아밀로이드 병리 및 영상

예 병 석
연세의대 신경과학교실

Amyloid pathology & imaging

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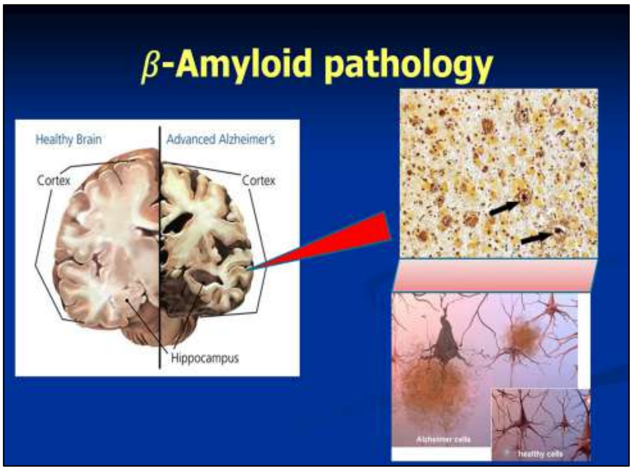
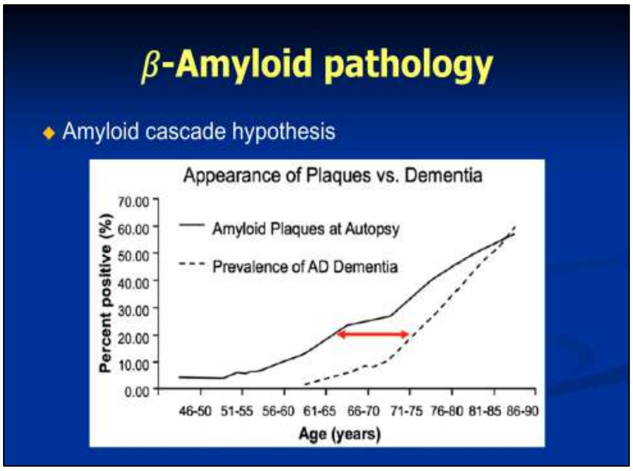
Department of Neurology Yonsei University College of Medicine



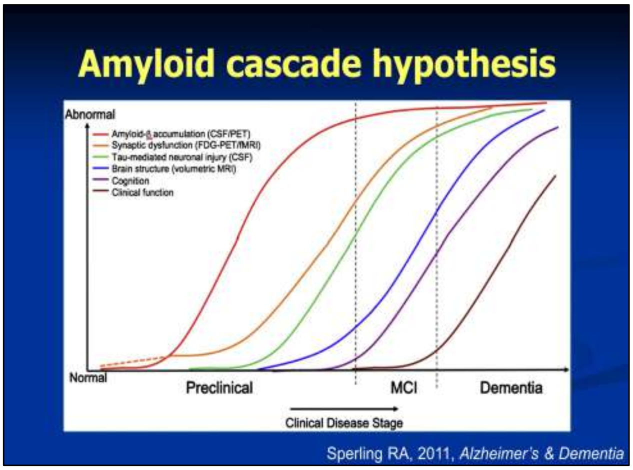
β-Amyloid pathology

Healthy Brain
Advanced Alzheimer's
Cortex
Cortex
Hippocampus
Alzheimer cells
healthy cells



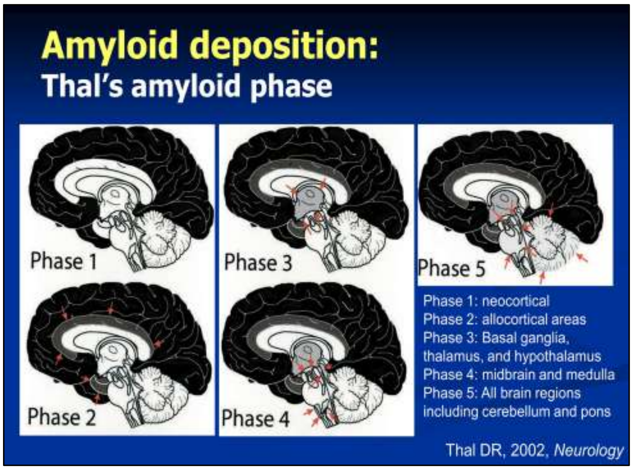
β-Amyloid pathology

- Amyloid cascade hypothesis



Amyloid cascade hypothesis

Sperling RA, 2011, *Alzheimer's & Dementia*



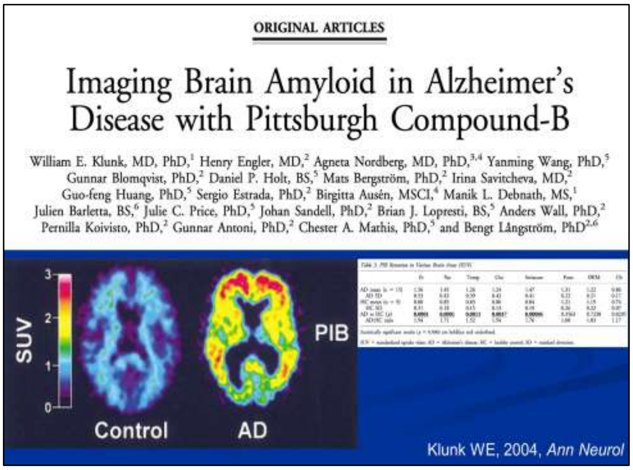
Amyloid deposition:

Thal's amyloid phase

Phase 1
Phase 2
Phase 3
Phase 4
Phase 5

Phase 1: neocortical
Phase 2: allocortical areas
Phase 3: Basal ganglia, thalamus, and hypothalamus
Phase 4: midbrain and medulla
Phase 5: All brain regions including cerebellum and pons

