UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE

Department of Radiology

Division of Nuclear Medicine

Didactic

Brain Amyloid Imaging

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Outline :

1. INTRODUCTION.

2. AD AND DEMENTIA - Clinical Characteristics of Dementia
   - Pathology Of AD
   - Prodromal AD
   - AD Pathology in Healthy Elderly

3. AMYLOID IMAGING - Pittsburgh Compound B (11C-PiB)
   - 18F-Labelled Radiopharmaceuticals for Amyloid Imaging

4. ACCURACY OF AMYLOID IMAGING

5. FUTURE REQUIREMENTS

Introduction:

• Beta-amyloid (Ab) plaques are present in moderate to frequent numbers in the cortical gray matter in all cases of Alzheimer disease (AD) and develop many years before the onset of dementia. In contrast, Ab plaques are not found in frontotemporal dementia.

•Applications for amyloid imaging will include:
-exclusion of AD,
-differential diagnosis of dementia, particularly for the distinction of AD from frontotemporal dementia

• 2001: first PET tracer specific for Ab : Chet Mathis and William Klunk at the University of Pittsburgh through modification of thioflavin T, : was labeled with 11C, and the compound was given the name Pittsburgh compound B (11C-PiB).

• 2008 : the first report of successful imaging in humans with an 18F-labeled amyloid tracer

Clinical Characteristics of Dementia

•Dementia is defined as cognitive impairment of sufficient severity that it prevents independent function in the patient's usual occupation or daily activities.

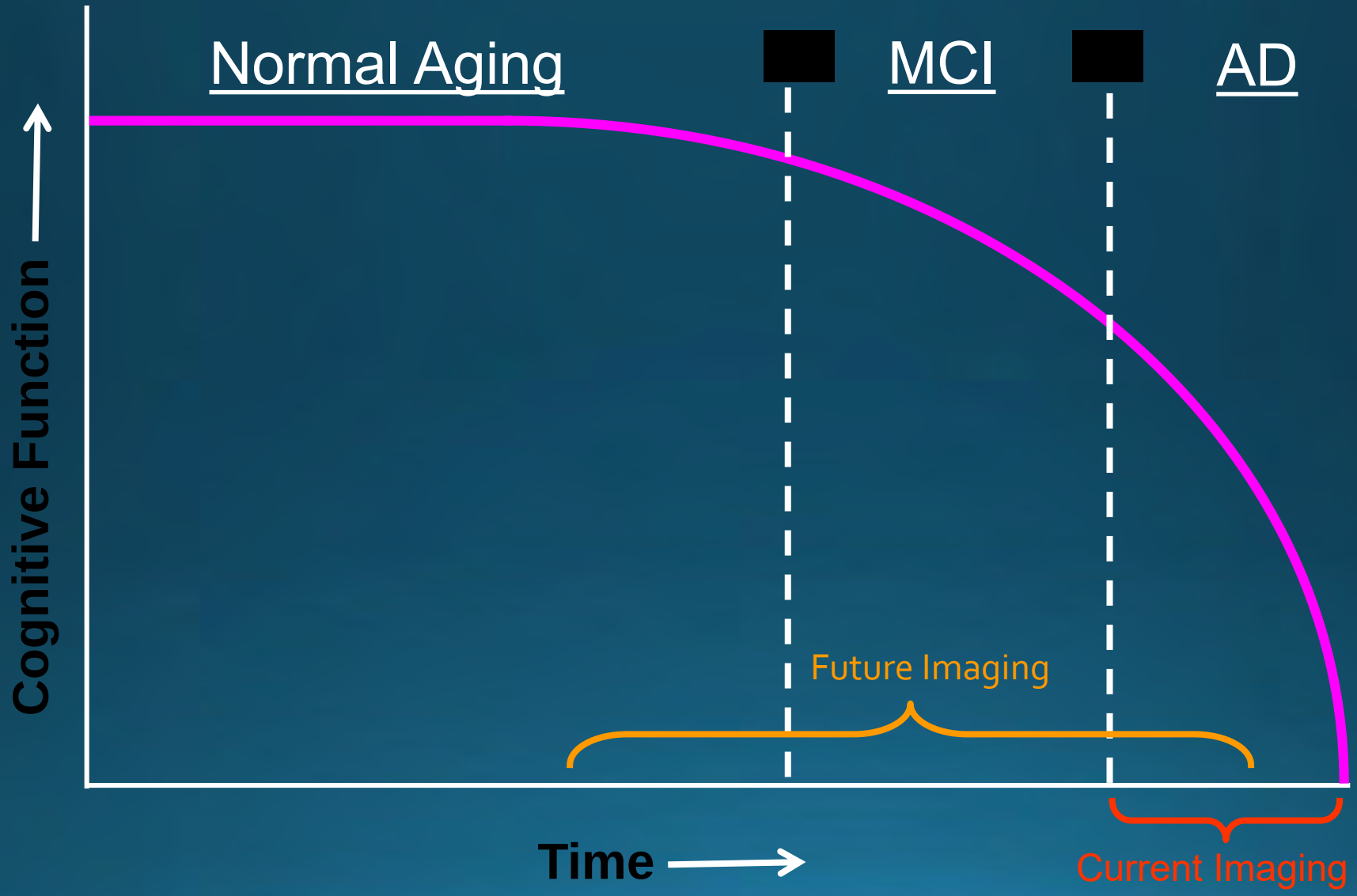
•Etiology: most common in the elderly is neurodegenerative disease. Metabolic problems such as hypothyroidism, severe vitamin B12 deficiency, chronic hypoxia, major organ failure, autoimmune encephalopathy, stroke, normal-pressure hydrocephalus, Creutzfeldt–Jakob disease and subdural hematoma need to be excluded.

