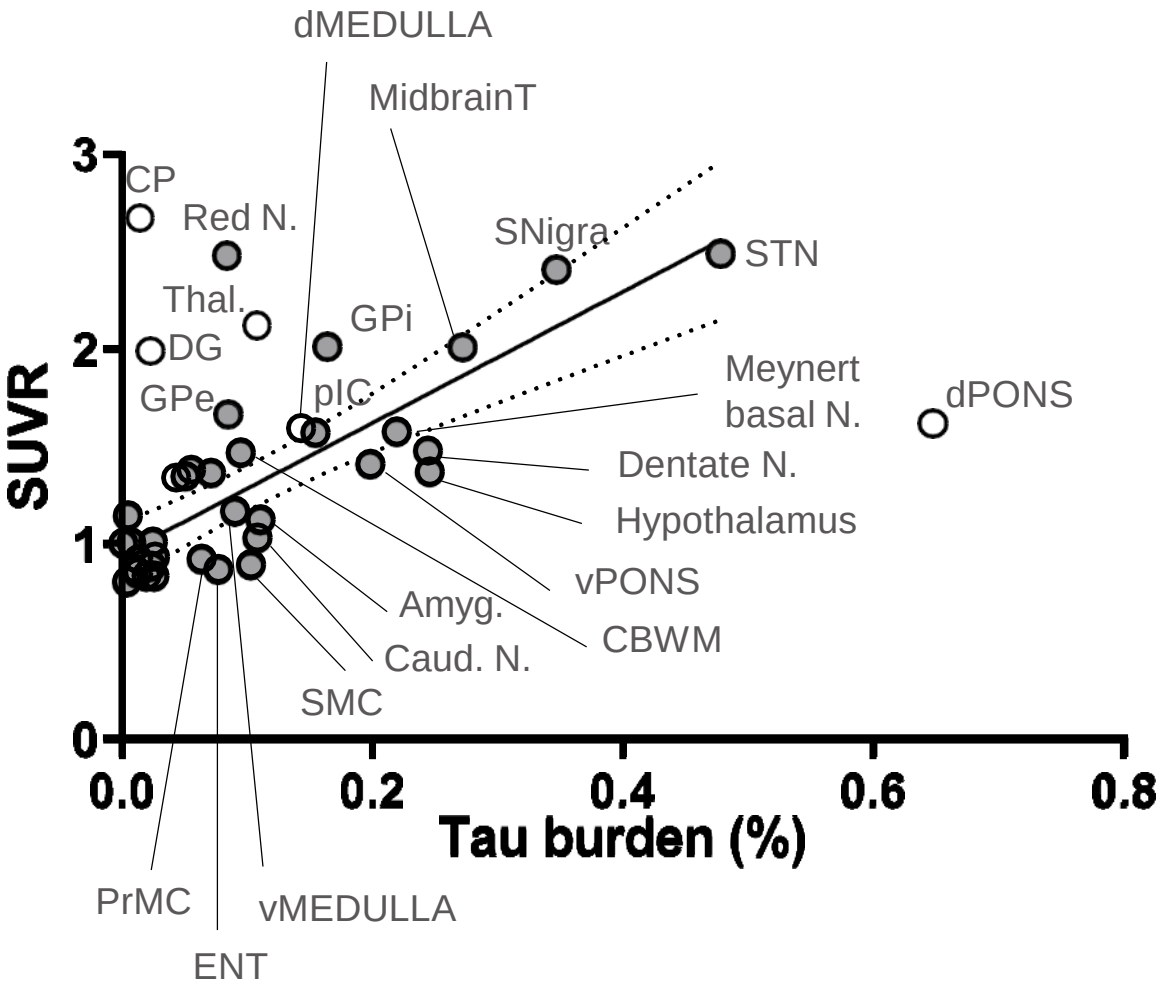
APRINOIA



Tagai et al, 2021

APN-1607 Imaging-neuropathology correlations in PSP

APRINOIA



All data
Spearman r 0.6135
95% confidence interval 0.3611 to 0.7821
P (two-tailed) < 0.0001
N 39

Without CP effected ROIs (gray)
Spearman r 0.7419
95% confidence interval 0.5272 to 0.8675
P (two-tailed) <0.0001
N 33

