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

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Disclosures

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- Employee and a share holder of Aprinoia Therapeutics

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

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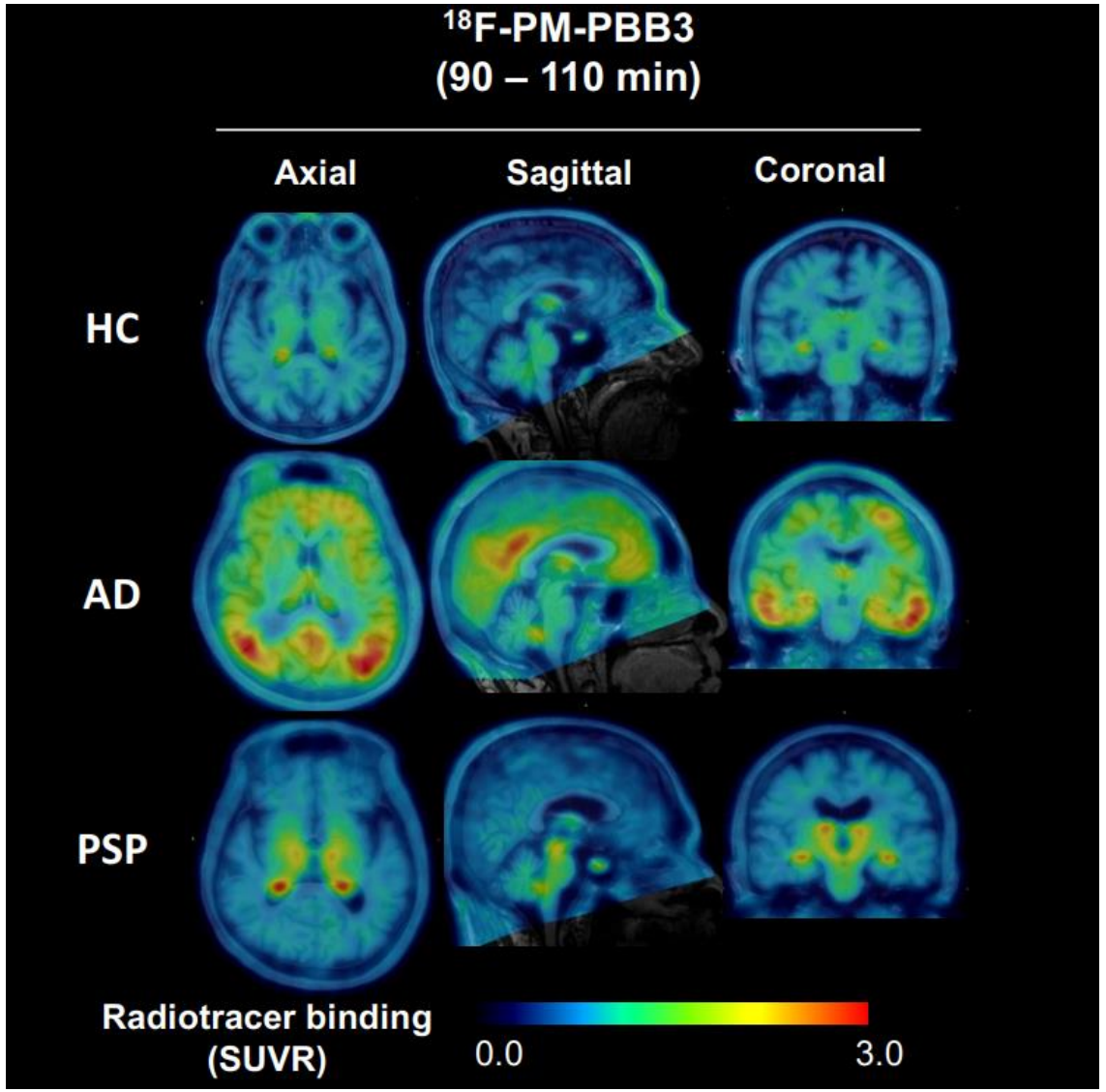

APN-1607: A Promising PET Tracer for Tauopathies of All Isoform Types

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- 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 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 can detect 3R/4R tau fibrils
  - APN-1607 may provide a useful PET tau tracer for the diagnosis of a broad range of 3R and 4R Tauopathies

Clinically Available Tau PET Probes

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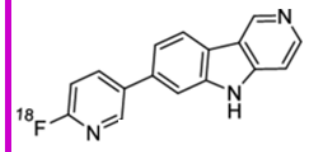
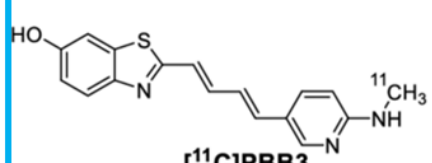
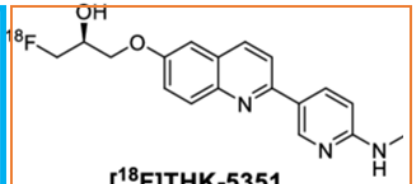
First generation



[^{18}F]flortaucipir



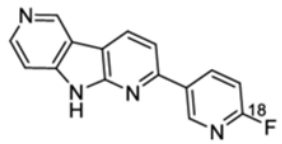
[^{11}C]PBB3



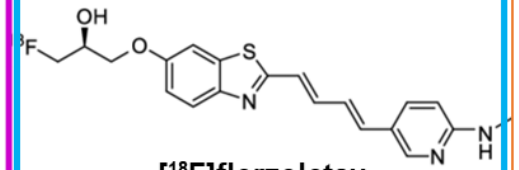
[^{18}F]THK-5351

	[^{18}F]flortaucipir	[^{11}C]PBB3	[^{18}F]THK-5351
AD-tau contrast	1.3 – 1.6	1.2 – 1.4	1.4 – 1.8
Non-AD-tau reactivity	4-repeat tau (low)	3-repeat tau 4-repeat tau	4-repeat tau?
Off-target binding	Melanocyte, MAO-A, choroid plexus, etc.	Choroid plexus, venous sinus	MAO-B

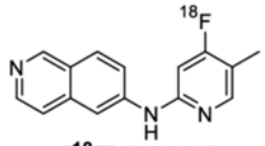
Second generation (1)



[^{18}F]RO948



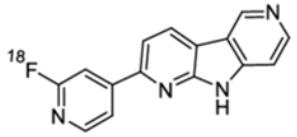
[^{18}F]florzolotau



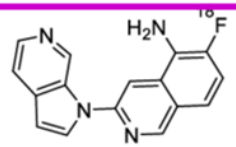
[^{18}F]JNJ-067

	[^{18}F]RO948	[^{18}F]florzolotau	[^{18}F]JNJ-067
AD-tau contrast	2.0 – 2.5	2.0 – 2.5	1.5 – 1.7
Non-AD-tau reactivity	Very low	3-repeat tau 4-repeat tau	Very low
Off-target binding	Melanin-containing neuron, retina, etc.	Choroid plexus	MAO-B

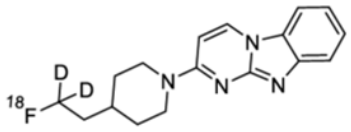
Second generation



[^{18}F]PI-2620



[^{18}F]MK-6240



[^{18}F]GTP1

	[^{18}F]PI-2620	[^{18}F]MK-6240	[^{18}F]GTP1
AD-tau contrast	2.0 – 2.5	2.0 – 3,0	2.0 – 3.0
Non-AD-tau reactivity	4-repeat tau	Very low	Very low
Off-target binding	Meniges, scalp, venous sinus, etc.	Meninges, skull	Choroid plexus, basal ganglia?

Courtesy Makoto Higuchi

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

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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)

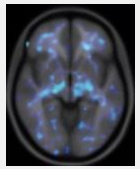
^{18}F-PI-2620 (Life Molecular Imaging)*

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

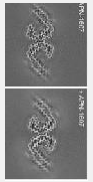
Useful in AD

^{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

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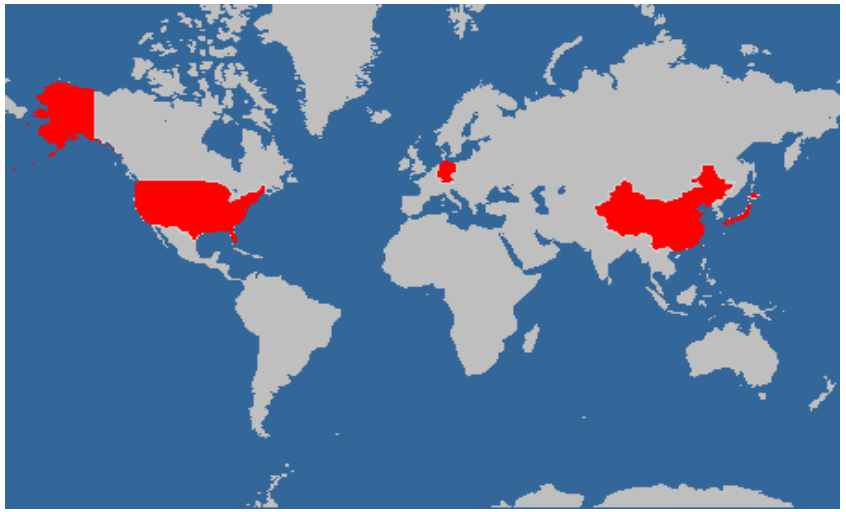
- >3000 individuals have been scanned to date at 15 sites in several countries.
  - Diverse diagnoses:
    - AD spectrum
    - 4R tauopathies (esp. PSP and variants); CBS; also various types of FTD, PiD (3R)
    - CTE
  - Cross-sectional and longitudinal studies
- Sponsored studies:
  - Phase 1 studies 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: Cryo-EM Identifies Binding in AD Tau folds

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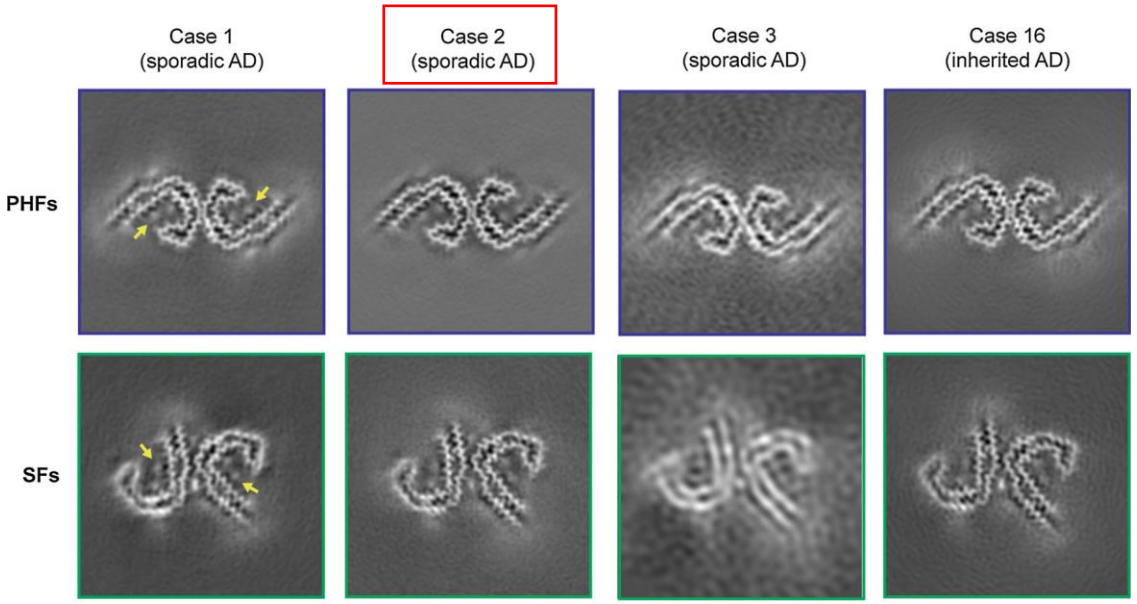
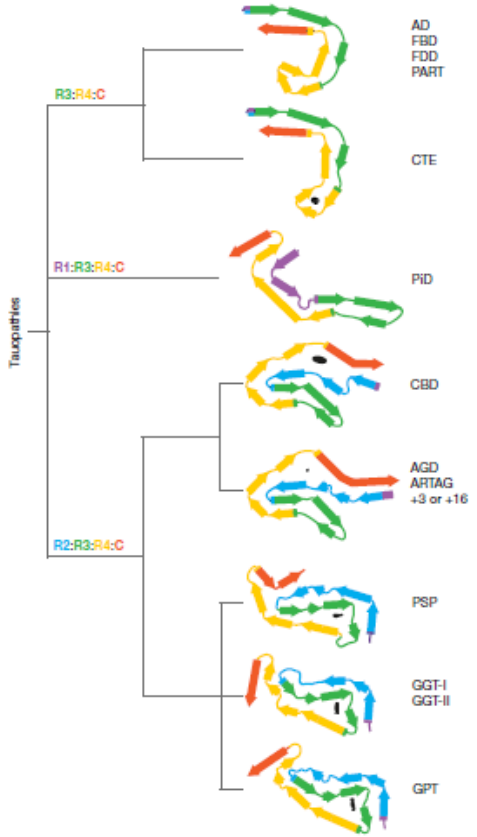
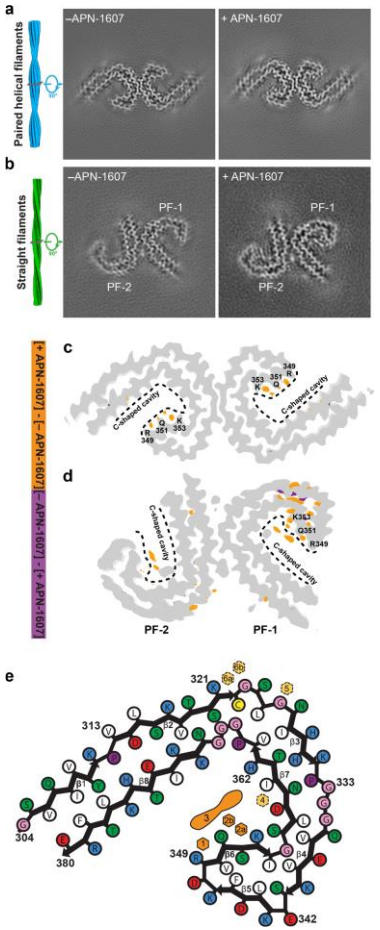
- Cryo-EM to determine the binding sites of the Alzheimer tau folds in PHF and SF
- Two major sites in the β-helix of PHFs and SFs and a third major site in the C-shaped cavity of SFs.
- Binding sites 1 and 2 have Q351 in common, which adopts an extended conformation