Thal DR, 2002, *Neurology*

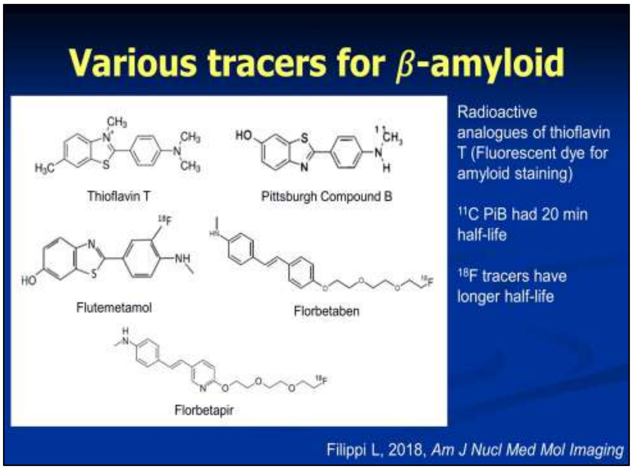

SUV
3
2
1
0
PIB
Control
AD

ORIGINAL ARTICLES

Imaging Brain Amyloid in Alzheimer's Disease with Pittsburgh Compound-B

William E. Klunk, MD, PhD,[1] Henry Engler, MD,[2] Agneta Nordberg, MD, PhD,[3,4] Yanming Wang, PhD,[5] Gunnar Blomqvist, PhD,[2] Daniel P. Holt, BS,[5] Mats Bergström, PhD,[2] Irina Savitcheva, MD,[2] Guo-feng Huang, PhD,[5] Sergio Estrada, PhD,[2] Birgitta Ausén, MSCI,[4] Manik L. Debnath, MS,[1] Julien Barletta, BS,[6] Julie C. Price, PhD,[5] Johan Sandell, PhD,[2] Brian J. Lopresti, BS,[5] Anders Wall, PhD,[2] Pernilla Koivisto, PhD,[2] Gunnar Antoni, PhD,[2] Chester A. Mathis, PhD,[5] and Bengt Långström, PhD[2,6]

Klunk WE, 2004, *Ann Neurol*



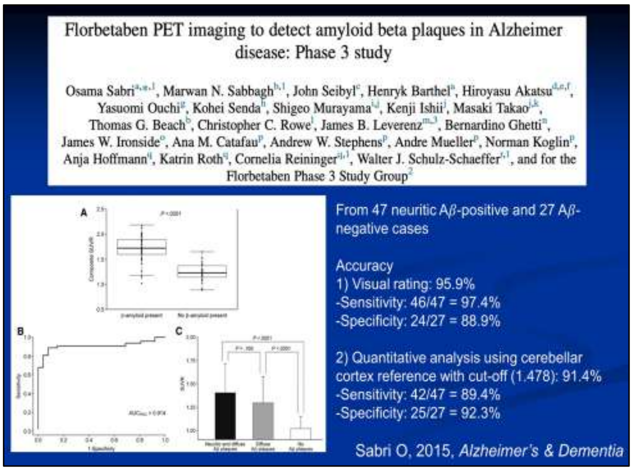
Various tracers for β-amyloid

Radioactive analogues of thioflavin T (Fluorescent dye for amyloid staining)

^{11}C PiB had 20 min half-life

^{18}F tracers have longer half-life

Filippi L, 2018, *Am J Nucl Med Mol Imaging*



Florbetaben PET imaging to detect amyloid beta plaques in Alzheimer disease: Phase 3 study

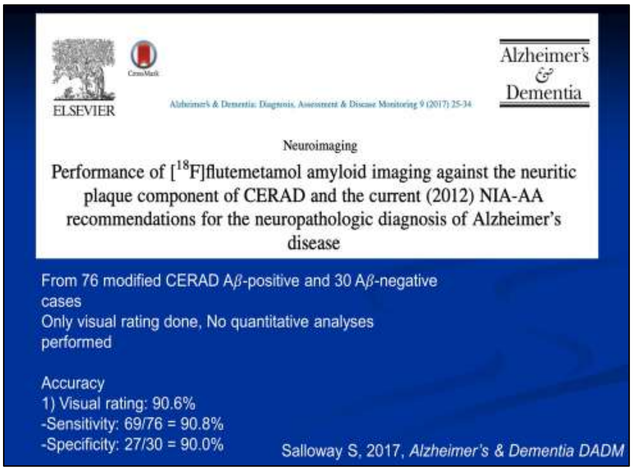
Osama Sabri[a,*,1], Marwan N. Sabbagh[b,1], John Seibyl[c], Henryk Barthel[a], Hiroyasu Akatsu[d,e,f], Yasuomi Ouchi[g], Kohei Senda[h], Shigeo Murayama[i,j], Kenji Ishii[j], Masaki Takao[j,k], Thomas G. Beach[b], Christopher C. Rowe[l], James B. Leverenz[m,3], Bernardino Ghetti[n], James W. Ironside[o], Ana M. Catafau[p], Andrew W. Stephens[p], Andre Mueller[p], Norman Koglin[p], Anja Hoffmann[q], Katrin Roth[q], Cornelia Reininger[p,1], Walter J. Schulz-Schaeffer[r,1], and for the Florbetaben Phase 3 Study Group[2]

From 47 neuritic Aβ-positive and 27 Aβ-negative cases

Accuracy
1) Visual rating: 95.9%
-Sensitivity: 46/47 = 97.4%
-Specificity: 24/27 = 88.9%

2) Quantitative analysis using cerebellar cortex reference with cut-off (1.478): 91.4%
-Sensitivity: 42/47 = 89.4%
-Specificity: 25/27 = 92.3%