•MC cause of neurodegenerative disease in the older population :
-AD (70 %)
-dementia with Lewy bodies (about 20%)
-frontotemporal dementia (more common in late middle age and the younger elderly)
-

•prevalence of AD is age-dependent, affecting 1% of the population at age 60 y and then doubling every 5 y, with the result that 25% of persons aged 85 y have the disease.

•at this point there is no cure for AD, nor is there a proven way to slow the rate of neurodegeneration. Symptomatic treatment with an acetylcholinesterase inhibitor (donepezil, galantamine, rivastigmine) or a glutamatergic moderator (memantine) provides modest benefit.

Future Clinical Imaging in Dementia



Pathology of AD

•gross cortical atrophy
•earlier stages: atrophy is predominantly seen on MRI in the hippocampi and adjacent mesial temporal regions

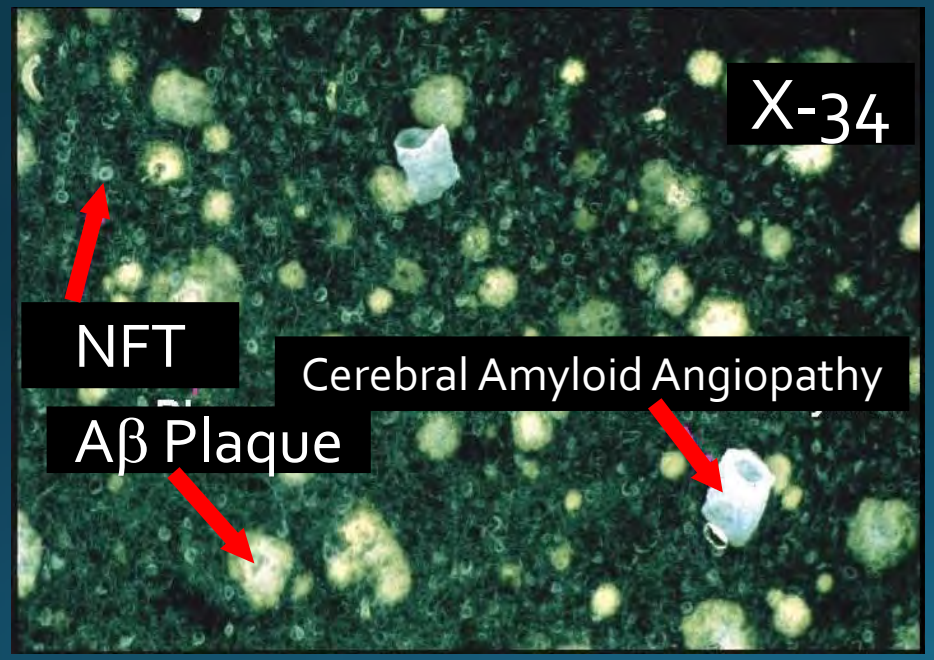
• Microscopically: widespread cellular degeneration and the presence of the pathologic hallmarks of the disease: intracellular neurofibrillary tangles and extracellular amyloid plaques