Falcon 2018

Shi et al; Acta Neuropath ,2021





Cryo-EM identifies Binding Sites in AD Tau Folds

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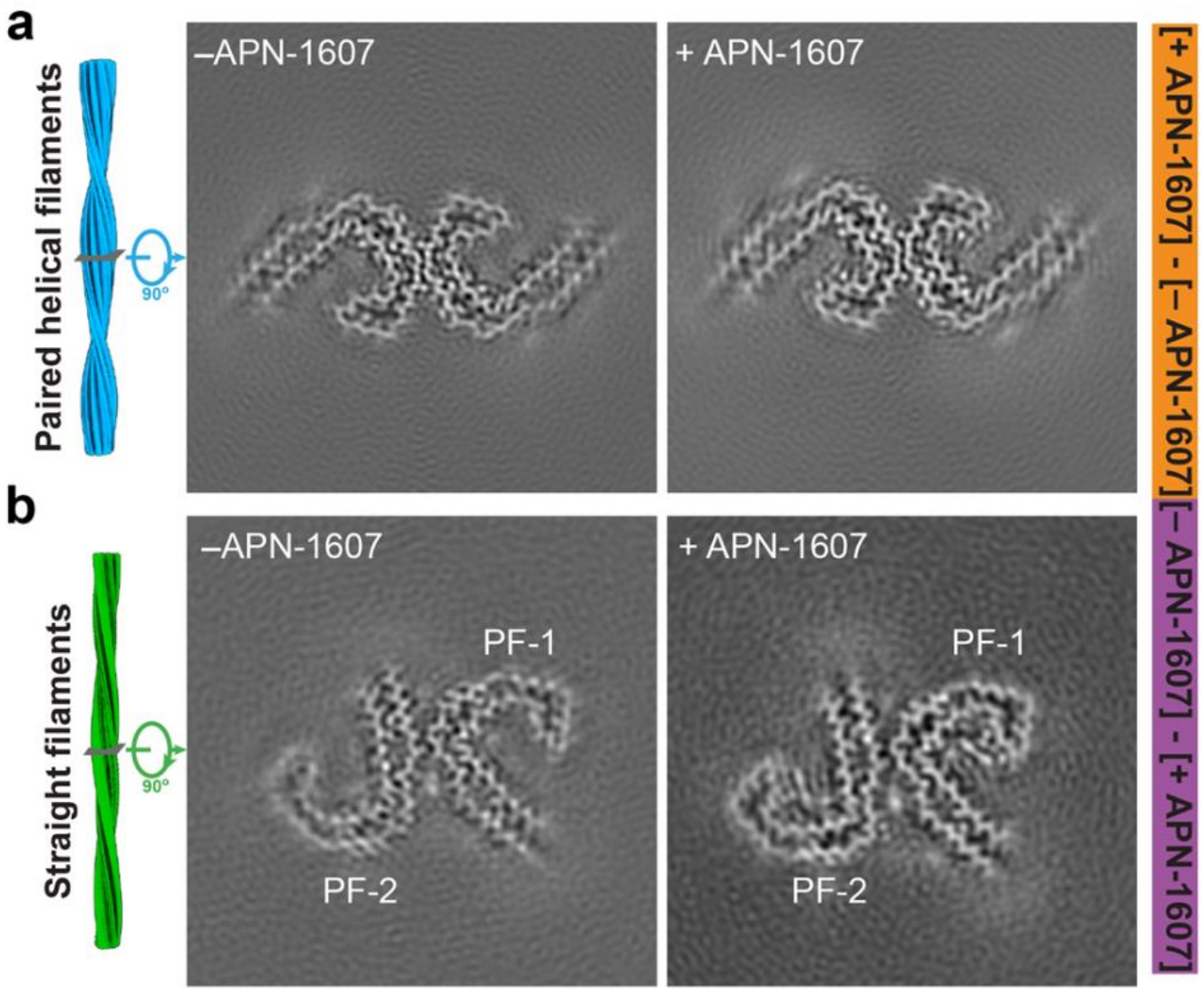