Sabri O, 2015, *Alzheimer's & Dementia*



ELSEVIER

Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 9 (2017) 25-34

Alzheimer's & Dementia

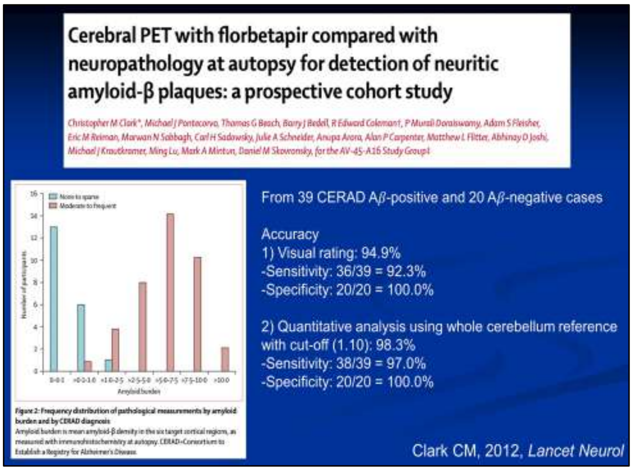
Neuroimaging

Performance of [^{18}F]flutemetamol amyloid imaging against the neuritic plaque component of CERAD and the current (2012) NIA-AA recommendations for the neuropathologic diagnosis of Alzheimer's disease

From 76 modified CERAD Aβ-positive and 30 Aβ-negative cases
Only visual rating done, No quantitative analyses performed

Accuracy
1) Visual rating: 90.6%
-Sensitivity: 69/76 = 90.8%
-Specificity: 27/30 = 90.0%

Salloway S, 2017, *Alzheimer's & Dementia DADM*


None to sparse
Moderate to frequent
Number of participants
Amyloid burden
0–0·1
>0·2–1·0
>1·0–2·5
>2·5–5·0
>5·0–7·5
>7·5–10·0
>10·0

Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid-β plaques: a prospective cohort study

Christopher M Clark, Michael J Pontecorvo, Thomas G Beach, Barry J Bedell, R Edward Coleman†, P Murali Doraiswamy, Adam S Fleisher, Eric M Reiman, Marwan N Sabbagh, Carl H Sadowsky, Julie A Schneider, Anupa Arora, Alan P Carpenter, Matthew L Flitter, Abhinay D Joshi, Michael J Krautkramer, Ming Lu, Mark A Mintun, Daniel M Skovronsky, for the AV-45-A16 Study Group‡*

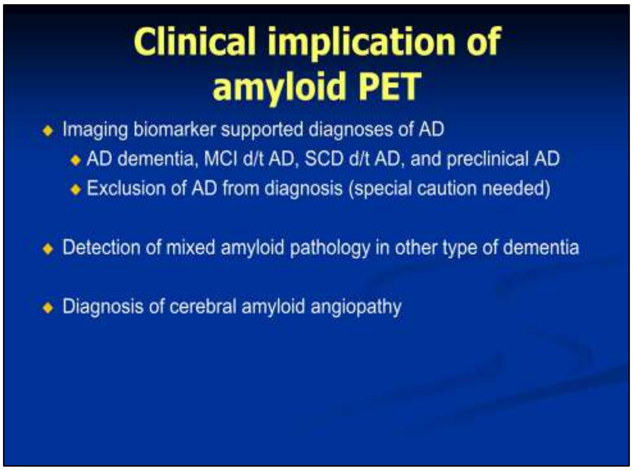
Figure 2: Frequency distribution of pathological measurements by amyloid burden and by CERAD diagnosis
Amyloid burden is mean amyloid-β density in the six target cortical regions, as measured with immunohistochemistry at autopsy. CERAD=Consortium to Establish a Registry for Alzheimer's Disease.

From 39 CERAD Aβ-positive and 20 Aβ-negative cases

Accuracy
1) Visual rating: 94.9%
-Sensitivity: 36/39 = 92.3%
-Specificity: 20/20 = 100.0%

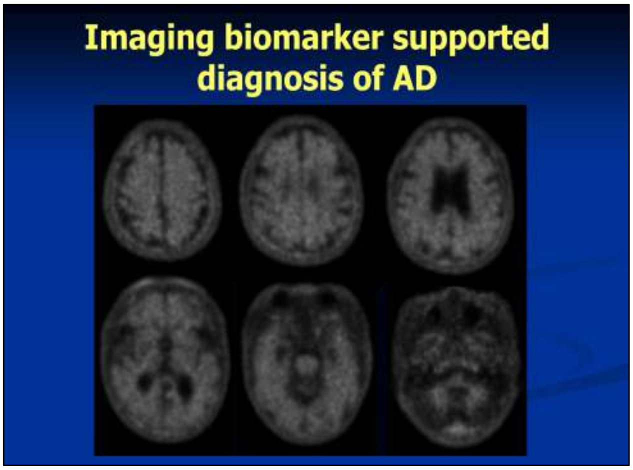
2) Quantitative analysis using whole cerebellum reference with cut-off (1.10): 98.3%
-Sensitivity: 38/39 = 97.0%
-Specificity: 20/20 = 100.0%