•Amyloid plaques : most abundant in the frontal cortex (orbital and medial frontal) cingulate gyrus, precuneus, and lateral parietal and temporal regions: relatively fewer plaques in the primary sensorimotor and occipital cortex and the mesial temporal areas

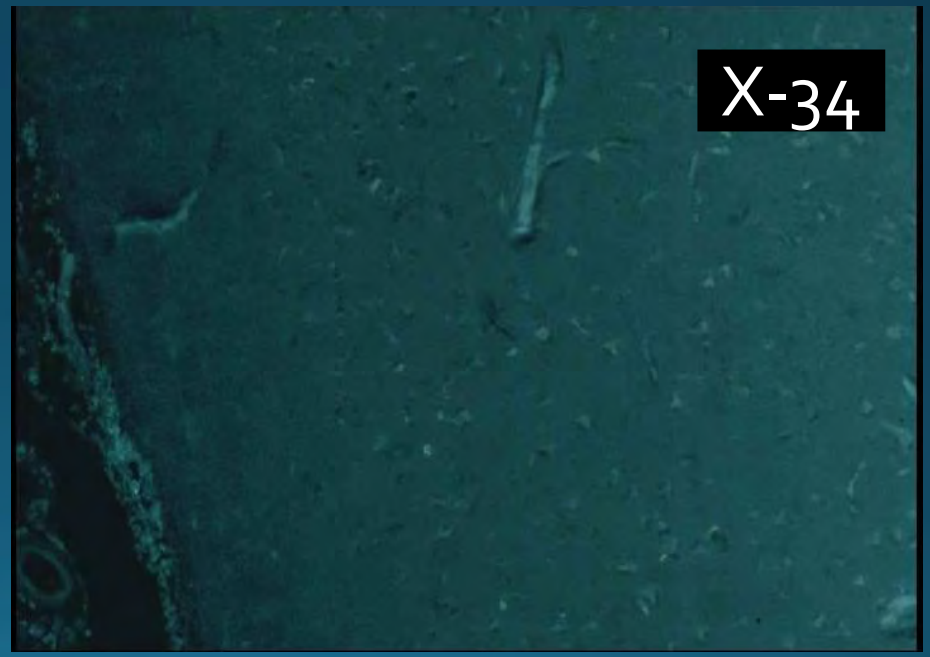
• in contrast , neurofibrillary tangles: highest density in the mesial temporal areas, including the hippocampi