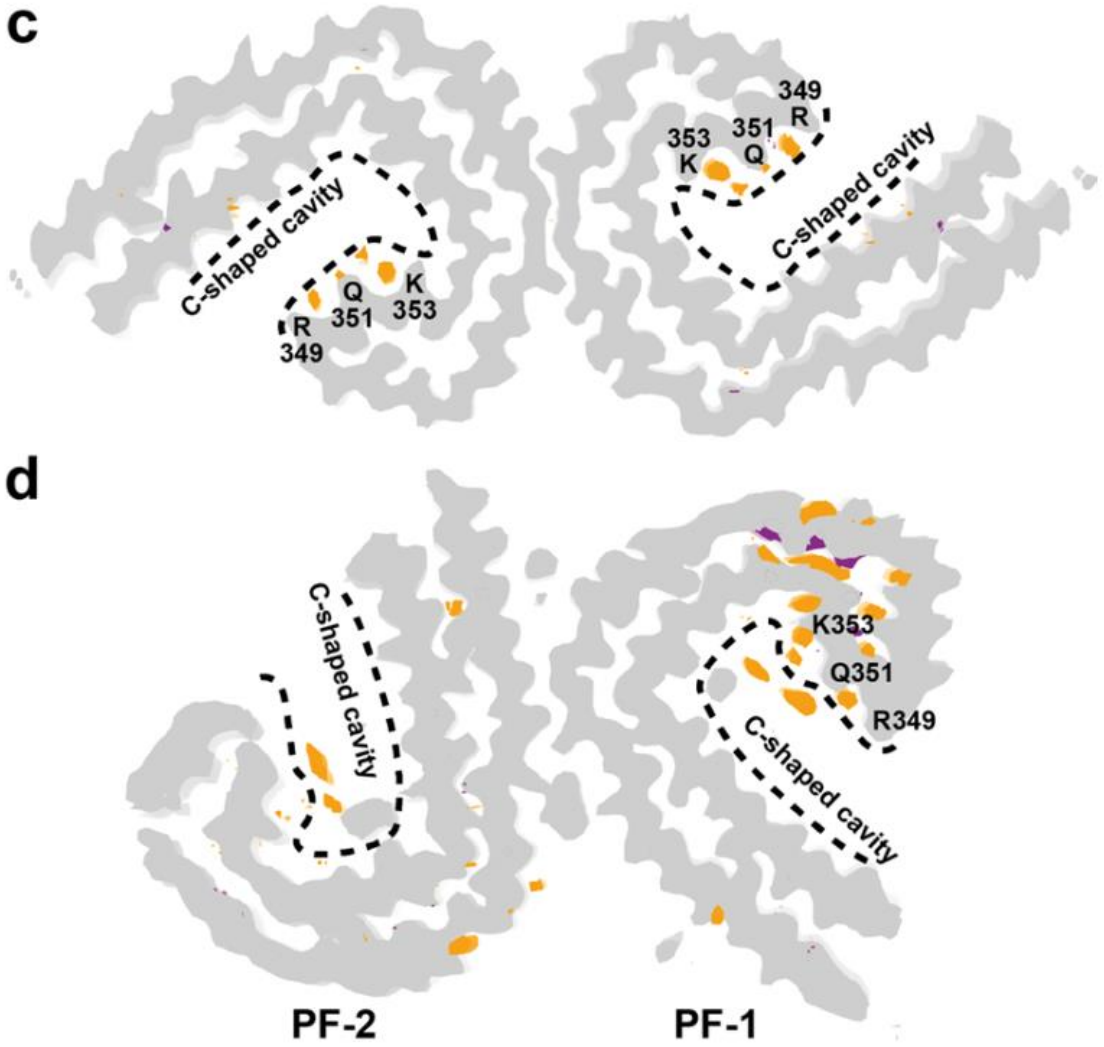

APN-1607: Nonclinical Profile

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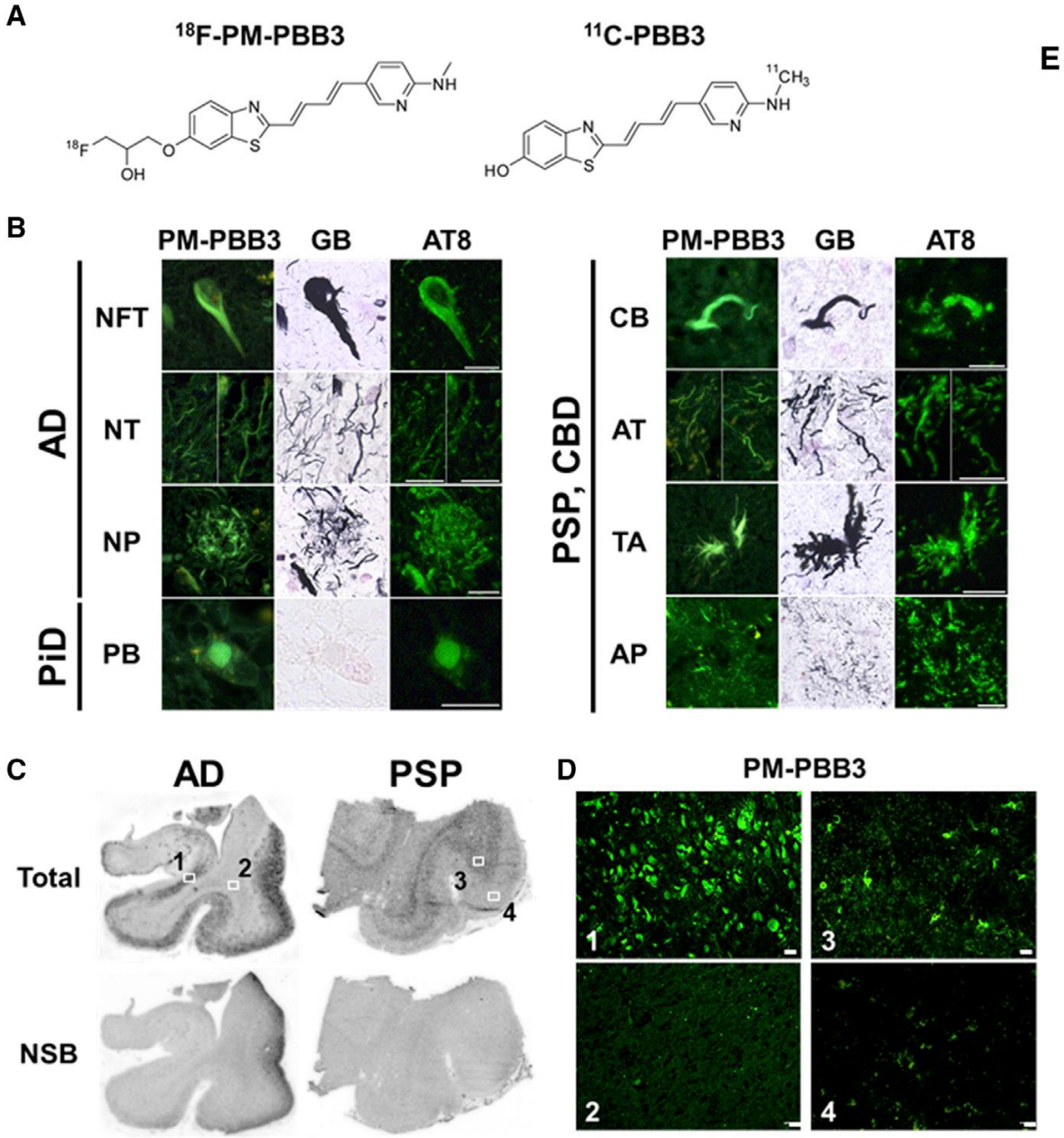
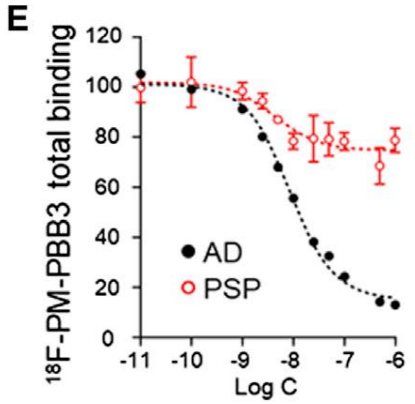
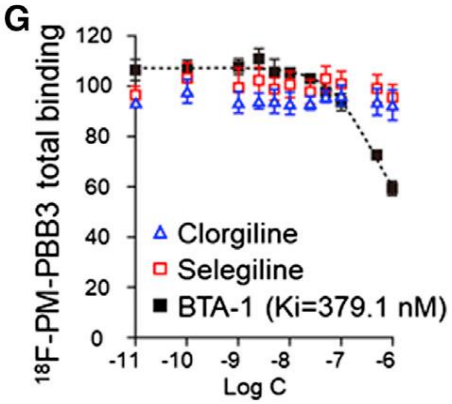




F

	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)

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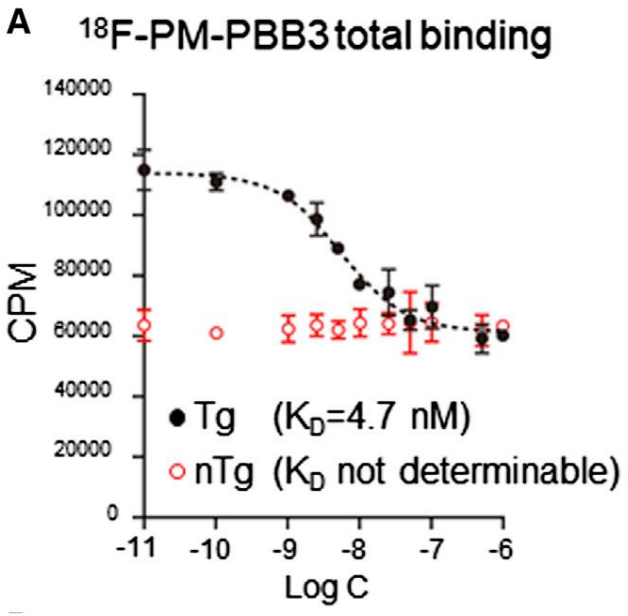

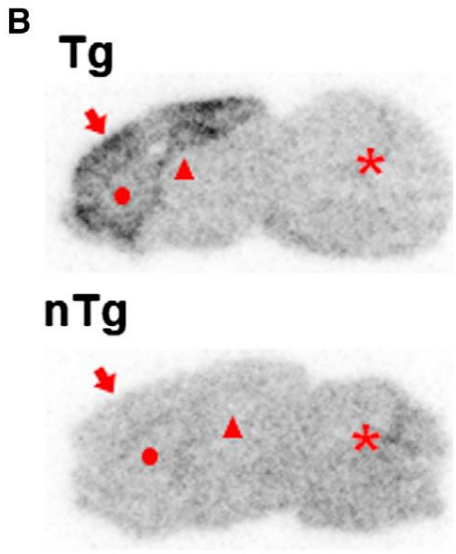

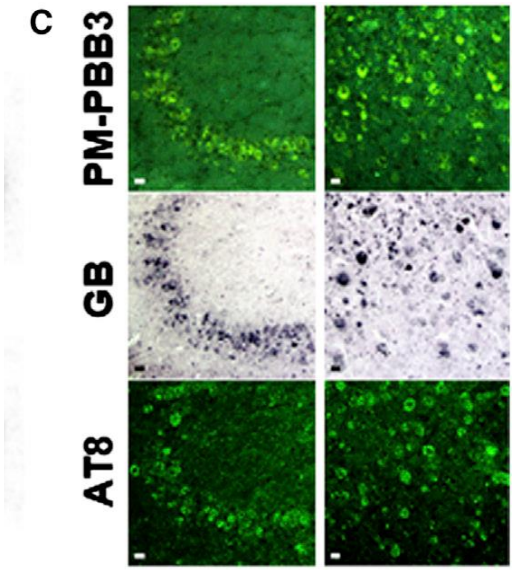

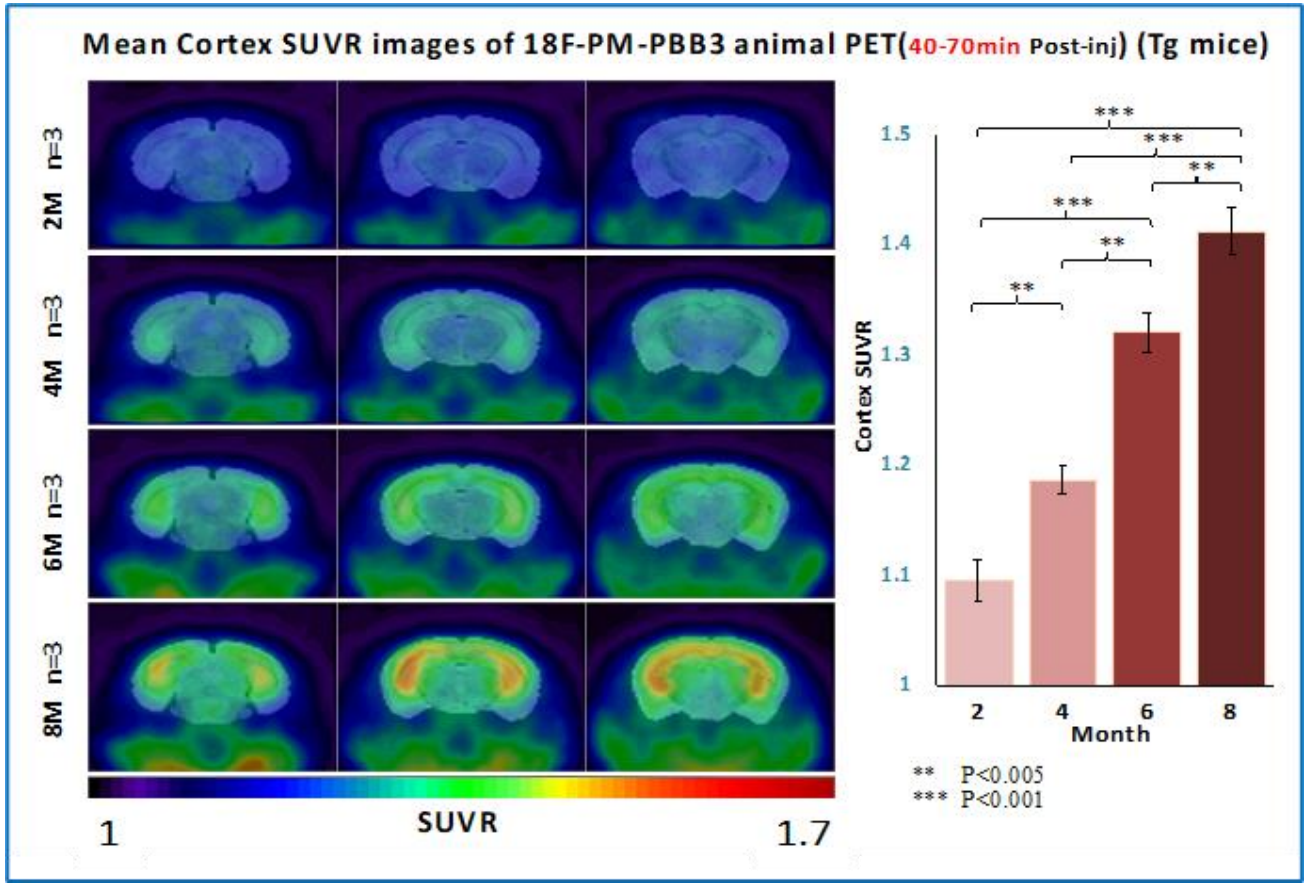

(Weng 2020; data on file)

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 in AD: Topology and Visualization of Spread

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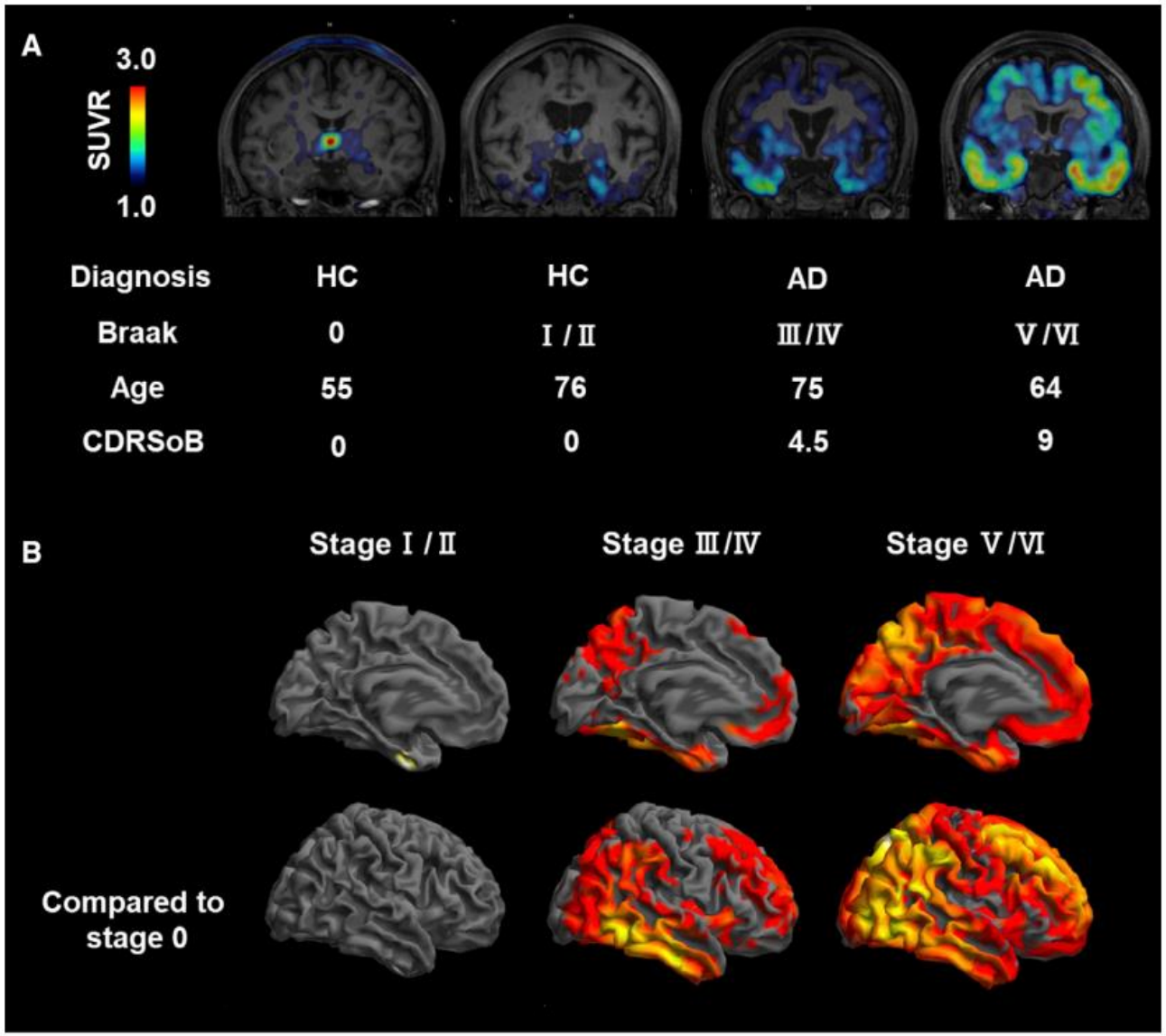