Higuchi et al, Unpublished da

APN-1607: First- in-Class 4R Tau Tracer for PSP

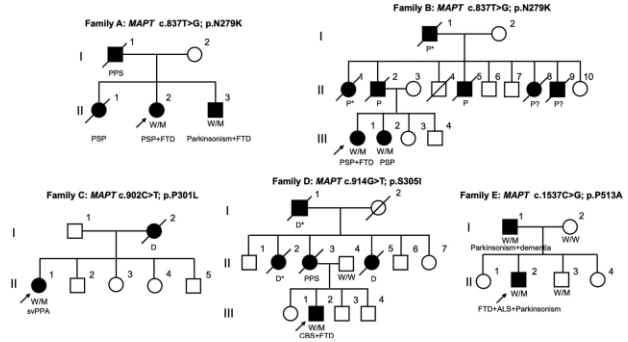
APRINOIA

- Together, the published results in nearly 180 PSP patients demonstrate that PET imaging with APN-1607 can serve as pathological marker of 4R tau fibrils and capture the core subcortical pathology of PSP

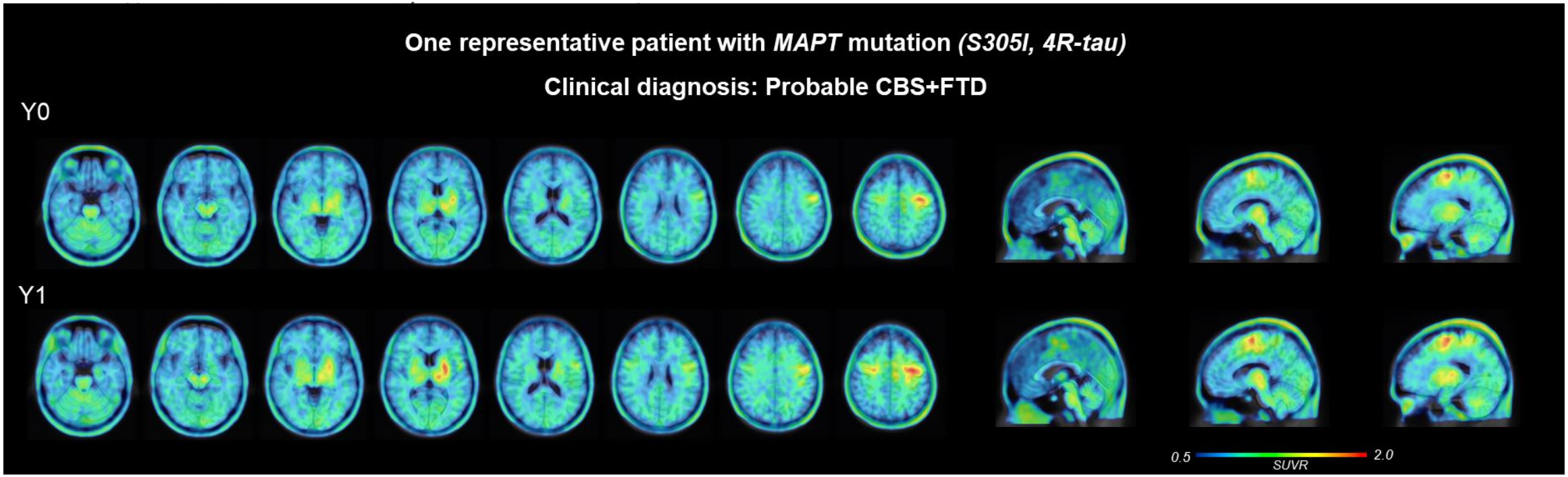
- These results support the claim that APN-1607 can serve as a useful diagnostic agent in the management of patients suspected to have PSP

APN-1607: Findings in *Mapt* Mutation Carriers

APRINOIA



- Study of 7 patients with various *Mapt* mutations (Zhou 2021)
  - Exon 10, 4R tau-associated (6): N279K (4), P301L (1), S305I (1)
  - Non-exon 10, 3R/4R tau-associated: P513A (1)
  - Various ages, phenotypes and diagnoses; MRI, FDG, and DAT profiling
- Baseline APN 1607 PET scans in all subjects; positive signal in phenotype-associated regions
- Follow-up scans in 3 subjects with clinical deterioration after 10-14 months revealed increased signal



(Zhou, Mov Disorders 2021)