Clark CM, 2012, *Lancet Neurol*

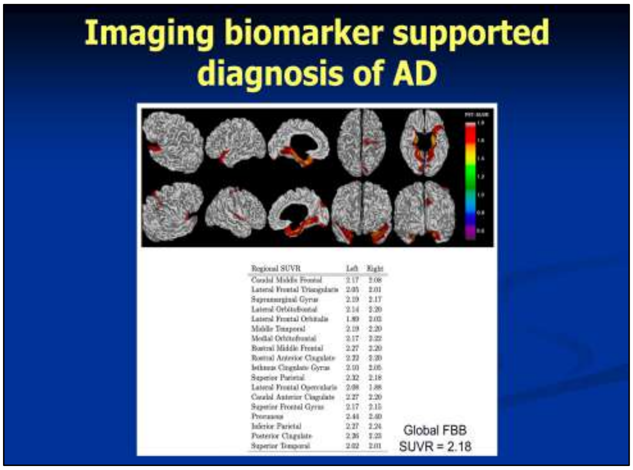


Clinical implication of amyloid PET

- Imaging biomarker supported diagnoses of AD
  - AD dementia, MCI d/t AD, SCD d/t AD, and preclinical AD
  - Exclusion of AD from diagnosis (special caution needed)
- Detection of mixed amyloid pathology in other type of dementia
- Diagnosis of cerebral amyloid angiopathy



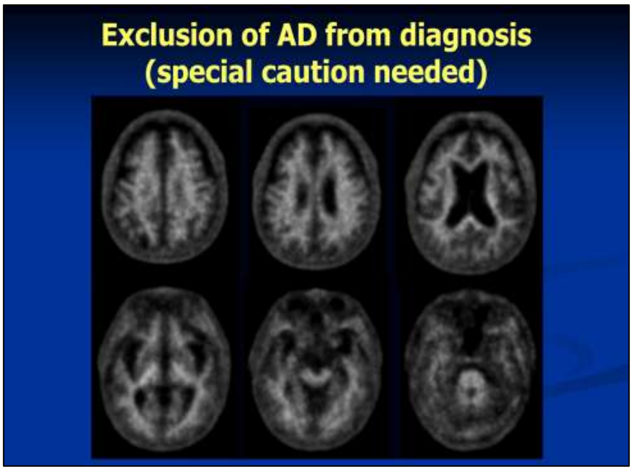
Imaging biomarker supported diagnosis of AD



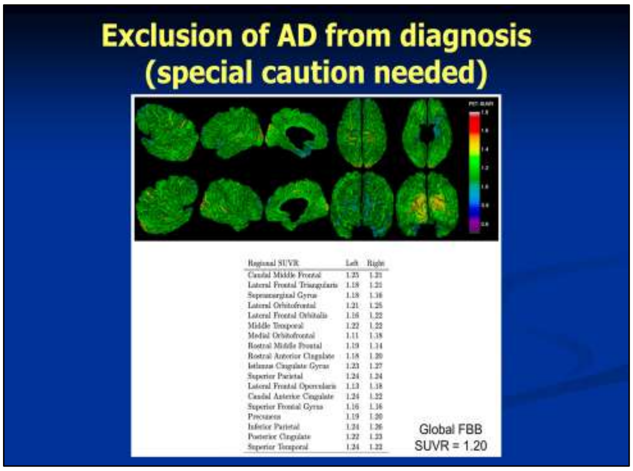
Imaging biomarker supported diagnosis of AD

Regional SUVR	Left	Right
Caudal Middle Frontal	2.17	2.08
Lateral Frontal Triangularis	2.05	2.01
Supramarginal Gyrus	2.19	2.17
Lateral Orbitofrontal	2.14	2.20
Lateral Frontal Orbitalis	1.89	2.03
Middle Temporal	2.19	2.20
Medial Orbitofrontal	2.17	2.22
Rostral Middle Frontal	2.27	2.20
Rostral Anterior Cingulate	2.22	2.30
Isthmus Cingulate Gyrus	2.10	2.05
Superior Parietal	2.32	2.18
Lateral Frontal Opercularis	2.08	1.88
Caudal Anterior Cingulate	2.27	2.20
Superior Frontal Gyrus	2.17	2.15
Precuneus	2.44	2.40
Inferior Parietal	2.27	2.24
Posterior Cingulate	2.26	2.23
Superior Temporal	2.02	2.01

Global FBB
SUVR = 2.18



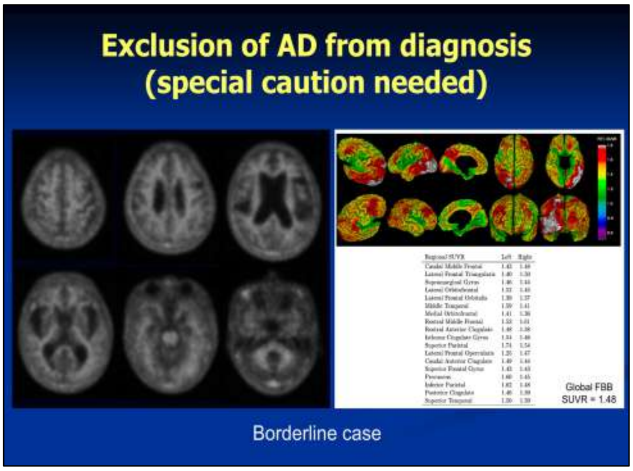
Exclusion of AD from diagnosis (special caution needed)



Exclusion of AD from diagnosis (special caution needed)

Regional SUVR	Left	Right
Caudal Middle Frontal	1.25	1.21
Lateral Frontal Triangularis	1.18	1.21
Supramarginal Gyrus	1.18	1.16
Lateral Orbitofrontal	1.21	1.25
Lateral Frontal Orbitalis	1.16	1.22
Middle Temporal	1.22	1.22
Medial Orbitofrontal	1.11	1.18
Rostral Middle Frontal	1.19	1.14
Rostral Anterior Cingulate	1.18	1.20
Isthmus Cingulate Gyrus	1.23	1.27
Superior Parietal	1.24	1.24
Lateral Frontal Opercularis	1.13	1.18
Caudal Anterior Cingulate	1.24	1.22
Superior Frontal Gyrus	1.16	1.16
Precuneus	1.19	1.20
Inferior Parietal	1.24	1.26
Posterior Cingulate	1.22	1.23
Superior Temporal	1.24	1.22