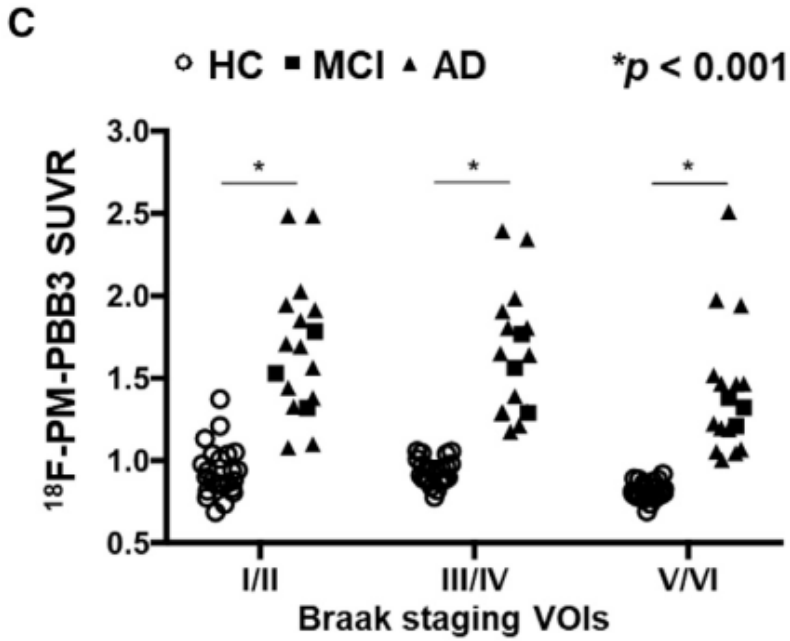

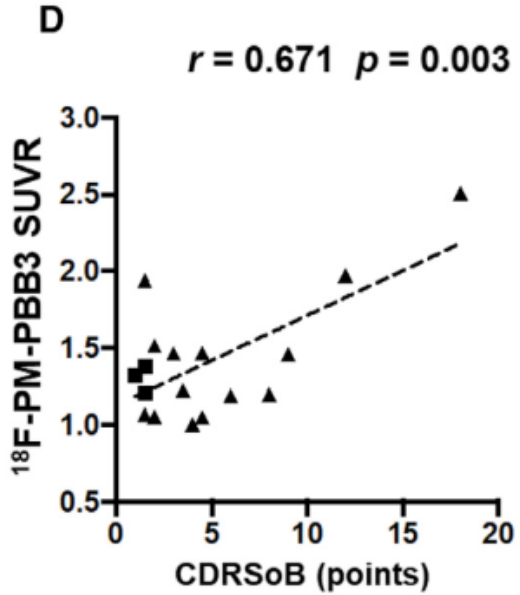

HC=23, MCI=3
AD=14

Tagai,et al; Neuron 2021

APN-1607 in PSP and Correlation with Disease Severity

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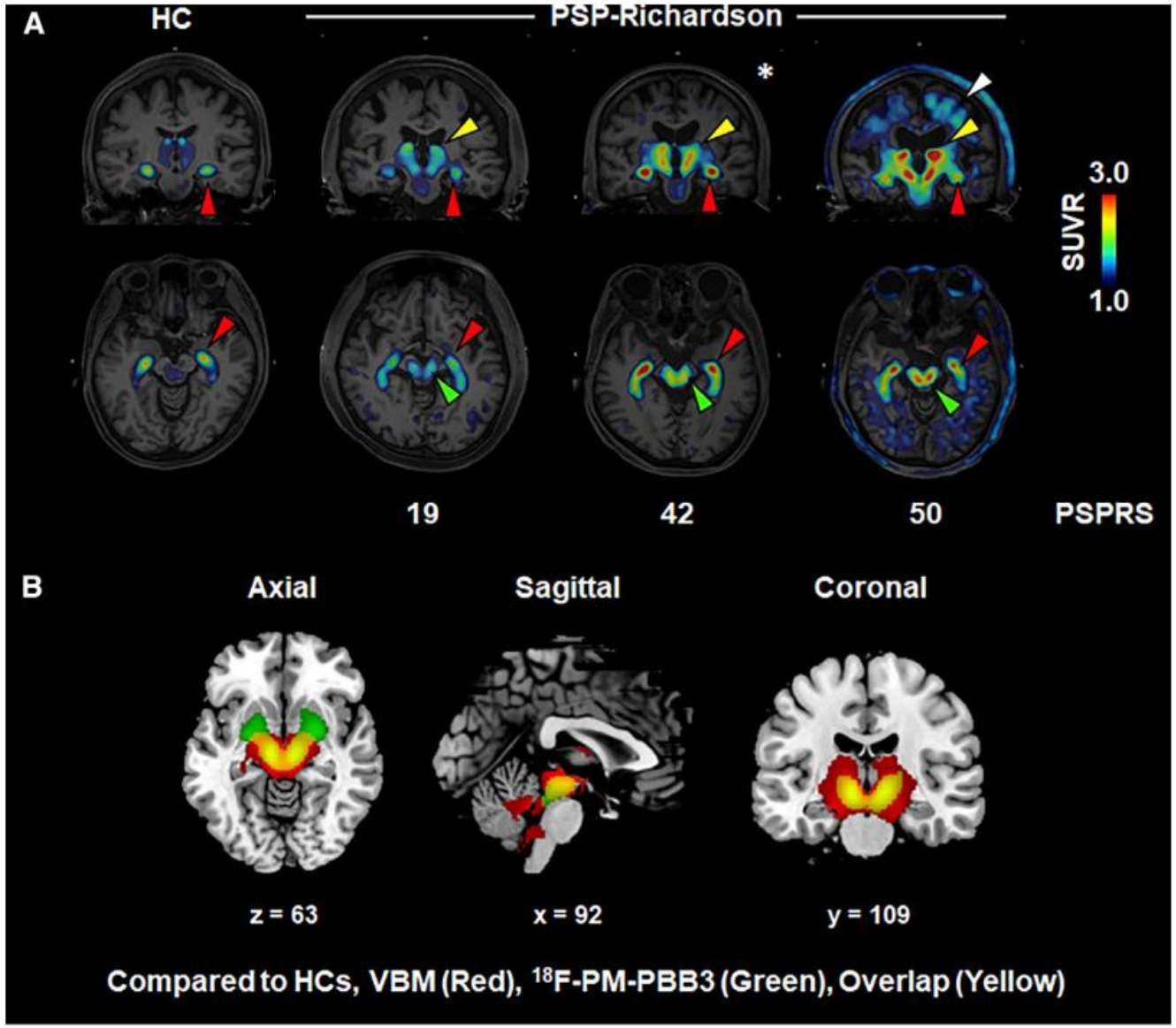
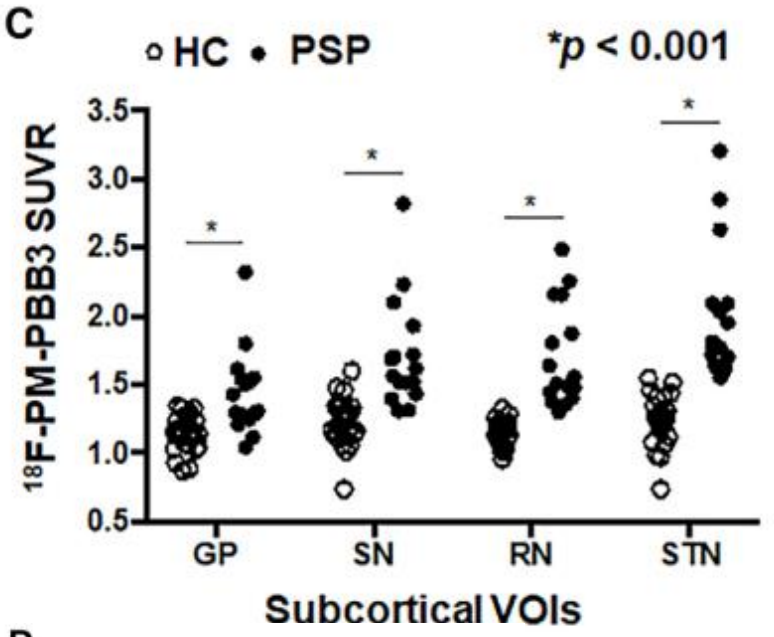
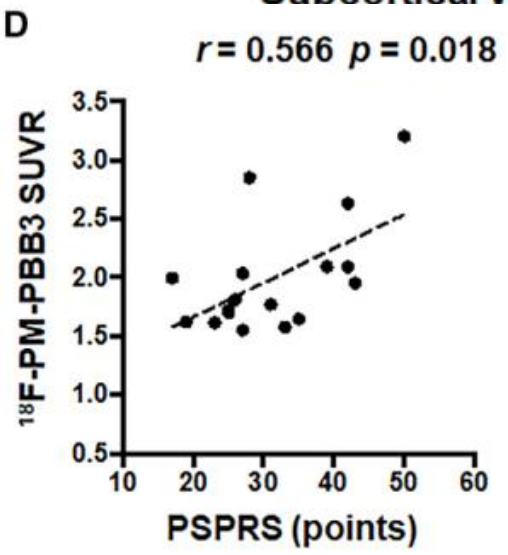




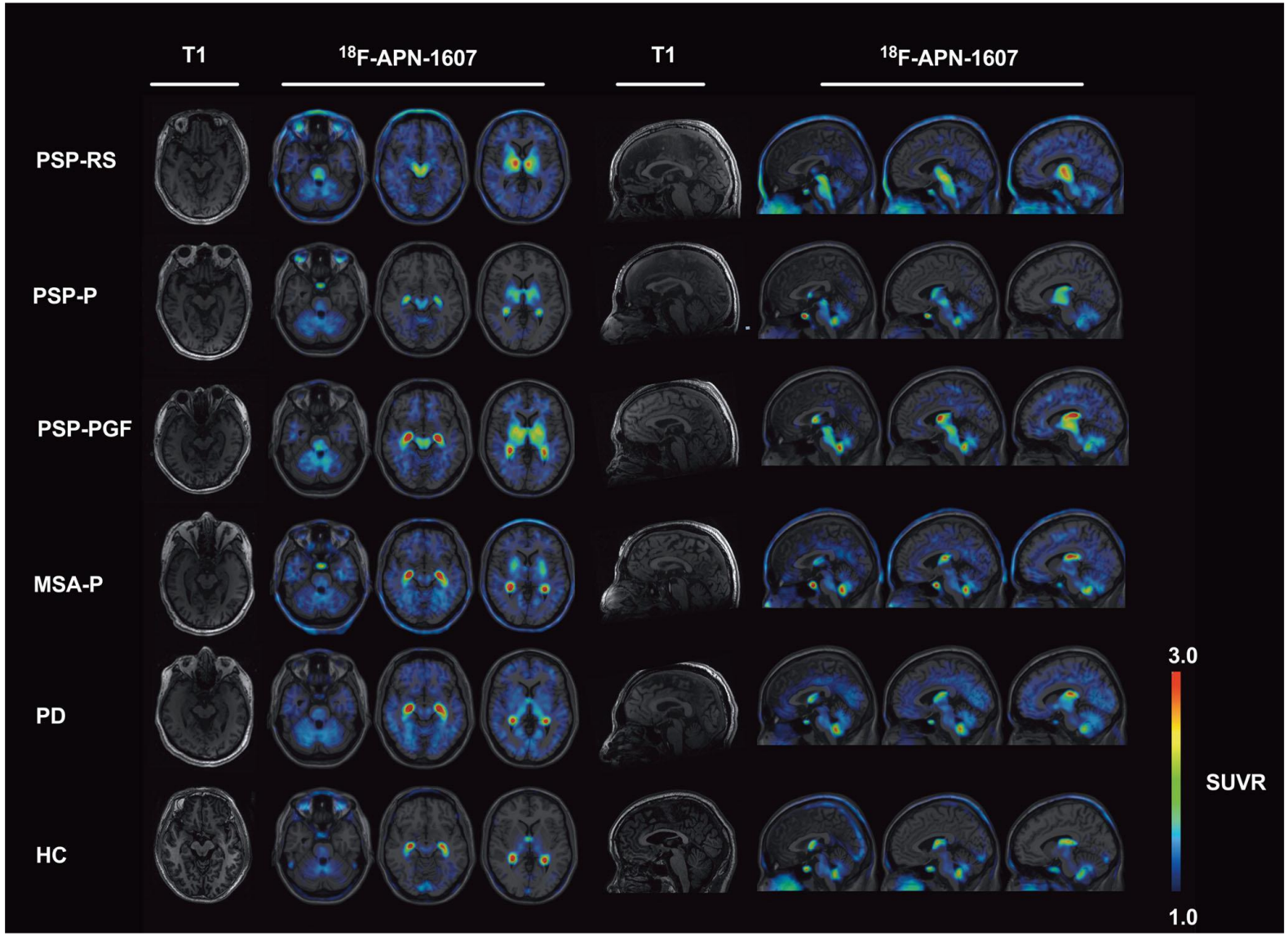


N= 16

Tagai,et al; 2021
)

