^{18}F-AV-1451 PET in movement disorders

류 철 형
연세대학교 의과대학 신경과학교실

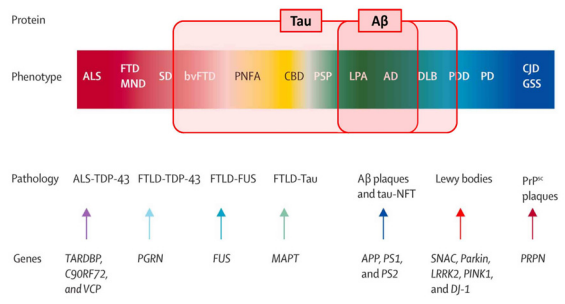
Chul Hyoung Lyoo
Department of Neurology, Yonsei University College of Medicine, Seoul, Korea

Outline of Talk

1. Background and brief summary of new radiotracers for tau
2. Distinct ^{18}F-AV-1451 binding pattern in PSP and CBS
3. Tau accumulation in Lewy body diseases spectrum
4. Age-related iron accumulation and ^{18}F-AV-1451 binding in basal ganglia
5. ^{18}F-AV-1451 PET as new biomarker for differential diagnosis of parkinsonism

Development of radiotracers for tau PET imaging

Clinical, genetic, and pathological spectrum of neurodegenerative diseases with the accumulation of misfolded protein



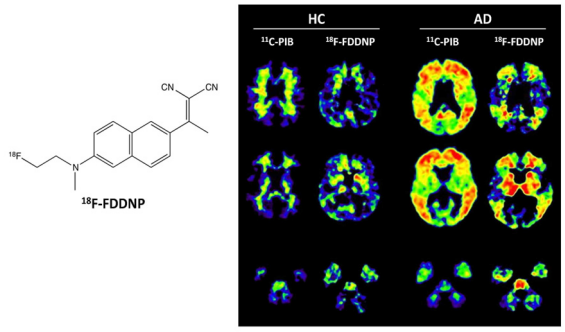
Villemagne VL, Lancet Neurol 2015;14:114

Tau isoforms for specific diseases

	Tauopathy	Histopathology	
		Light microscopy	Electron microscopy
Type 1			
3R and 4R isoform	Alzheimer's disease	Neurofibrillary tangles	Paired helical filaments; straight filaments*
3R and 4R isoform	Down's syndrome	Neurofibrillary tangles	Paired helical filaments; straight filaments*
3R and 4R isoform	Chronic traumatic encephalopathy	Neurofibrillary tangles	Paired helical filaments; straight filaments*
3R and 4R isoform	Niemann-Pick disease type C	Neurofibrillary tangles	Paired helical filaments; straight filaments*
Type 2			
4R isoform	Corticobasal degeneration	Astrocytic plaques	Straight filaments; twisted filaments*
4R isoform	Progressive supranuclear palsy	Globose tangles; tufted astrocytes	Straight filaments; twisted filaments*
4R isoform	Argyrophilic grain disease	Limbic argyrophilic grains; oligodendroglial coiled bodies	Straight filaments
Type 3			
3R isoform	Pick's disease	Pick's bodies	Twisted filaments; straight filaments*
Type 4			
Short 0N3R isoform	Myotonic dystrophy	Neurofibrillary tangles	NA

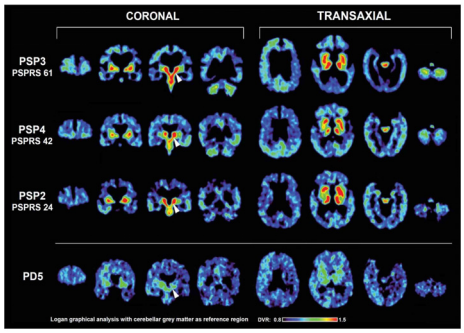
Villemagne VL, Lancet Neurol 2015;14:114

^{18}F-FDDNP binds to both β-amyloid and tau protein.



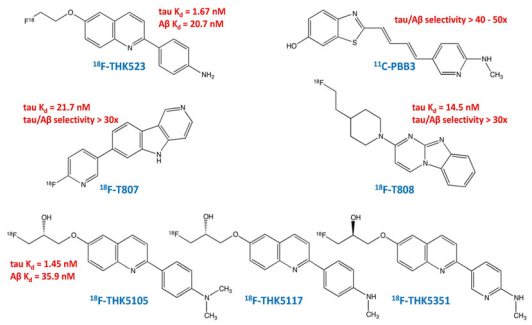
Tolboom N, J Nucl Med 2009;50:191

^{18}F-FDDNP PET in PSP patients showed increased binding in striatum, thalamus, subthalamus, midbrain, and cerebellar WM.