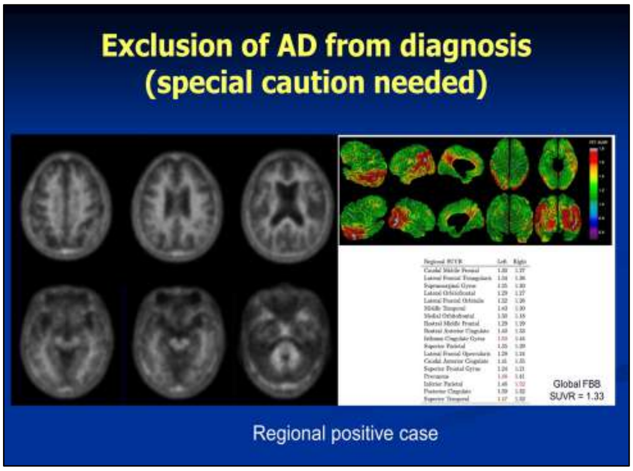
Global FBB
SUVR = 1.20



Exclusion of AD from diagnosis (special caution needed)

Global FBB
SUVR = 1.48

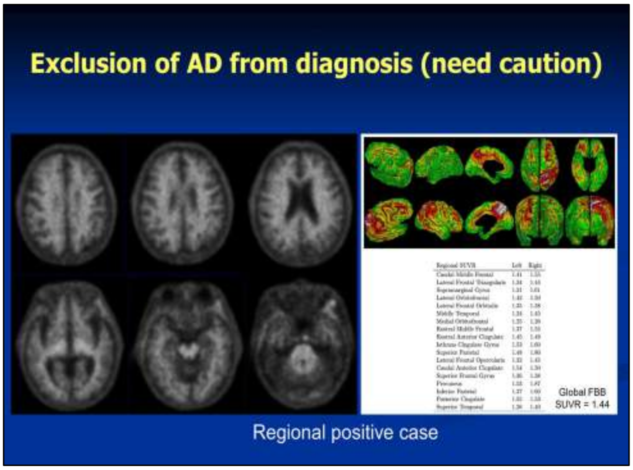
Borderline case



Exclusion of AD from diagnosis (special caution needed)

Global FBB
SUVR = 1.33

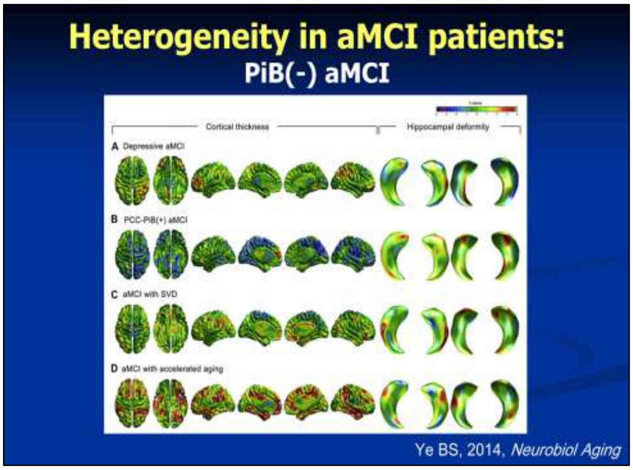
Regional positive case



Exclusion of AD from diagnosis (need caution)

Global FBB
SUVR = 1.44

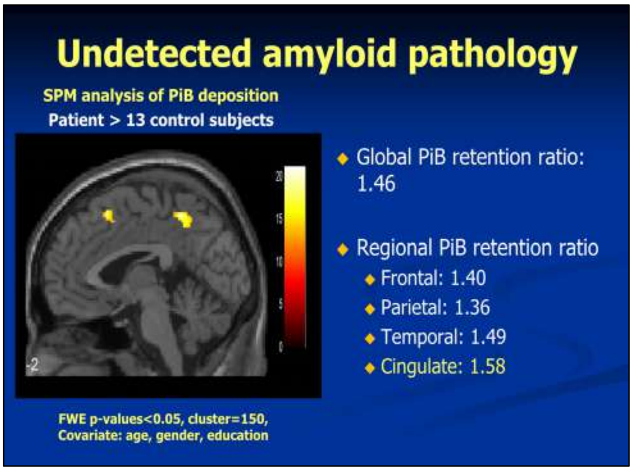
Regional positive case



Heterogeneity in aMCI patients:
PiB(-) aMCI

Cortical thickness
Hippocampal deformity
A Depressive aMCI
B PCC-PiB(+) aMCI
C aMCI with SVD
D aMCI with accelerated aging

Ye BS, 2014, *Neurobiol Aging*

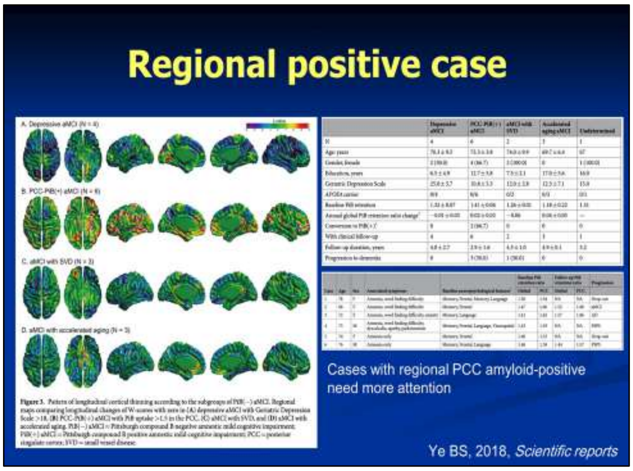


Undetected amyloid pathology

SPM analysis of PiB deposition
Patient > 13 control subjects

- Global PiB retention ratio: 1.46
- Regional PiB retention ratio
  - Frontal: 1.40
  - Parietal: 1.36
  - Temporal: 1.49
  - Cingulate: 1.58