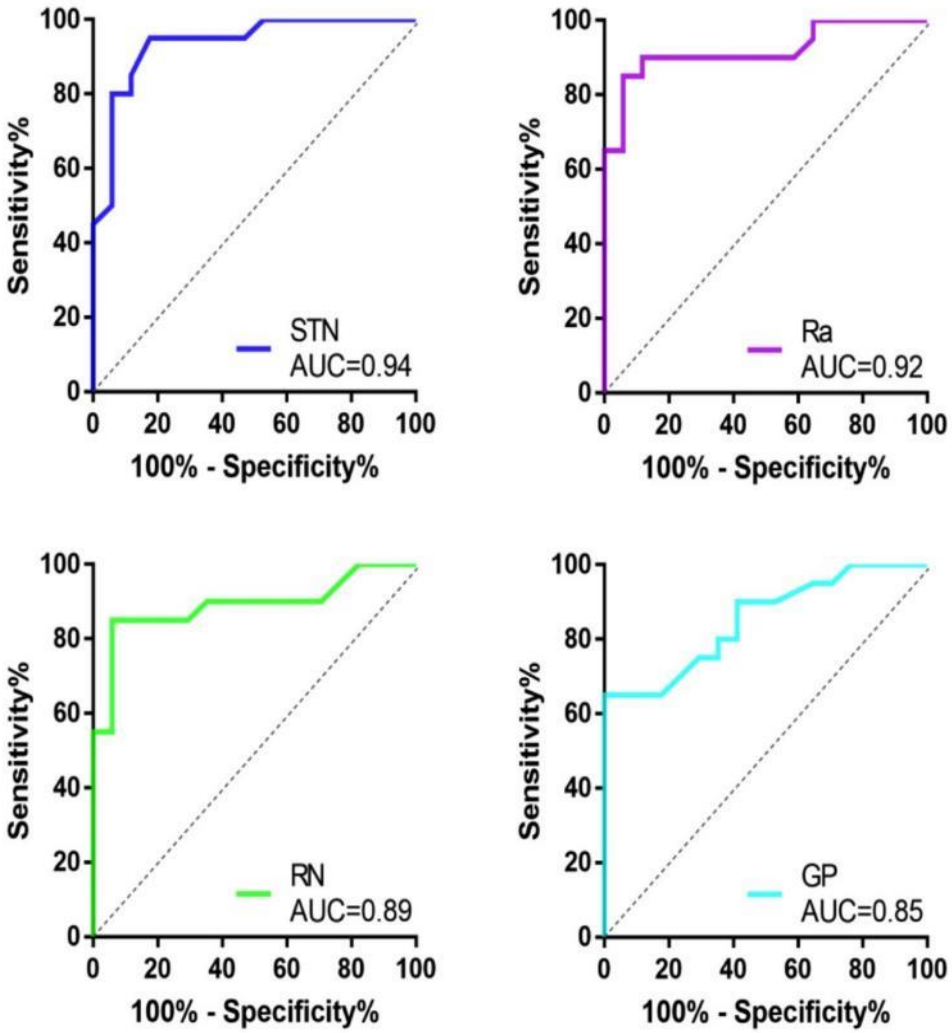
APN-1607 in PSP and Correlation with Disease Severity