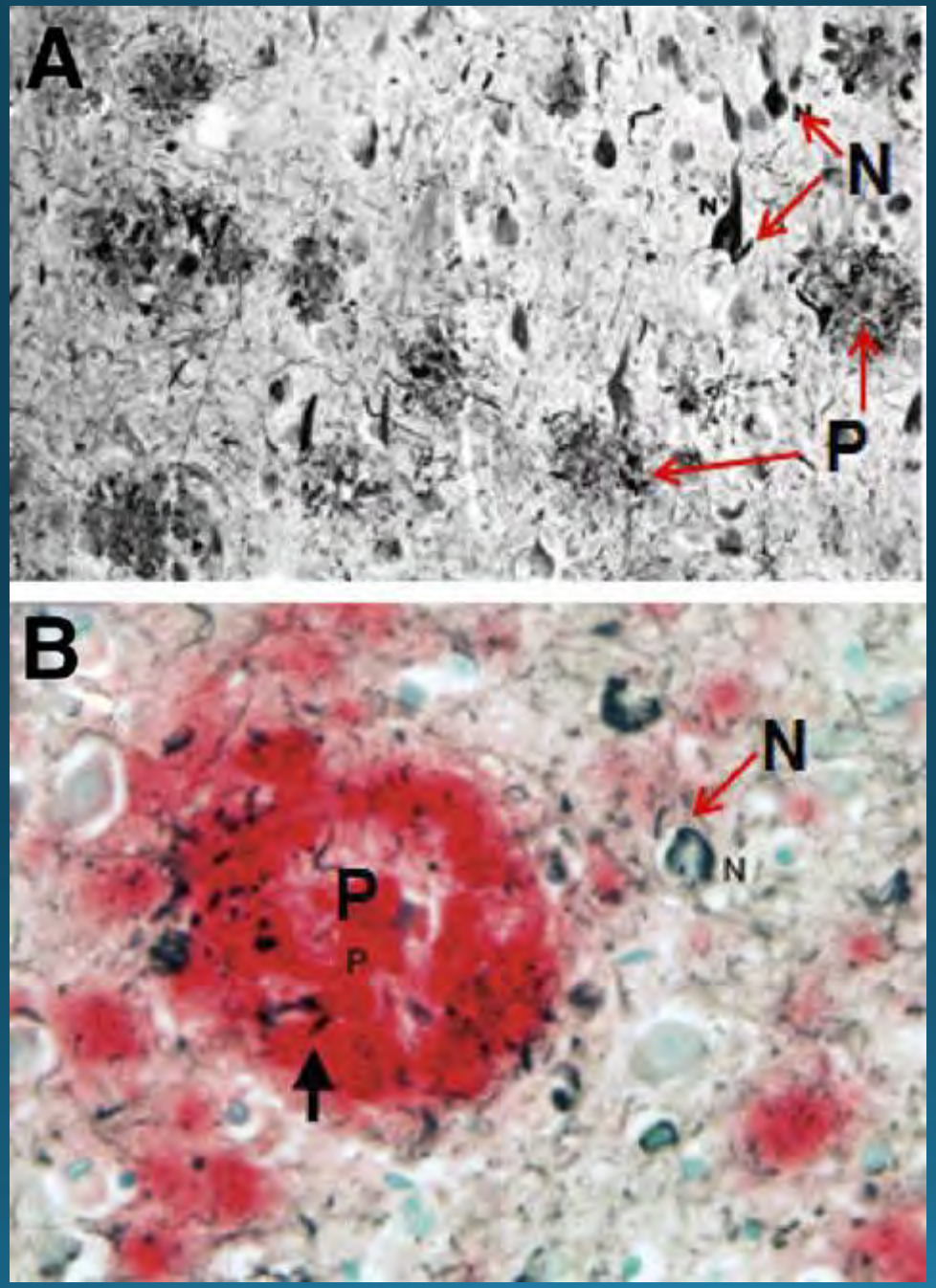
The Definitive Biomarkers of AD:
Amyloid-b Plaques & Neurofibrillary Tangles Imaged With the Highly Fluorescent Dye X-34