Kepe V, JAD 2013;36:145

New tau-selective radiotracers

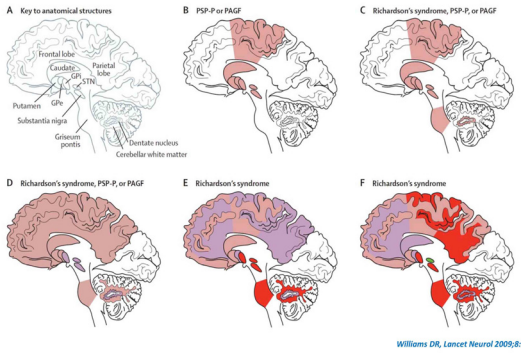


Characteristics of tau PET ligands

	Pros and cons
^{18}F-THK523	high WM uptake, lower affinity difficult to discriminate specific binding from background visually
^{18}F-THK5105	high WM uptake, high brainstem uptake
^{18}F-THK5117	high WM uptake, high brainstem uptake
^{18}F-THK5351	much lower WM uptake than other THKs high brainstem uptake may binds to various forms of tau or non-specificity
^{18}F-AV-1451 (^{18}F-flortaucipir) (^{18}F-T807)	very low non-specific white matter binding high contrast between background and specific binding rare skull uptake due to defluorination high affinity to AD tau, intermediate to FTD tau, and low to PSP or CBD tau "off-target" binding in the striatum, substantia nigra, and choroid plexus unstable kinetics and unstable SUVR
^{18}F-T808	stable kinetics and stable SUVR frequent defluorination and high skull uptake
^{11}C-PBB3	high retention in the venous sinus contamination of brain by large amount of radiometabolites

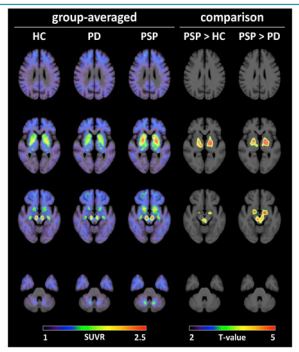
^{18}F-AV-1451 PET studies in parkinsonian diseases

Topographical pattern of tau pathology in different clinical phenotypes of PSP



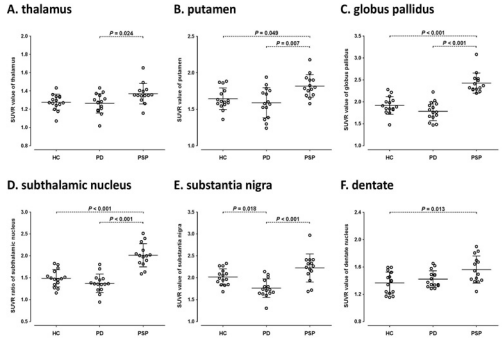
Williams DR, Lancet Neurol 2009;8:270

PSP patients show increased ^{18}F-AV-1451 binding in the globus pallidus and midbrain.



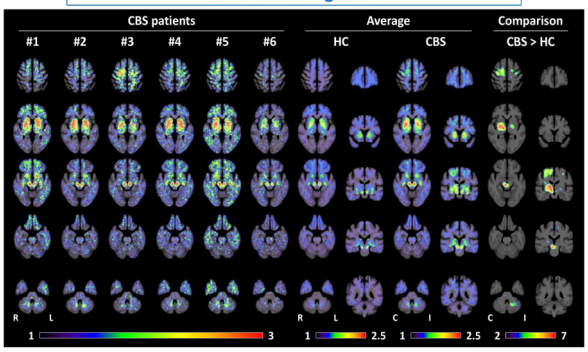
Cho H, Mov Disord 2017;32:134

^{18}F-AV-1451 PET can be helpful for the differential diagnosis of parkinsonism.



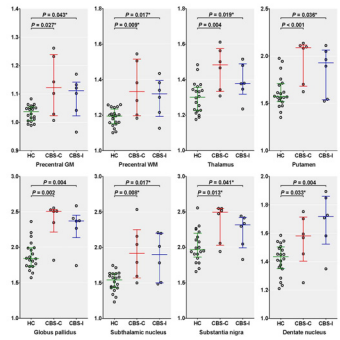
Cho H, Mov Disord 2017;32:134

CBS patients shown asymmetrically increased ^{18}F-AV-1451 binding in the motor-related cortical and subcortical regions.