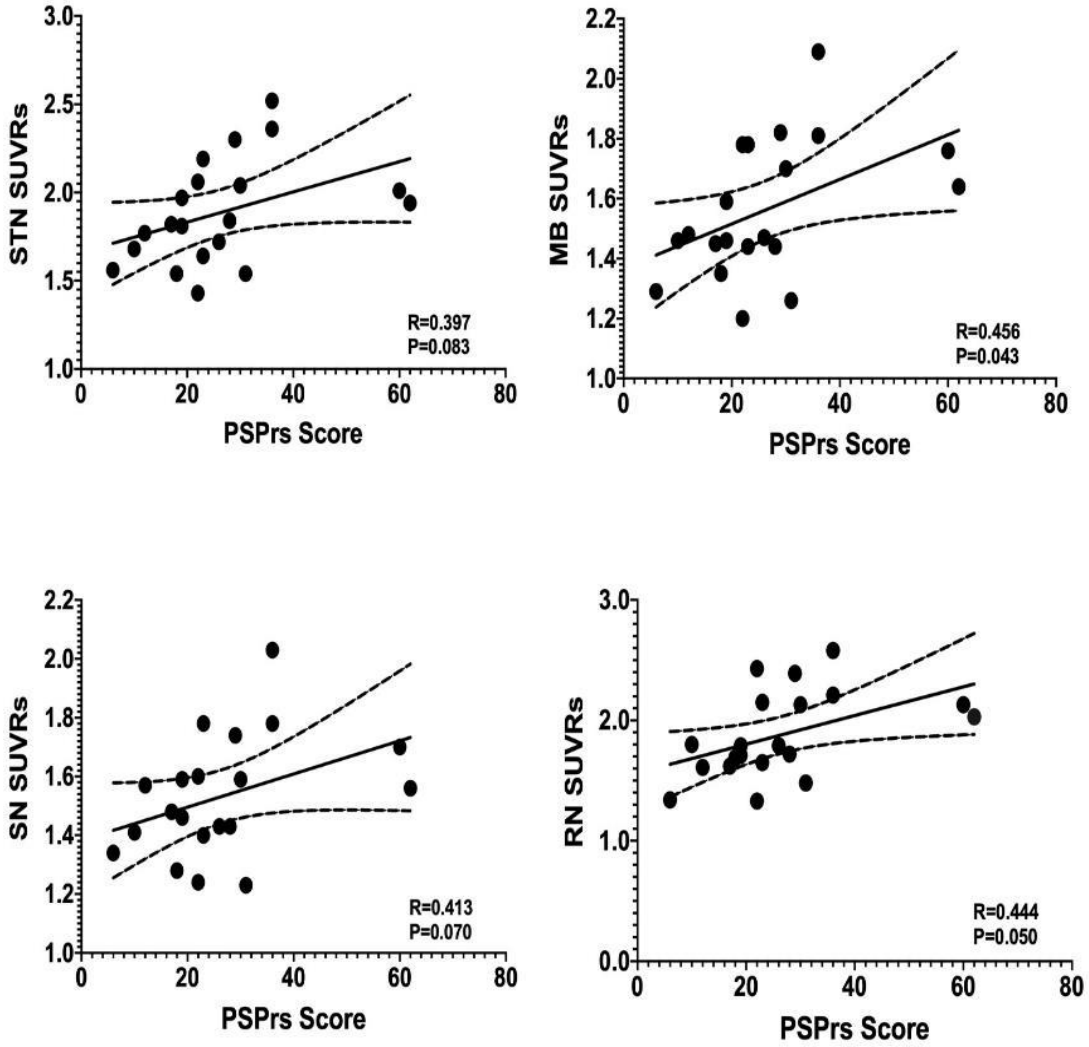
PSP=20,
{PSPRS=16)
MSA-P=7
PD=10
HC=13



Li, et al Mov Dis,2021

APN-1607 in PSP and Correlation with Disease Severity





Li et al , Mov Dis 2021

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

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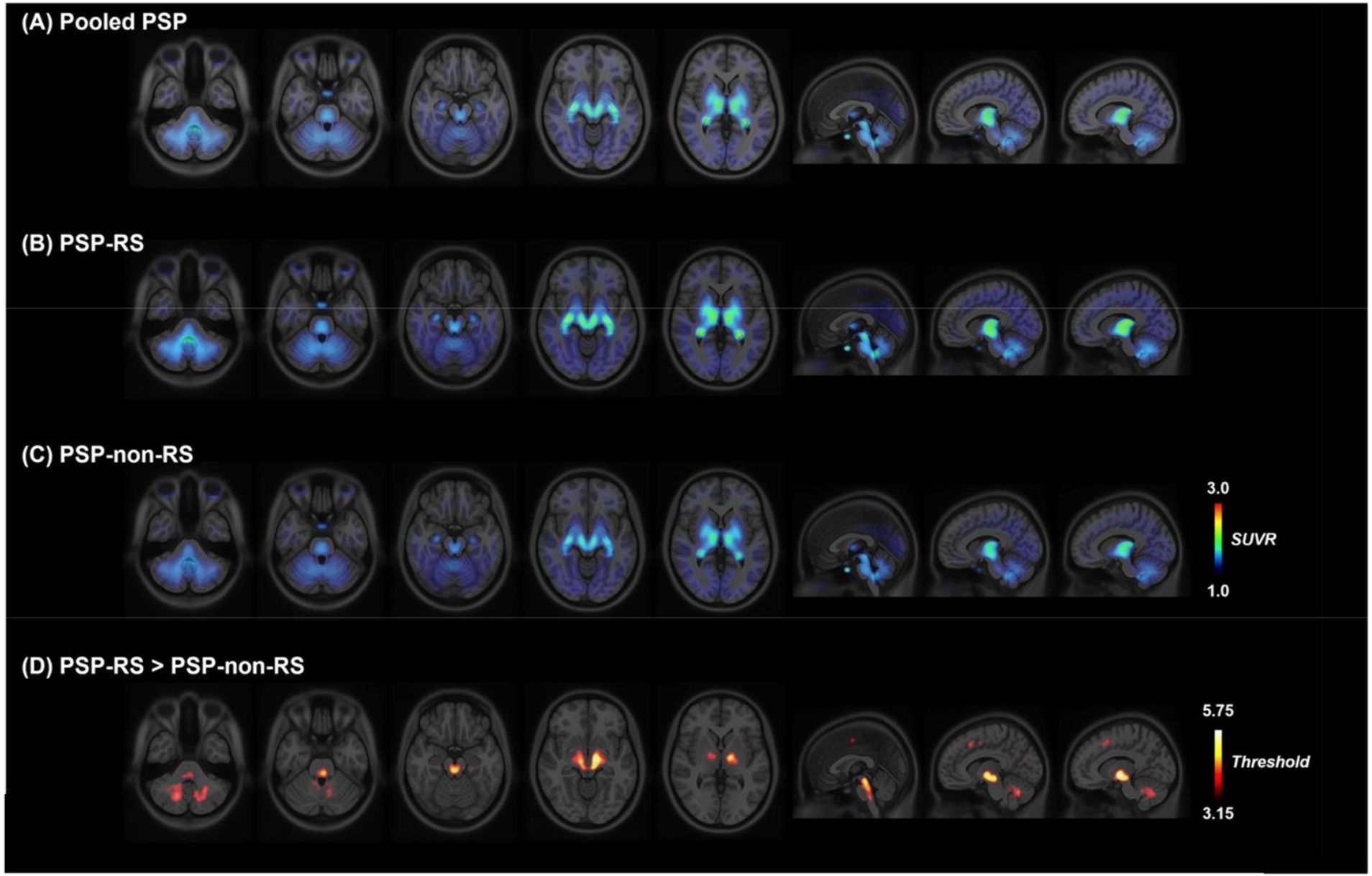
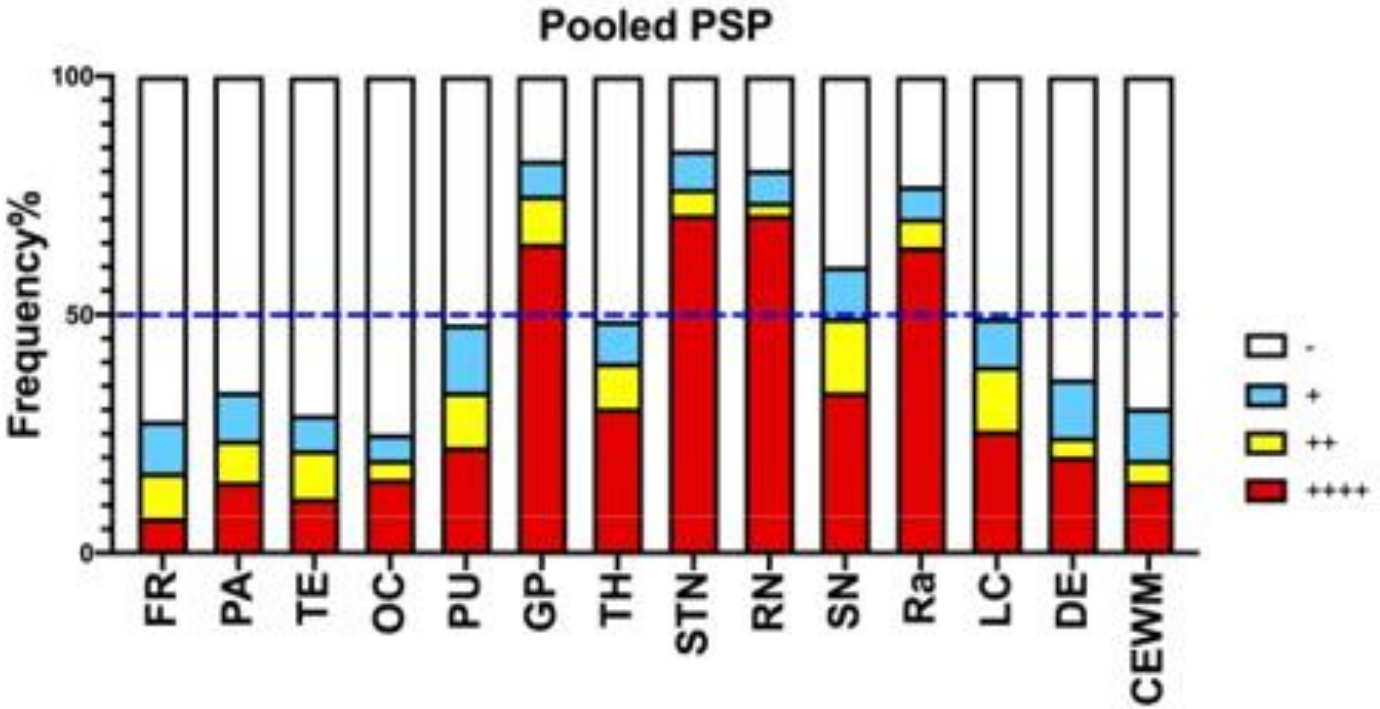
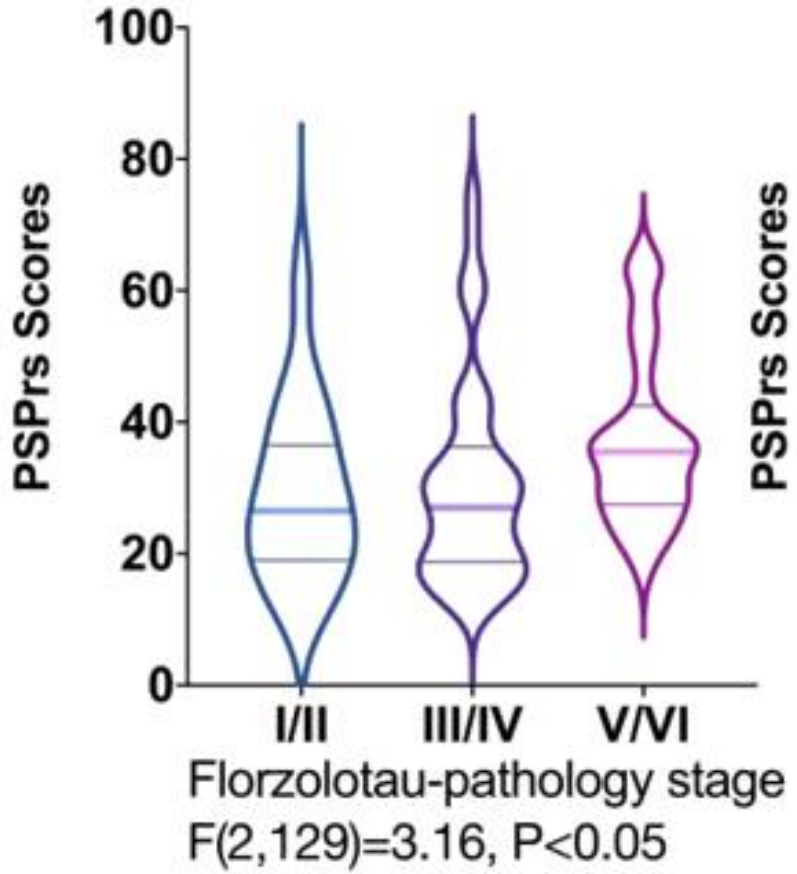
PSP=148
PSPRS=84
nonRS=64



Liu, et al, J Nucl Med & Mol Imag 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: J NuclMed & Mol Imag 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 are similar to the reconstructed maps of tau propagation in *postmortem* studies (Kovacs et al, Acta Neuropath, 2020)
- APN-1607 offers promising approach for the diagnosis of PSP and related tauopathies

APN-1607 in FTD: Findings in *Mapt* Mutation Carriers

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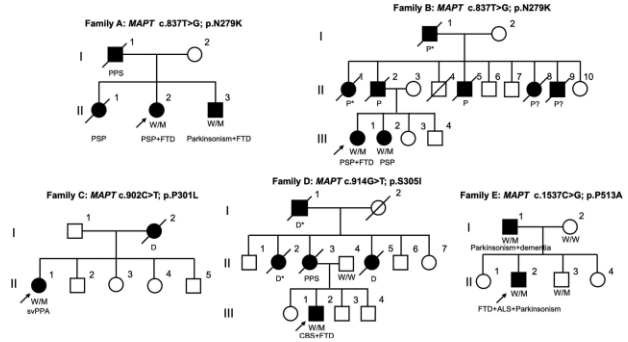
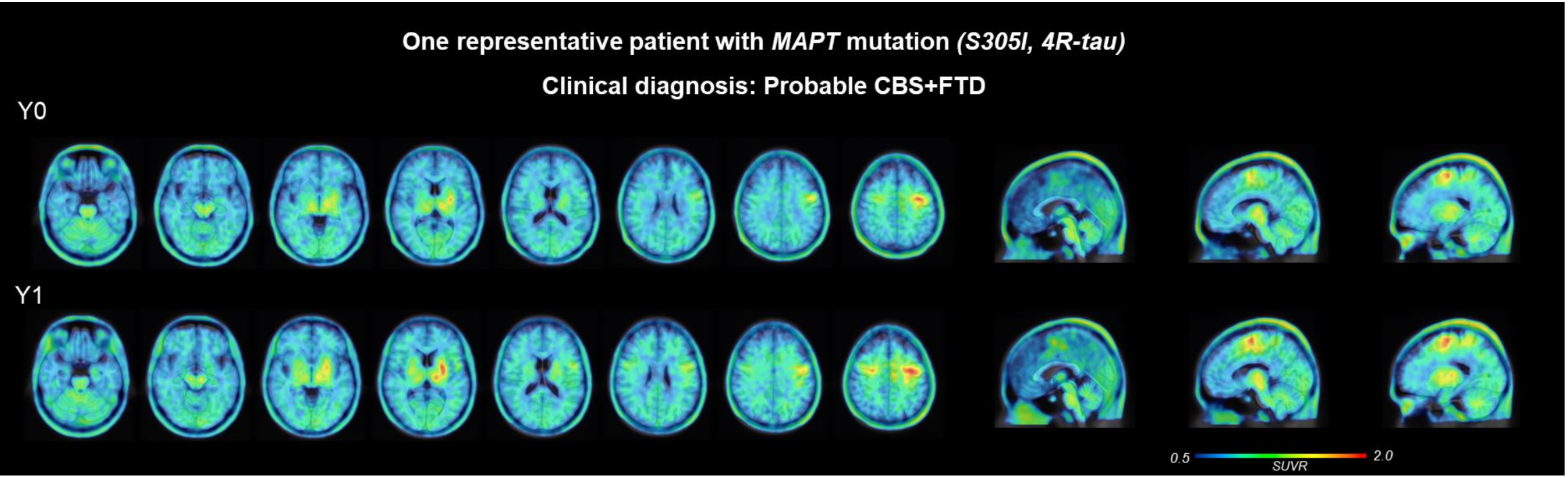


- Study of 7 patients with various *Mapt* mutations (Zhou 2021)
  - Exon 10, 4R tau-associated (6): N279K (4), P301L (1), S305I (1)
  - Non-exon 10, 3R/4R tau-associated: P513A (1)
  - Various ages, phenotypes and diagnoses; MRI, FDG, and DAT profiling
- Baseline APN 1607 PET scans in all subjects; positive 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 in Pathology Confirmed Cases of CBS, PSP and PiD