APN 1607-Phase 3 for PSP
First- in- Class 4R Tau Tracer
Path to Approval

APRINOIA

Development of APN-1607 for PSP: Path to Approval

APRINOIA

- Reliable diagnosis, during the early stages of disease, remains a major clinical challenge
- No approved in vivo imaging or fluid-based biomarkers for the detection of 4R tau aggregates in the PSP brain
- **Aprinoia plans to initiate a single pivotal, prospective, global Phase 3 study to develop APN-1607 as a novel PET tracer for the diagnosis of PSP**
- Primary Goal: Demonstrate that APN-1607 can improve diagnostic certainty of PSP at early stages of the disease in patient suspected to have PSP
- “May Proceed” for Phase 3 trial granted December 8, 2023

Development of APN-1607 for PSP: Path to Approval

APRINOIA

- Clinical Development Plan:
  - A global, single phase 3 prospective trial could provide the basis of approval
  - Pathological study as Standard of Truth is not necessary
  - Clinical reference-> Standard of Truth : Possible PSP patients with the APN-1607 “PSP” pattern convert to Probable PSP at 6 or 12 months
  - Study Population: Possible, Probable PSP patients, nonPSP (PD and atypical PS) based on consensus diagnosis by an independent panel
  - 5 imagng readers will utilize a newly developed and validated visual read algorithm (John Seibyl and colleagues)

Development of APN-1607 for PSP: Path to Approval

A Phase 3 Trial to evaluate the efficacy and safety of APN 1607 as Diagnostic Marker in Patients with Suspected PSP

- Patients with atypical parkinsonism referred from all sources, community and hospital based
- Patients will be diagnosed as PSP or nonPSP by study investigator
- Consensus panel of three movement disorder experts will confirm diagnosis,
  - PSP based on MDS criteria (Probable, possible or suggestive of PSP)
- APN-1607 PET imaging/MRI at baseline
- Six and 12 months to evaluate for progression to Probable PSP
- Visual interpretation of PSP vs nonPSP pattern based visual read method by 5 independent readers (Method developed by John Seibyl)

Development of APN-1607 for PSP: Path to Approval

- Co-primary endpoints of sensitivity and specificity based on APN-1607 PET imaging at 12 months compared to the expert panel consensus diagnosis
- A sample size of 130 subjects: 90 PSP (70 Possible and 20 Probable) and 40 nonPSP
  - Assumes approx. 40 possible PSP will convert to probable by 12 months
- For sensitivity and specificity , >90% power to demonstrate the lower bound of the 95% confidence interval (CI) >60% for the same 3 of 5 individual readers
- For the key secondary endpoint of inter-reader agreement between 5 blinded readers, 80% power to demonstrate the lower bound of the 95% CI for Fleiss' kappa >0.6 if the true kappa is 0.74

Development of A Visual Read Method for the Diagnosis of PSP

APRINOIA

Develop an evidence-based visual read algorithm for qualitative assessment of APN- 1607 In PSP and other tauopathies