AD Brain
Frontal Cortex



Elderly Control Brain
Frontal Cortex

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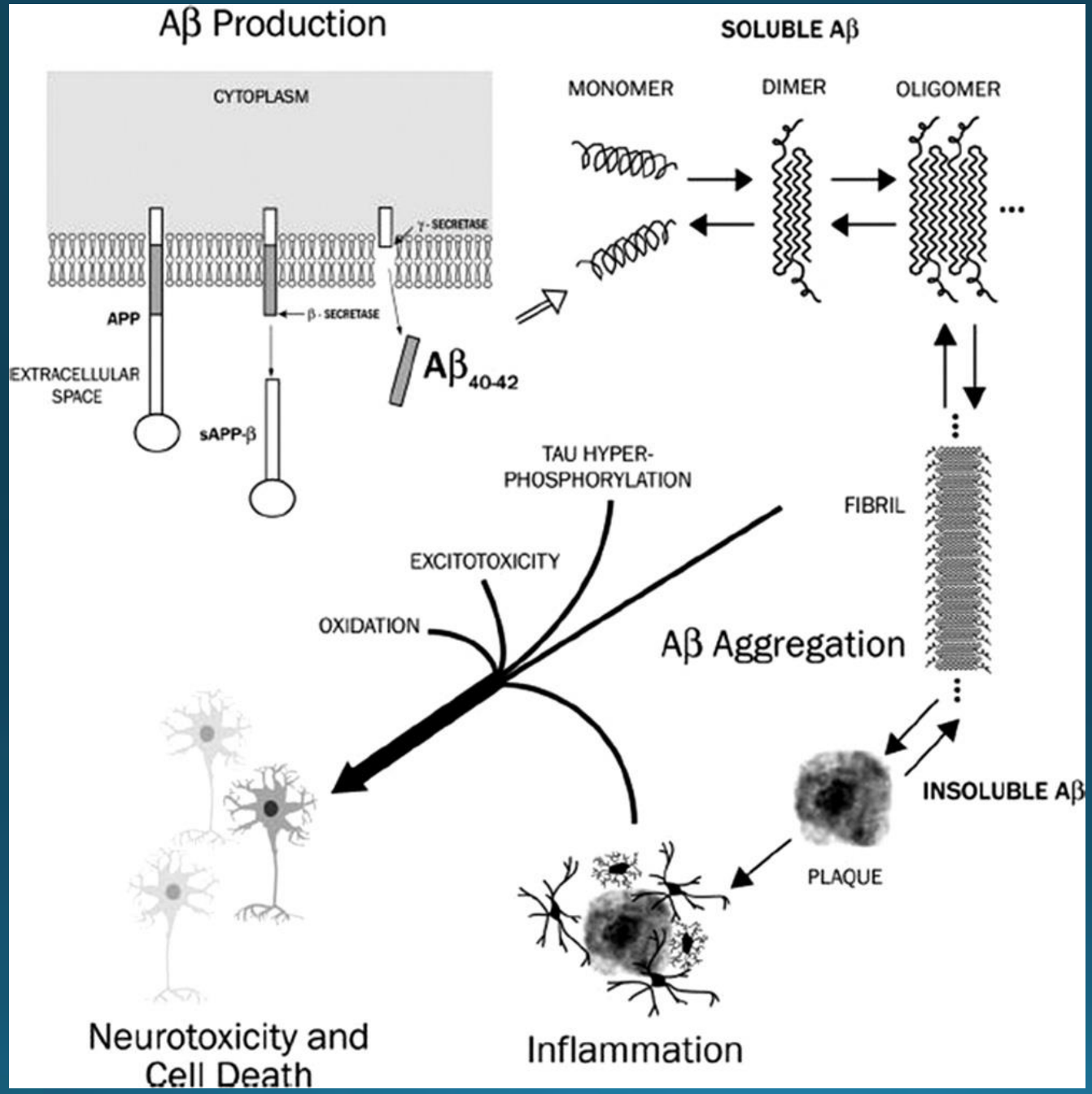

Aβ Production
SOLUBLE Aβ
CYTOPLASM
MONOMER
DIMER
OLIGOMER
γ - SECRETASE
β - SECRETASE
APP
EXTRACELLULAR SPACE
sAPP-β
Aβ40-42
TAU HYPER-PHOSPHORYLATION
FIBRIL
EXCITOTOXICITY
OXIDATION
Aβ Aggregation
INSOLUBLE Aβ
PLAQUE
Neurotoxicity and Cell Death
Inflammation

•diffuse or dense

. diffuse plaque : early phase of plaque formation

. Dense plaques (compact, dense, or cored or neuritic): local neuronal damage and inflammation: characteristic of AD.

. PET amyloid tracers : low affinity for diffuse plaque, and scans may be negative when only diffuse plaque is present.

. degree of cognitive impairment in AD: best correlation with neurofibrillary tangles and soluble levels of Ab . These soluble forms of Ab, in equilibrium with the insoluble Ab in plaques, are neurotoxic through several possible mechanisms

Genetic component

•3 gene mutations have been linked to autosomal dominant, early-onset familial AD: genes for amyloid precursor protein, presenilin 1, and presenilin 2.