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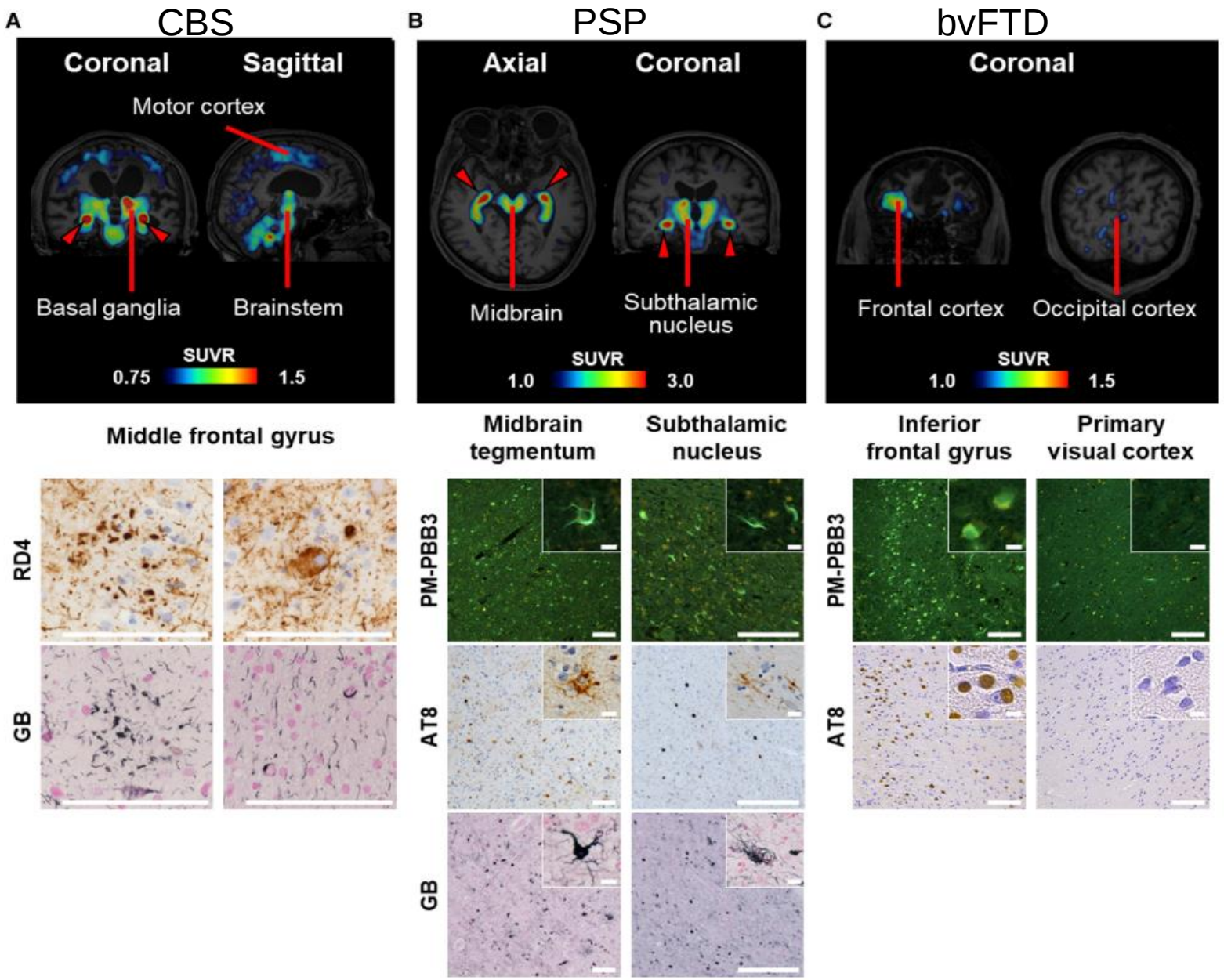
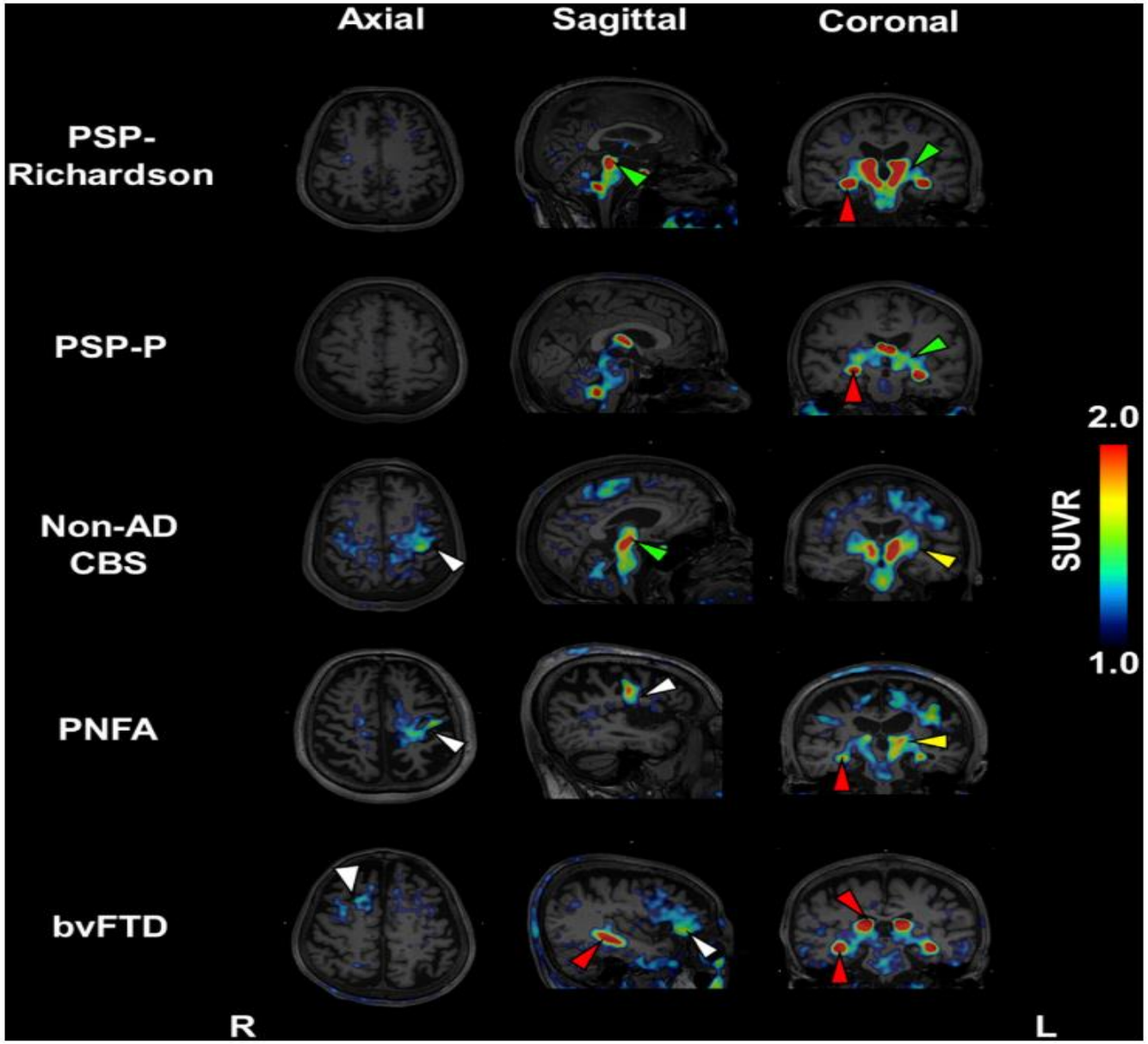


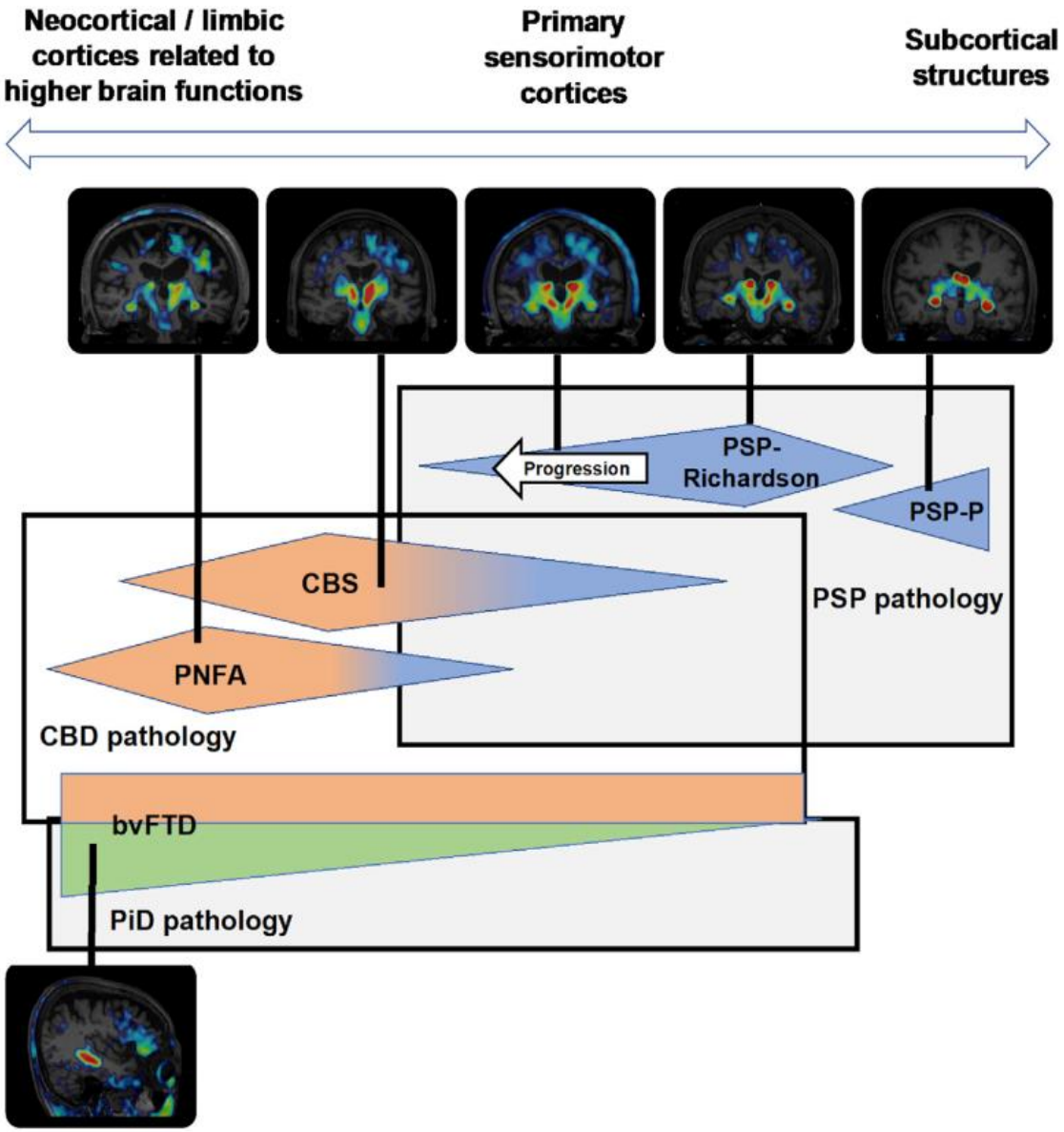
Tagai et al, 2021

APN-1607 Differentiates Anatomical Patterns Across nonAD Tauopathies



(Tagai,et al 2021)

APN-1607 Can Detect Distinct Anatomical Patterns across Different Tauopathies



(Tagai, 2021)

APN 1607-Phase 3 for PSP
First- in- Class 4R Tau Tracer
Next Steps

APRINOIA

Development of APN-1607 for PSP: Path to Approval

APRINOIA

- No approved biomarkers for the detection of 4R tau in patients suspected to have PSP
- Published data in approx.180 PSP patients (RS and nonRs) have shown consistent patterns of APN -1607 uptake (e.g., subthalamus) with correlations with clinical severity
- Sensitivities and specificities >85%
- The distribution and dynamics of APN-1607 accumulation in PSP similar to the reconstructed maps of tau propagation in *postmortem* studies (Kovacs et al, Acta Neuropath, 2020)
- FDA issued a “May Proceed” for Phase 3 trial on December 8, 2023, indicating that single pivotal, prospective global Phase 3 study may serve as the primary basis for the approval of APN-1607 as a diagnostic marker for early PSP without pathology confirmation
- ADDF award for Phase 3 Trial, May, 2023
- Visual Read in Development (John Seibyl)
- Fast track designation granted May 8, 2024
- Planned FPI: 4Q,2024

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

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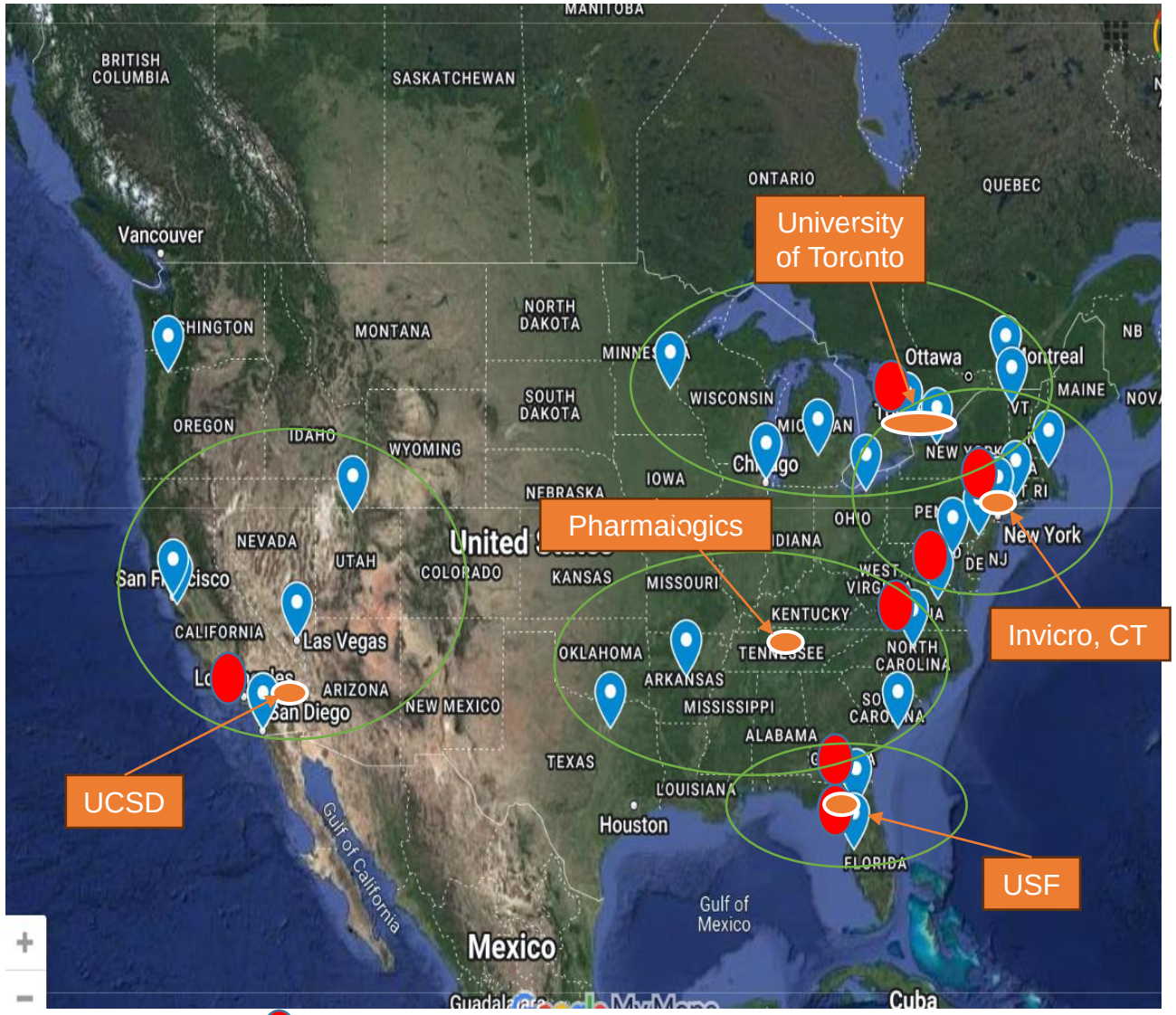