John Seibyl, unpublished data

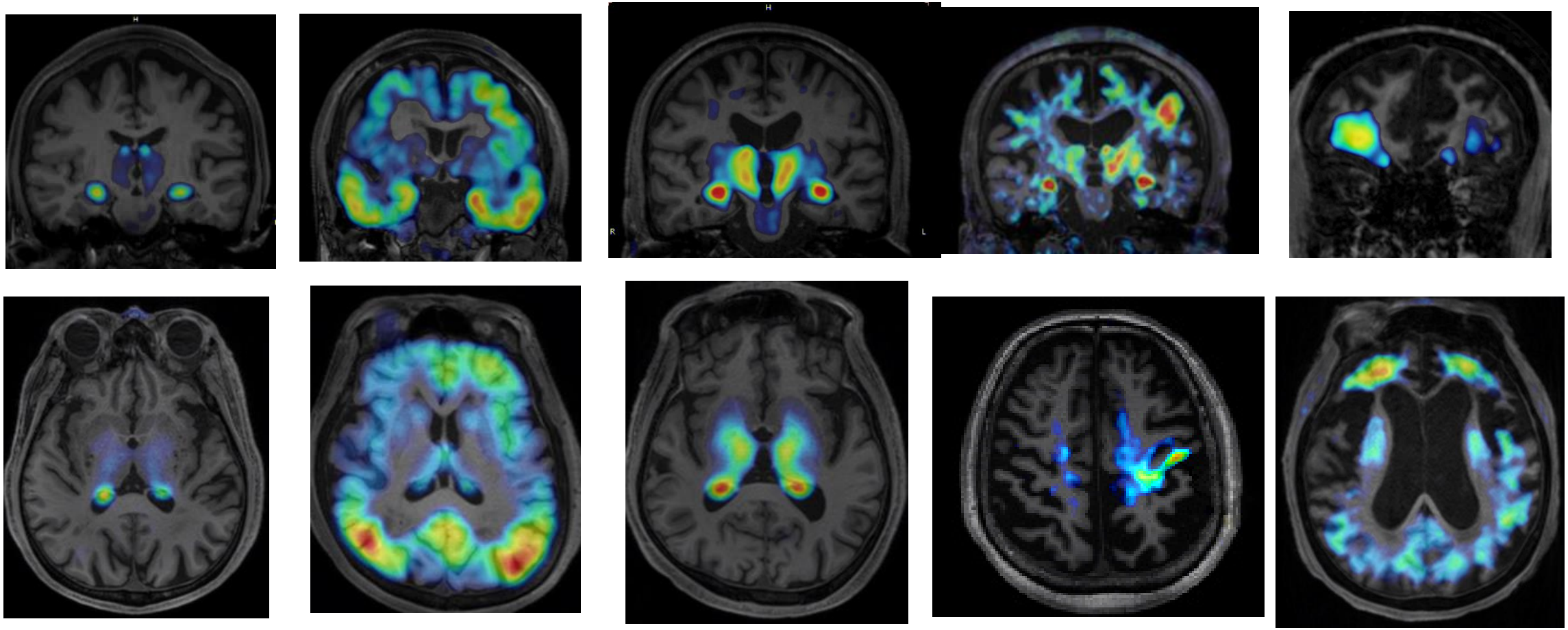
Conclusions

- Preliminary Visual Read results recapitulate the core pathologic regions associated with PSP (“PSP pattern”) differentiating PSP from non-PSP patients with sensitivities and specificities of >90%
- Consistent with previously reported findings (Tagai et al 2021; Li et al 2021; Liu et al 2023), and further support the clinical utility of APN-1607 as a diagnostic marker for PSP
- Additional test analyses and validation are underway

Conclusions

APN-1607 Captures Aggregated Tau in Relevant Brain Regions in AD and non AD Tauopathies

Healthy control	Alzheimer's disease	Progressive supranuclear palsy	Corticobasal degeneration	Pick's disease