FWE p-values<0.05, cluster=150,
Covariate: age, gender, education

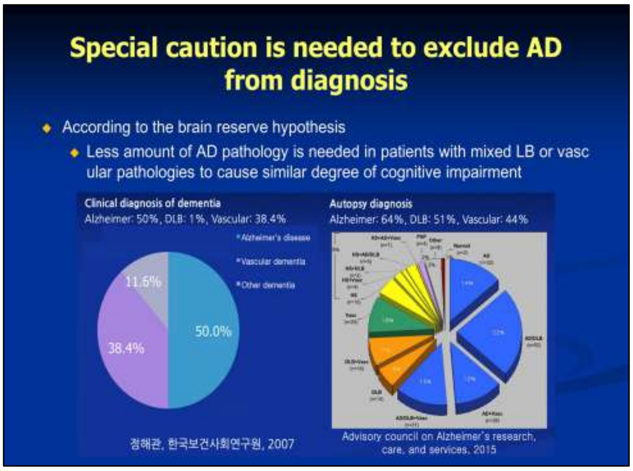


Regional positive case

A. Depressive aMCI (N = 4)
B. PCC-PiB(+) aMCI (N = 6)
C. aMCI with SVD (N = 3)
D. aMCI with accelerated aging (N = 3)

Cases with regional PCC amyloid-positive need more attention

Ye BS, 2018, *Scientific reports*



Special caution is needed to exclude AD from diagnosis

- According to the brain reserve hypothesis
  - Less amount of AD pathology is needed in patients with mixed LB or vascular pathologies to cause similar degree of cognitive impairment

Clinical diagnosis of dementia
Alzheimer: 50%, DLB: 1%, Vascular: 38.4%

정해관, 한국보건사회연구원, 2007

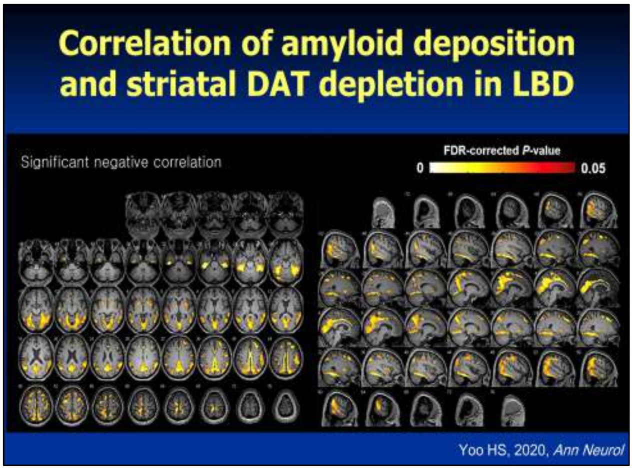
Autopsy diagnosis
Alzheimer: 64%, DLB: 51%, Vascular: 44%

Advisory council on Alzheimer's research, care, and services, 2015

Mixed LB pathologies in AD

- LB pathologies in familial AD[1, 2]
  - Amygdala: 63.2%[1]; 84.2%[2]
  - Cingulate gyrus: 24.0%[1]; 44.1%[2]
  - Parahippocampal gyrus: 22.2%[1]
  - Substantia nigra: 39.5%[2]
- Alpha-synuclein immunohistochemistry in sporadic AD[3]
  - Any LB: 60.7%
  - About 35% of LB(+) sporadic AD cases showed numerous LB in the amygdala and often had LB in the entorhinal cortex: About 20% of sporadic AD patients have Amygdala-only LB
  - Remaining 65% of LB(+) sporadic AD cases had LB pathologies in other brain regions: About 40% of sporadic AD patients showed widespread and numerous neocortical LB: AD with LBD

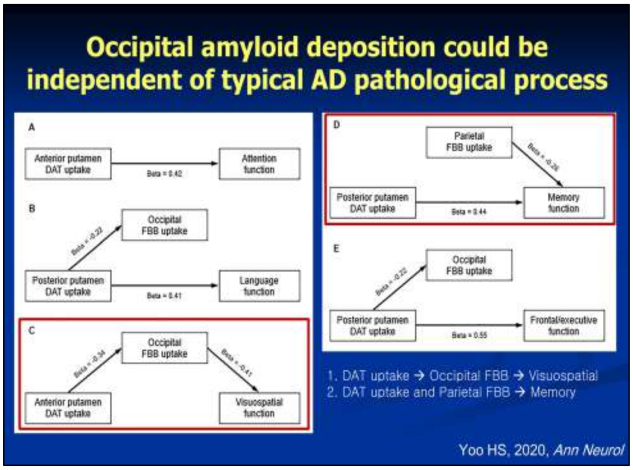
[1] Lippa CF et al., 1998, *American Journal of Pathology*
[2] Leverenz JB, 2006, *Arch Neurol*
[3] Hamilton RL, 2000, *Brain Pathology*