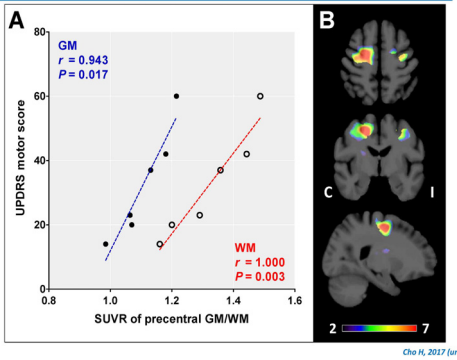
Cho H, 2017 (under review)

In CBS, increased ^{18}F-AV-1451 binding is little more prominent in the motor-related subcortical gray and white matter regions than cortical gray matter.



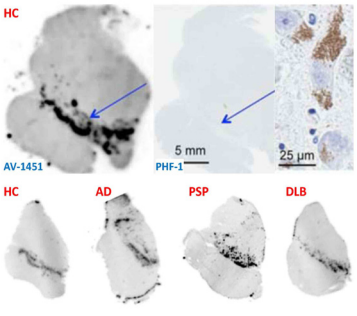
Cho H, 2017 (under review)

Severity of motor dysfunction correlated with ^{18}F-AV-1451 binding in the precentral GM and WM.



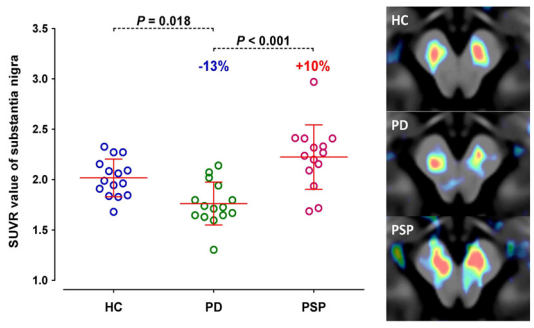
Cho H, 2017 (under review)

^{18}F-AV-1451 binds to melanin pigmentation in brain. This causes 'off-target' binding to SN due to neuromelanin pigmentation.



Lowe VJ, Acta Neuropathol Commun 2016;4:58, Marquie M, Ann Neurol 2015;78:787

Mean nigral SUVR value of PD patients was 13% lower than that of the controls due to reduced ^{18}F-AV-1451 binding to neuromelanin.



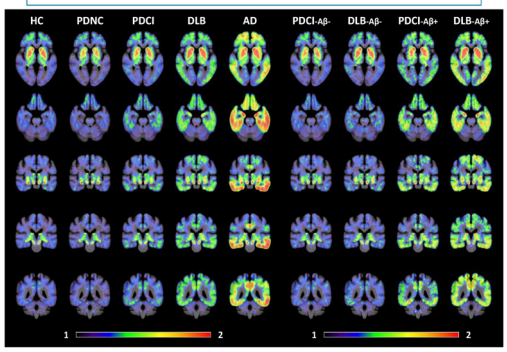
Cho H, Mov Disord 2017;32:134

^{18}F-AV-1451 PET study in Lewy body diseases

	HC	PDNC	PDCI	DLB	AD
n	25	12	22	18	25
Age (years)	73.2 ± 3.5	67.6 ± 6.3	71.3 ± 6.8	73.3 ± 8.3	74.0 ± 4.0[b]
Gender (M : F)	10 : 15	7 : 5	7 : 15	11 : 7	2 : 23[ab]
Education (years)	10.8 ± 5.1	10.5 ± 4.0	8.8 ± 5.4	9.0 ± 4.3	8.8 ± 6.3
Duration (months)	n.a.	42.1 ± 34.9	76.8 ± 60.9	28.3 ± 19.3	42.7 ± 19.3
Clinical symptoms					
Cognitive fluctuation	-	0 (0%)	3 (14%)	14 (78%)[b]	-
Hallucination	-	0 (0%)	5 (23%)	9 (50%)[b]	-
Parkinsonism	-	12 (100%)	22 (100%)	16 (89%)	-
RBD	-	3 (25%)	8 (36%)	15 (83%)[b]	-
Assessments					
MMSE	**27.2 ± 2.2**	**27.2 ± 1.9**	**22.7 ± 5.8[a]**	**19.5 ± 6.2[ab]**	**19.4 ± 5.9[ab]**
CDR-SB	0	0	3.3 ± 3.7[a]	5.4 ± 4.8[ab]	5.1 ± 2.7[ab]
UPDRS motor	n.a.	25.8 ± 11.3	32.9 ± 14.6	20.6 ± 14.6	n.a.
ApoE ε4 (%)	6 / 25 (24%)	2 / 12 (17%)	8 / 19 (42%)	7 / 18 (39%)	14 / 23 (61%)[ab]
Amyloid positivity	**0 (0%)**	**0 (0%)**	**7 (32%)**	**10 (56%)**	**25 (100%)[ab]**
Treatment					
Use of AchE inhibitor	0 (0%)	0 (0%)	6 (27%)[ab]	17 (94%)[a]	24 (96%)[ab]
Use of memantine	0 (0%)	0 (0%)	2 (9%)	6 (33%)	10 (40%)[ab]
LEDD (mg)	n.a.	471.2 ± 454.8	681.0 ± 476.6	150, 500[†]	n.a.