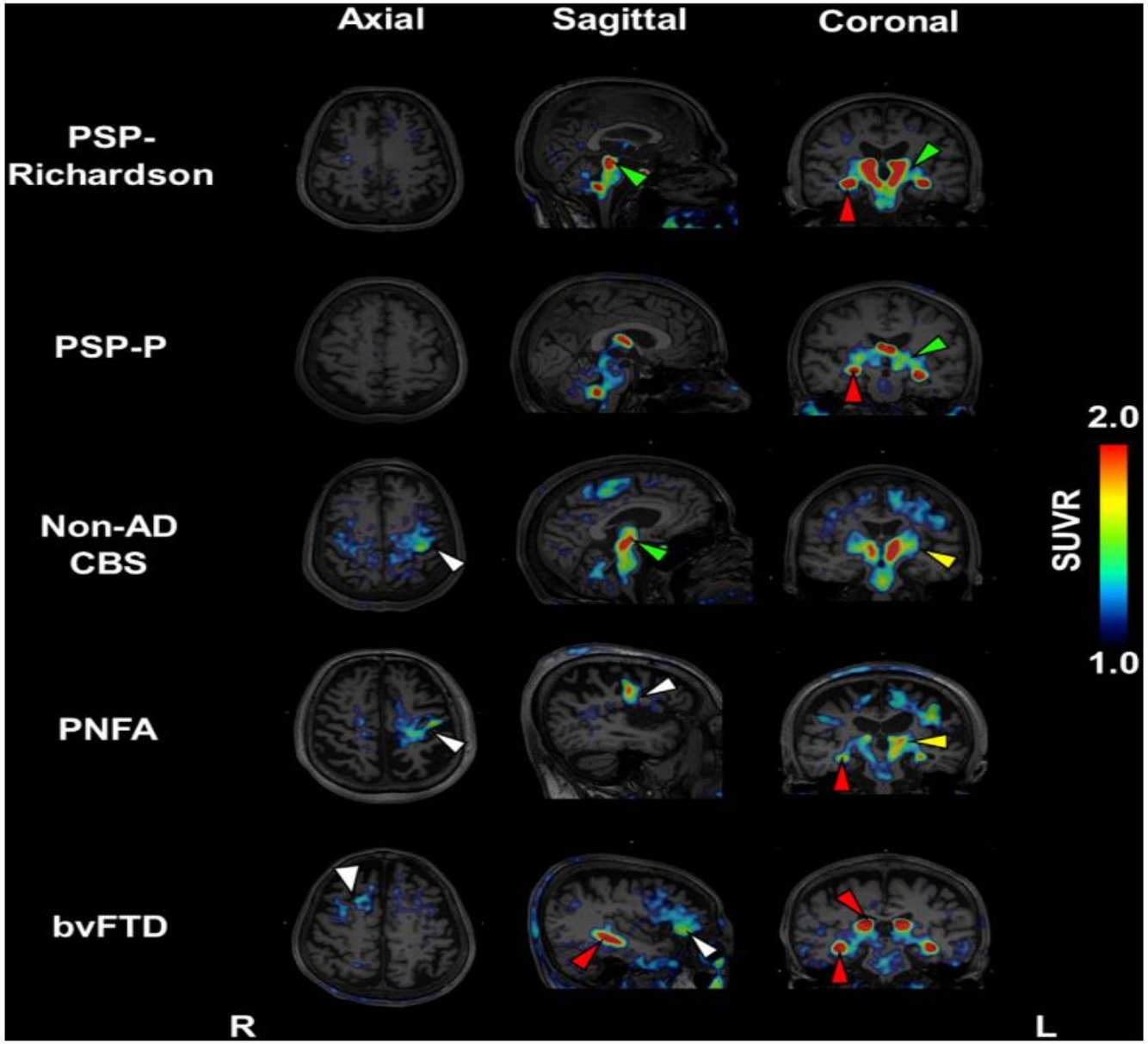


Tau probe binding

Min — Max

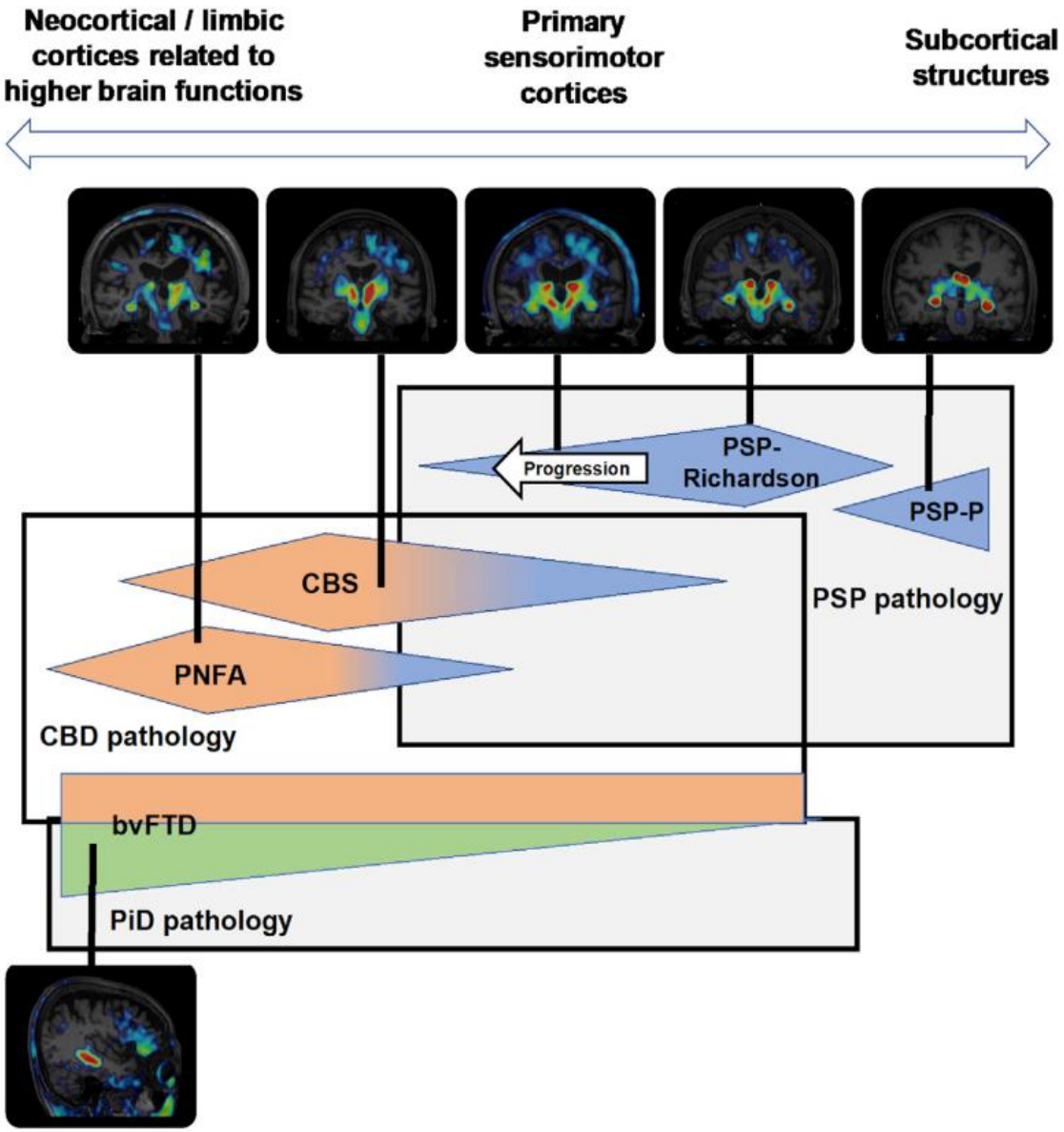
(Tagai, et al 2021)