Correlation of amyloid deposition and striatal DAT depletion in LBD

Significant negative correlation
FDR-corrected *P*-value
0
0.05

Yoo HS, 2020, *Ann Neurol*

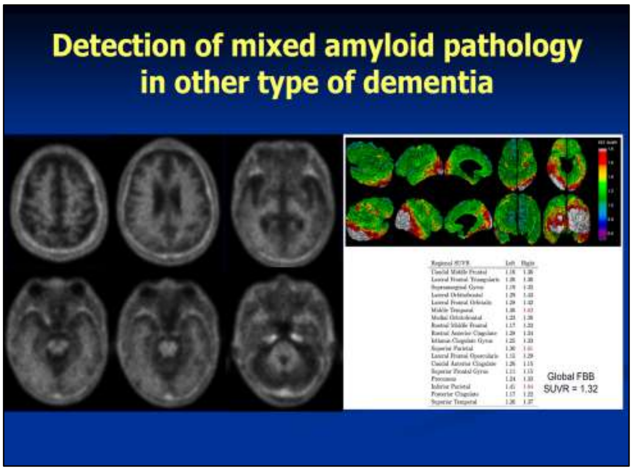


Occipital amyloid deposition could be independent of typical AD pathological process

A
Anterior putamen DAT uptake
Beta = 0.42
Attention function
B
Occipital FBB uptake
Beta = -0.22
Posterior putamen DAT uptake
Beta = 0.41
Language function
C
Occipital FBB uptake
Beta = -0.34
Beta = -0.41
Anterior putamen DAT uptake
Visuospatial function
D
Parietal FBB uptake
Beta = -0.26
Posterior putamen DAT uptake
Beta = 0.44
Memory function
E
Occipital FBB uptake
Beta = -0.22
Posterior putamen DAT uptake
Beta = 0.55
Frontal/executive function

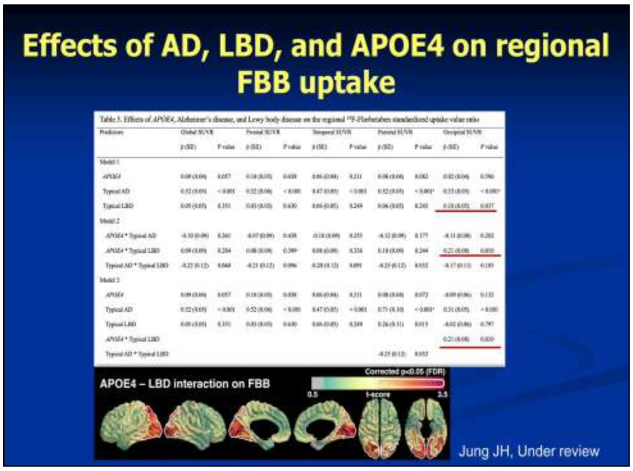
1. DAT uptake → Occipital FBB → Visuospatial
2. DAT uptake and Parietal FBB → Memory

Yoo HS, 2020, *Ann Neurol*



Detection of mixed amyloid pathology in other type of dementia

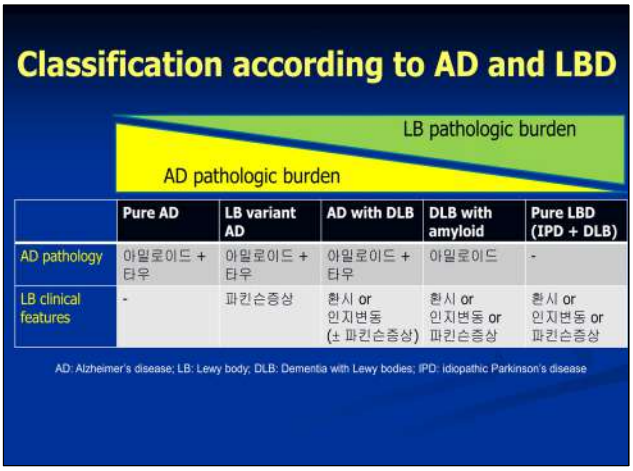
Global FBB
SUVR = 1.32



Effects of AD, LBD, and APOE4 on regional FBB uptake

APOE4 – LBD interaction on FBB
Corrected p<0.05 (FDR)
0.5
t-score
3.5

Jung JH, Under review

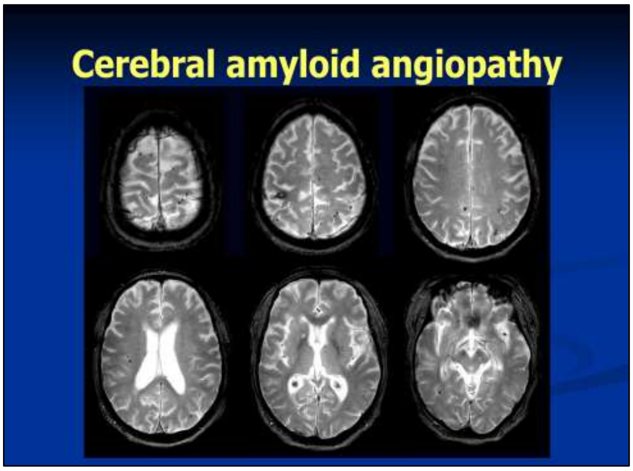


Classification according to AD and LBD

LB pathologic burden
AD pathologic burden

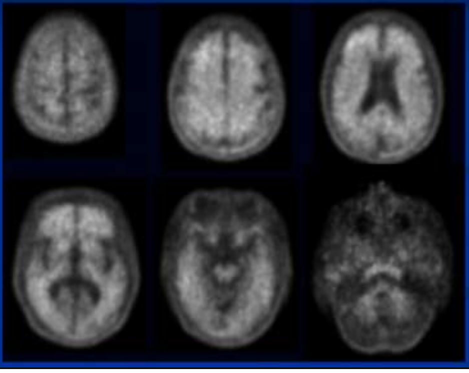
	Pure AD	LB variant AD	AD with DLB	DLB with amyloid	Pure LBD (IPD + DLB)
AD pathology	아밀로이드 + 타우	아밀로이드 + 타우	아밀로이드 + 타우	아밀로이드	-
LB clinical features	-	파킨슨증상	환시 or 인지변동 (± 파킨슨증상)	환시 or 인지변동 or 파킨슨증상	환시 or 인지변동 or 파킨슨증상