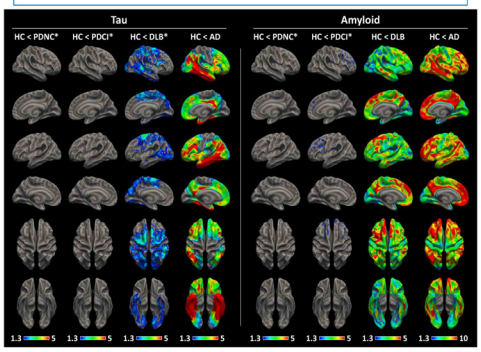
Lee SH, 2017 (under review)

Increasing tendency of cortical ^{18}F-AV-1451 binding with the advancement of Lewy body diseases



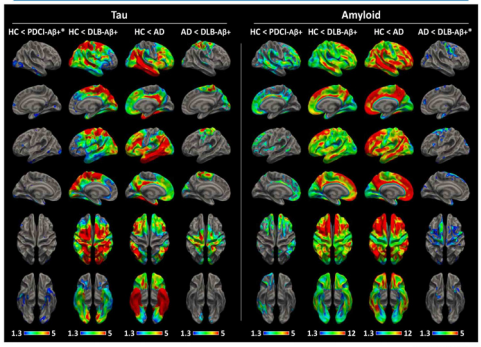
Lee SH, 2017 (under review)

Slightly increased ^{18}F-AV-1451 binding in the basal temporal, premotor, supplementary motor, precuneus, and primary sensorimotor and visual cortices in DLB



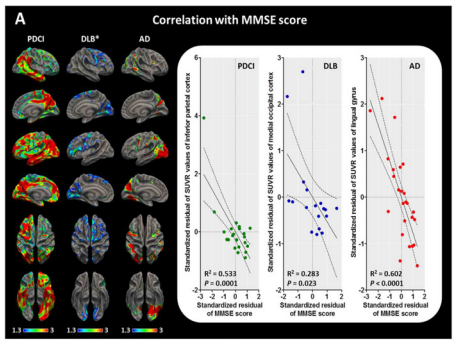
Lee SH, 2017 (under review)

Only the Aβ+ DLB patients show significantly increased ^{18}F-AV-1451 binding, especially premotor, supplementary motor, and primary sensorimotor and visual cortices.



Lee SH, 2017 (under review)

Tau burden in the areas showing increased ^{18}F-AV-1451 binding in DLB weakly correlated with global cognition and amyloid burden.



Lee SH, 2017 (under review)

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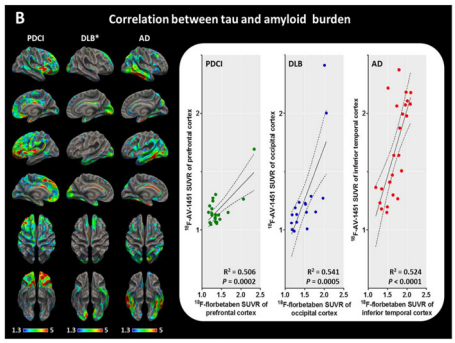
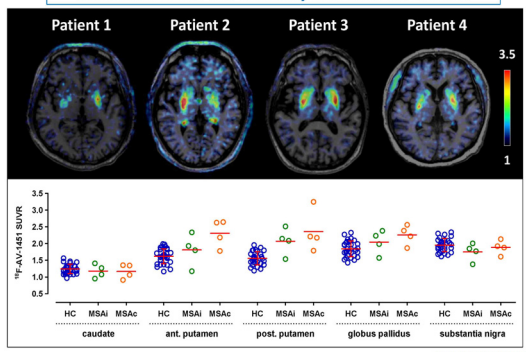


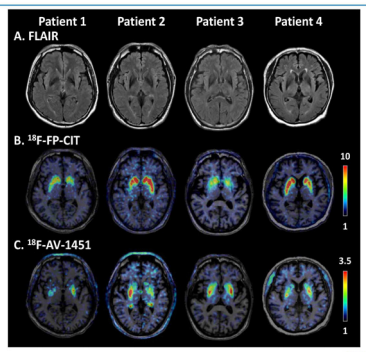
Lee SH, 2017 (under review)

Even in the MSA-P patients, ^{18}F-AV-1451 binds to posterior putamen, more prominently in the side contralateral to the clinically more affected side.