• e4 allele of apolipoprotein E is strongly implicated in late-onset sporadic AD.

• All these genes influence Ab handling, either by increased production or reduced clearance

Changing Approach to Diagnosis of AD

- cognitive impairment must be of sufficient severity to cause dementia: prevent individuals from undertaking their usual occupation or daily activities .
- Structural brain imaging with CT or MRI and blood tests are done to exclude alternate causes of dementia such as normal-pressure hydrocephalus, hypothyroidism, and stroke.
- However, clinical diagnosis in most centers is only 80%–85% sensitive and 70% specific for AD. Other causes of dementia such as frontotemporal dementia and dementia with Lewy bodies have many features in common with AD and are frequently misdiagnosed as AD.

2011 National Institute on Aging and Alzheimer Association workgroup :
“probable AD dementia with evidence of the AD pathophysiologic process”

↓

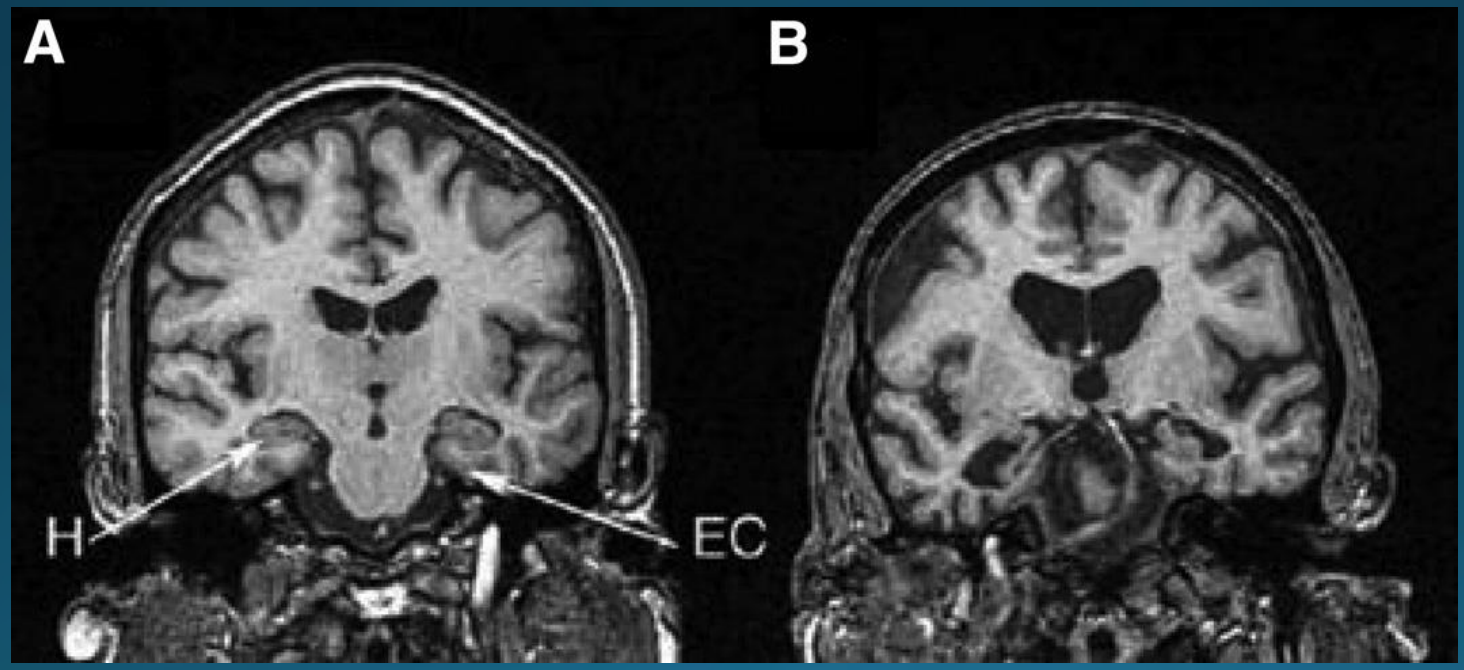
biomarkers

most validated biomarkers for AD fall under 2 categories:
- those that reflect the specific pathology of AD and
- those that reflect neuronal damage or dysfunction