AD: Alzheimer's disease; LB: Lewy body; DLB: Dementia with Lewy bodies; IPD: idiopathic Parkinson's disease

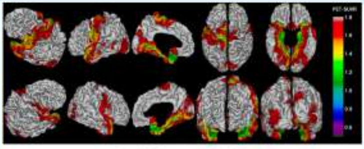


Cerebral amyloid angiopathy

Cerebral amyloid angiopathy

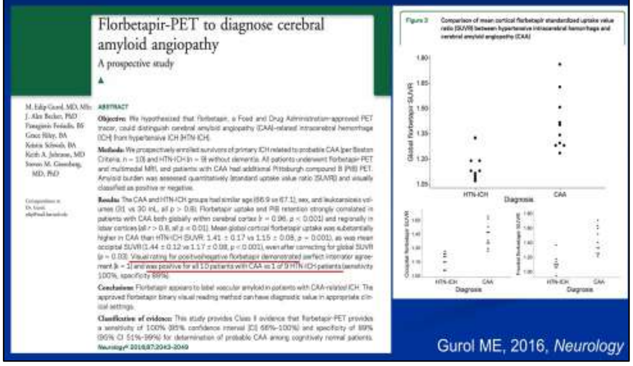


Cerebral amyloid angiopathy



Regional SUVR	Left	Right
Caudal Middle Frontal	2.27	2.22
Lateral Frontal Triangularis	2.20	2.30
Supramarginal Gyrus	2.06	2.14
Lateral Orbitofrontal	2.33	2.37
Lateral Frontal Orbitalis	2.20	2.13
Middle Temporal	1.87	2.03
Medial Orbitofrontal	2.16	2.18
Rostral Middle Frontal	2.46	2.70
Rostral Anterior Cingulate	2.26	2.47
Isthmus Cingulate Gyrus	2.05	2.16
Superior Parietal	2.15	2.19
Lateral Frontal Opercularis	2.05	2.11
Caudal Anterior Cingulate	2.07	2.31
Superior Frontal Gyrus	2.16	2.29
Precuneus	1.98	2.20
Inferior Parietal	2.06	2.24
Posterior Cingulate	1.95	2.15
Superior Temporal	1.80	1.94

Cerebral amyloid angiopathy



Florbetapir-PET to diagnose cerebral amyloid angiopathy

A prospective study

M. Edip Gurol, MD, MSc
J. Alex Becker, PhD
Panagiotis Fotiadis, BS
Grace Riley, BA
Kristin Schwab, BA
Keith A. Johnson, MD
Steven M. Greenberg, MD, PhD

ABSTRACT

Objective: We hypothesized that florbetapir, a Food and Drug Administration–approved PET tracer, could distinguish cerebral amyloid angiopathy (CAA)–related intracerebral hemorrhage (ICH) from hypertensive ICH (HTN-ICH).

Methods: We prospectively enrolled survivors of primary ICH related to probable CAA (per Boston Criteria, n = 10) and HTN-ICH (n = 9) without dementia. All patients underwent florbetapir PET and multimodal MRI, and patients with CAA had additional Pittsburgh compound B (PiB) PET. Amyloid burden was assessed quantitatively (standard uptake value ratio [SUVR]) and visually classified as positive or negative.

Results: The CAA and HTN-ICH groups had similar age (66.9 vs 67.1), sex, and leukoaraiosis volumes (31 vs 30 mL, all p > 0.8). Florbetapir uptake and PiB retention strongly correlated in patients with CAA both globally within cerebral cortex (r = 0.96, p < 0.001) and regionally in lobar cortices (all r > 0.8, all p < 0.01). Mean global cortical florbetapir uptake was substantially higher in CAA than HTN-ICH (SUVR 1.41 ± 0.17 vs 1.15 ± 0.08, p = 0.001), as was mean occipital SUVR (1.44 ± 0.12 vs 1.17 ± 0.08, p < 0.001), even after correcting for global SUVR (p = 0.03). Visual rating for positive/negative florbetapir demonstrated perfect interrater agreement (k = 1) and was positive for all 10 patients with CAA vs 1 of 9 HTN-ICH patients (sensitivity 100%, specificity 89%).

Conclusions: Florbetapir appears to label vascular amyloid in patients with CAA-related ICH. The approved florbetapir binary visual reading method can have diagnostic value in appropriate clinical settings.

Classification of evidence: This study provides Class II evidence that florbetapir-PET provides a sensitivity of 100% (95% confidence interval [CI] 66%–100%) and specificity of 89% (95% CI 51%–99%) for determination of probable CAA among cognitively normal patients.

Neurology® 2016;87:2043–2049

Figure 3 Comparison of mean cortical florbetapir standardized uptake value ratio (SUVR) between hypertensive intracerebral hemorrhage and cerebral amyloid angiopathy (CAA)

Gurol ME, 2016, *Neurology*

Summary + Take home message

- Amyloid PET is a useful imaging biomarker for exact diagnosis of AD
    - Special caution is needed to rule out AD
    - Regional positivity is common especially in cases with mixed pathologies (LBD, Vascular, etc)
- Amyloid PET is a biomarker for amyloid, not for AD (amyloid + tau)
    - AD, LB variant of AD, DLB with amyloid, AD with DLB, and even normal cognition subjects can show amyloid deposition
    - Biomarkers for disease staging or differential diagnosis are needed
    - AD and LBD could have direct interaction through occipital amyloid deposition
    - CAA could be diagnosed with amyloid PET