APN-1607 Differentiates Anatomical Patterns Across nonAD Tauopathies



(Tagai,et al 2021)

APN-1607 Can Detect Distinct Anatomical Patterns across Different Tauopathies



(Tagai, 2021)

Conclusions: APN-1607: First in Class 3R/4R Tau Tracer

- **Postmortem Correlation**
  - APN-1607 uptake correlates with postmortem regional and cellular tau deposits in 3R- and 4R tau disorders
  - CTE: preliminary APN-1607 findings consistent with pathological findings
- **Ex vivo studies to further characterize APN1607 binding in NADTs underway**
  - PSP and other NDATs: Collaboration with Tom Beach, Makoto Higuchi, Gabor Kovacs
  - CTE: Makoto Higuchi (QST) and BU (Ann McKee)
- **Clinical Development Plans**
  - Phase 2 and 3 studies are underway or planned for AD and PSP indications
  - A single global phase 3 without pathology for the approval of APN-1607 as diagnostic marker for PSP is planned for 2024
- **Next generation, light insensitive 4R tau tracers in development, in collaboration with Biogen**
  - Lead candidates identified

Acknowledgements

- Clinical and Regulatory Teams at Aprinoia Therapeutics and PPD
- Advisors
  - Larry Golbe-Rutgers
  - Irene Litvan-UCSD
  - Tony Lang- U Toronto
  - Huw Morris - UCL
  - Gunter Hulinger- Munich
  - Adam Boxer -UCSF
  - Tom Beach- Banner Inst.
- John Seibyl and Colleagues at Invicro
- CurePSP
- ADDF

Acknowledgements

QST
Makoto Higuchi
Kenji Tagai
Hironobu Endo
Keisuke Takahata
Manabu Kubota (Kyoto Univ)
Maiko Ono
Hiroyuki Takuwa
Yuji Nagai
Yuhei Takado
Ichio Aoki
Ming-Rong Zhang

Cambridge University
Yang Shi
Alexey G. Murzin
Sjors Scheres
Michel Goedert

APRINOIA Therapeutics, Inc.
Ming-Kuei Jang
Paul Tempest
Masaomi Miyamoto
Tzu-Chen Yen

Keio University
Yutaka Tomita
Norihiro Suzuki
Masaru Mimura
Daisuke Ito
Toshiki Tezuka

University of Freiberg
Joachim Blumberg
Phillip Meyer

Chang Gung Memorial Hospital, Linko
Kun-Ju Lin
Jung-Lung Hsu
Chin-Chang Huang

Huashan Hospital, Fudan University
Jian Wang
Feng-Tao Liu
Xin-Yue Zhou

Thank You / Questions

APRINOIA