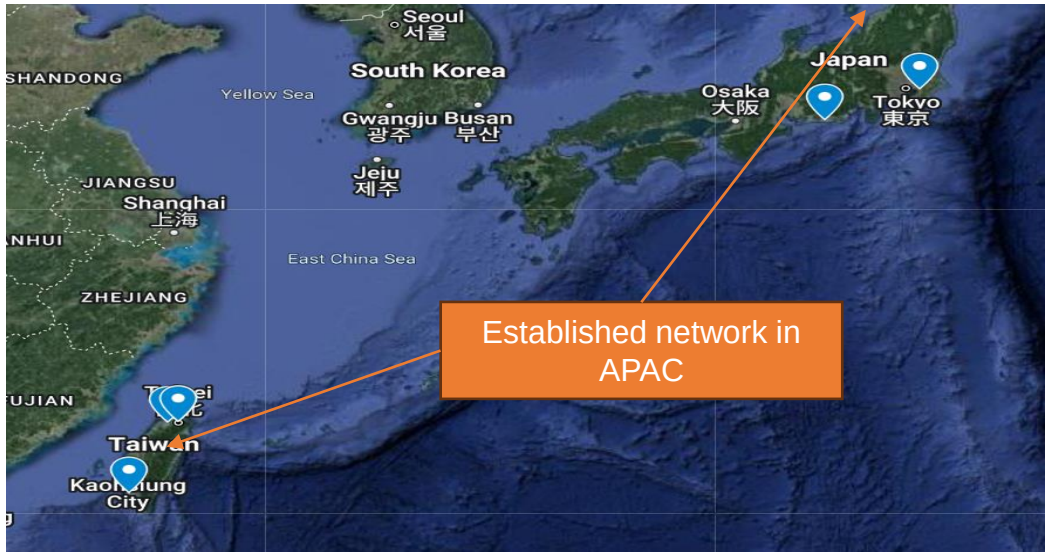

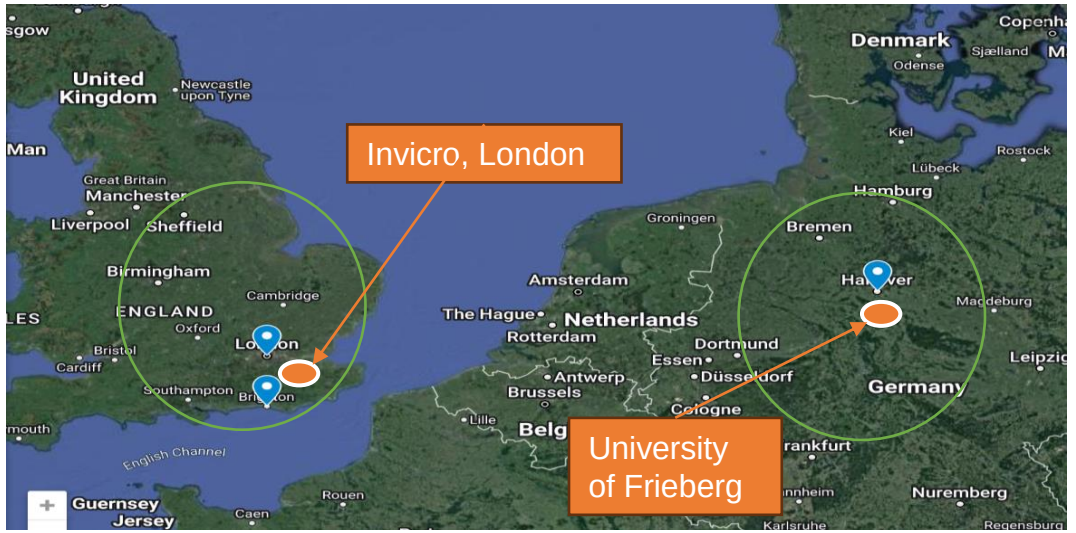

Key clinical sites

CMO Network

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

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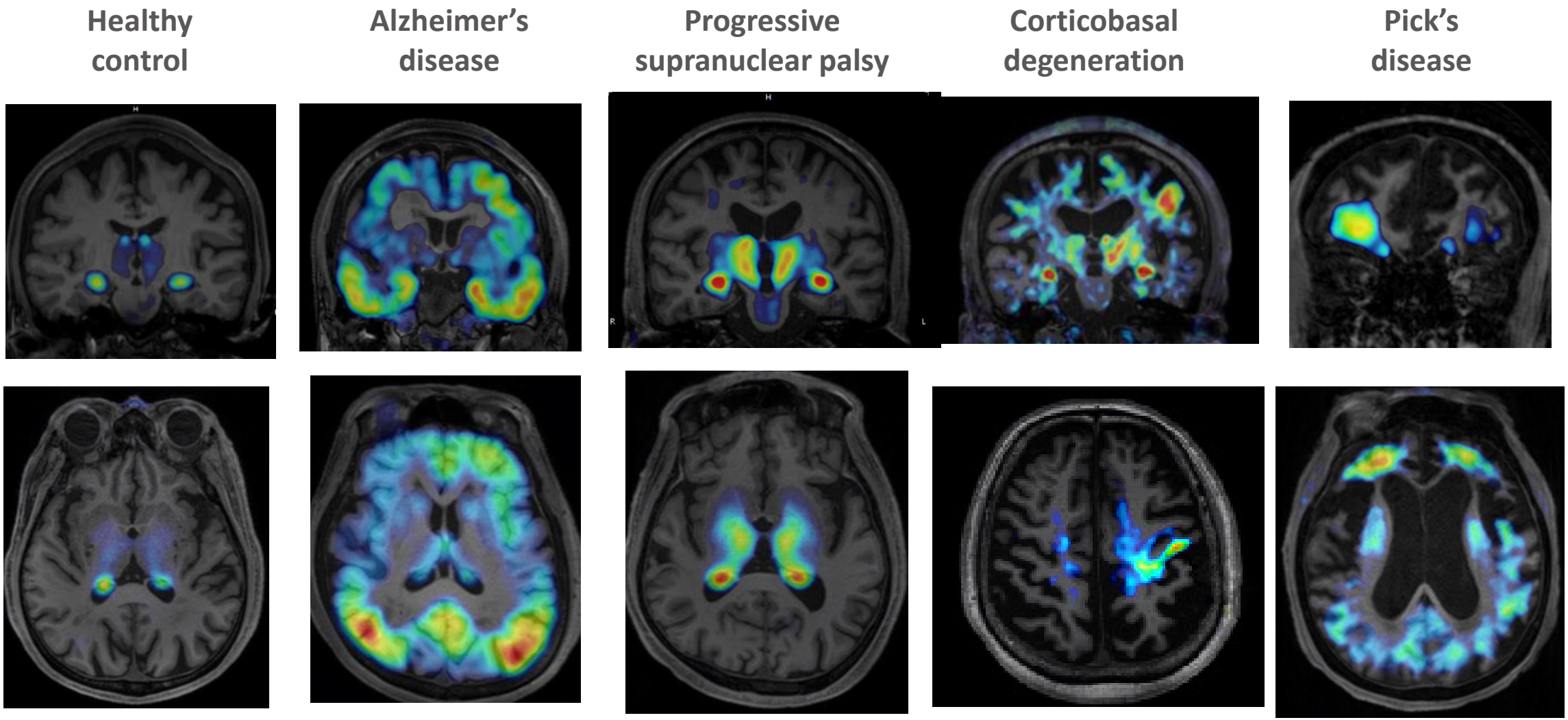

(Tagai, et al 2021)

APN 1607 Can Track Disease Progression in AD and PSP

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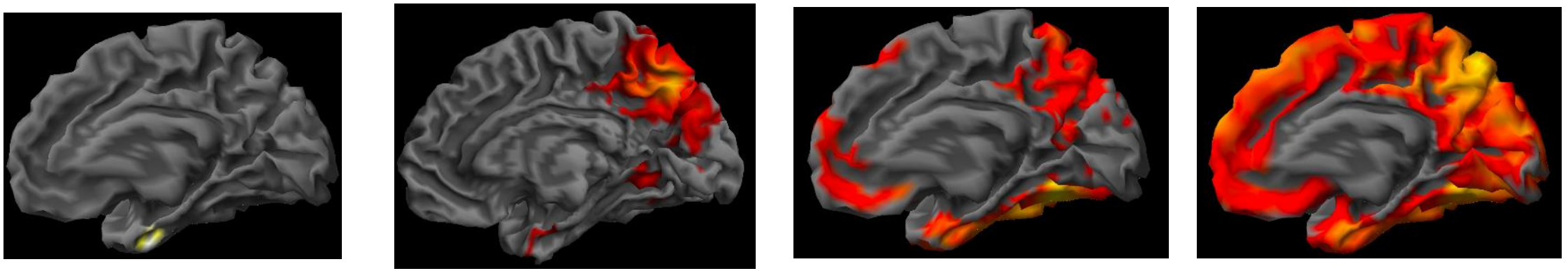
Aging

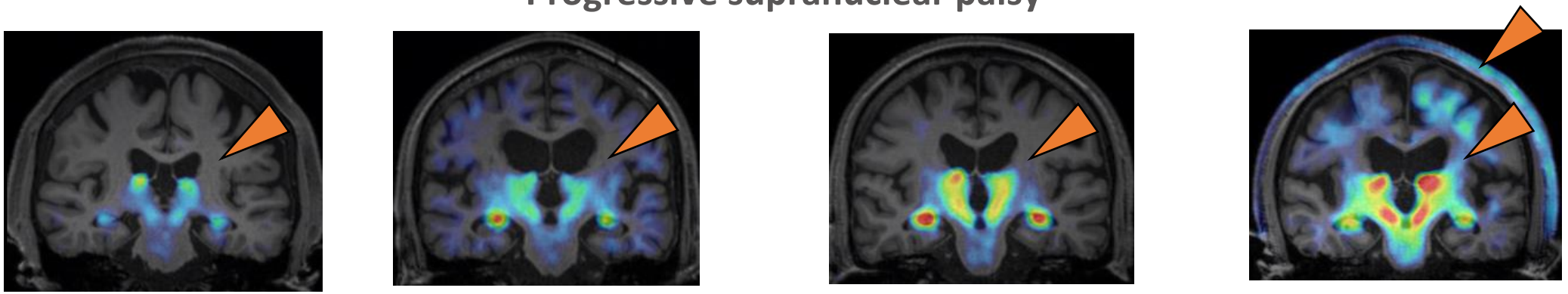
Mild cognitive impairment

Alzheimer dementia



Clinical severity

Progressive supranuclear palsy



Clinical severity

(Neuron 2021)

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

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Conclusions

- APN-1607 can detect multiple tau isoforms: AD-type (3R+4R), PSP/CBD-type (4R), PiD-type (3R) and CTE-type (3R +4R) tau aggregates
  - Unlike other PET tau tracers, APN-1607 binds to a groove-like pocket spanning β-sheet stacks in diverse tau filaments

- APN-1607 is widely used globally to aid the diagnosis of various tauopathies, including AD, PSP and FTD

- Emerging data suggests APN 1607 may also be useful in the diagnosis of CTE

- Fast track designation granted to APN 1607 for the PSP program, May 8, 2024

- A single global phase 3 for the approval of APN-1607 as diagnostic marker for early PSP is planned for Q4, 2024

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