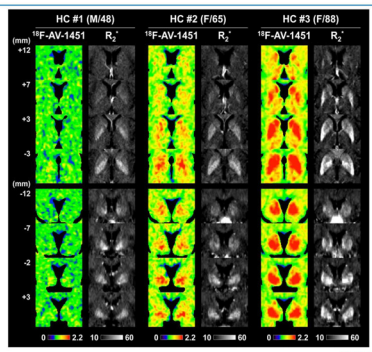
Cho H, Mov Disord 2017;32:171

^{18}F-AV-1451 binds to the atrophic posterior putamen where the ^{18}F-FP-CIT binding is reduced.



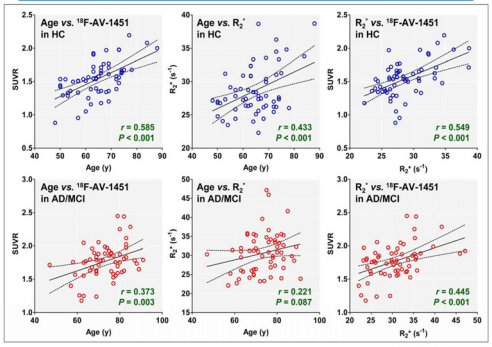
Cho H, Mov Disord 2017;32:171

Is the "Off target" ^{18}F-AV-1451 binding to basal ganglia related to aging and iron accumulation?



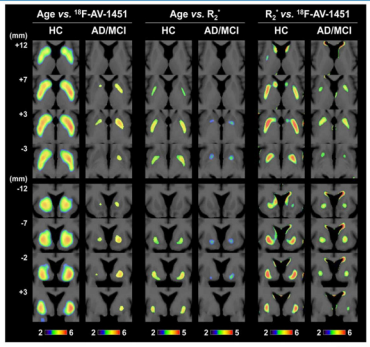
Choi JY, J Nucl Med 2017 (In Press)

There was strong correlation between the age, ^{18}F-AV-1451 binding and iron level.



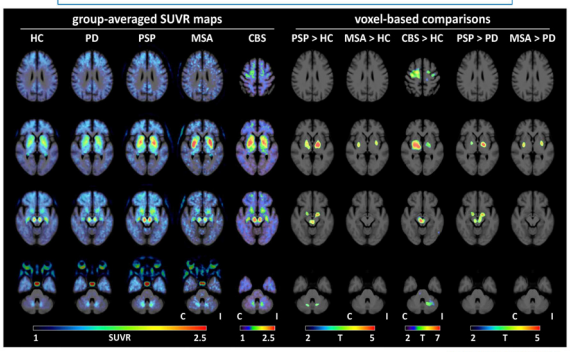
Choi JY, J Nucl Med 2017 (In Press)

"Off target" ^{18}F-AV-1451 binding in the basal ganglia correlates with age-related iron accumulation



Choi JY, J Nucl Med 2017 (In Press)

In summary, ^{18}F-AV-1451 PET can be helpful for the differential diagnosis of parkinsonism.



Cho H, 2016 (unpublished data)

Summary

1. ^{18}F-AV-1451 (^{18}F-flortaucipir; ^{18}F-T807), a commercial radiotracer for tau, is currently the most promising ^{18}F-labeled radiotracer which strongly binds to PHF-tau in AD and weakly binds to straight filament of non-AD tauopathies.
2. In parkinsonisms, disease-specific ^{18}F-AV-1451 binding patterns reflect the regional distribution patterns of tau pathology and may be helpful for the differential diagnosis (PD: ↓ SN, PSP: ↑ GP, midbrain, CBS: ↑ premotor, motor WM > GM, GP with asymmetry, DLB: ↑ visual, motor, premotor, parietal in amyloid-positive, MSA: ↑ posterior putamen with asymmetry).
3. Tau accumulation increased with the advancement of Lewy body diseases. Only the amyloid-positive LBD patients showed increased ^{18}F-AV-1451 binding in the regions distinct from AD.
4. "Off-target" ^{18}F-AV-1451 binding in the basal ganglia is associated with the age-related increases in iron accumulation.