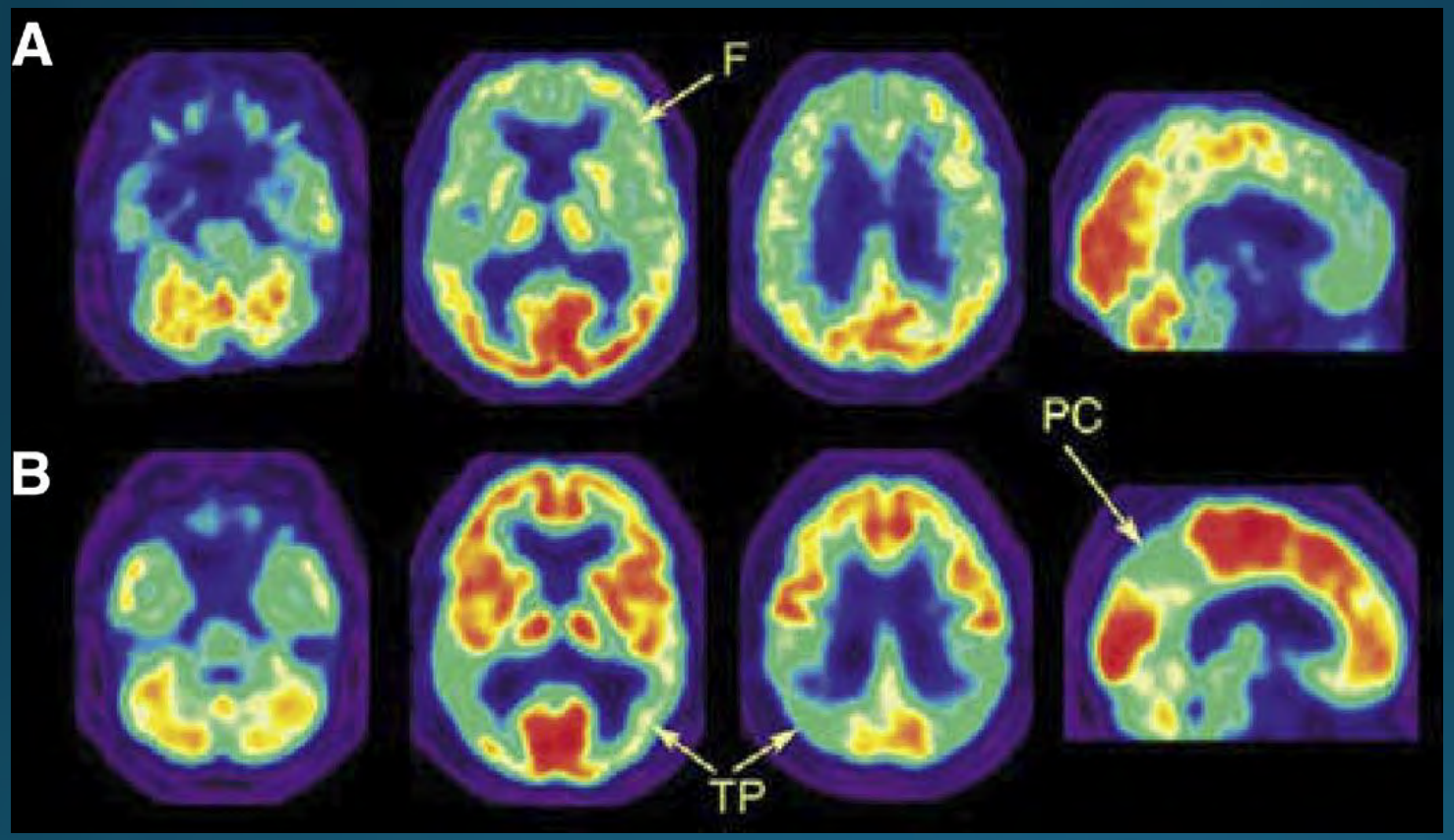
pathologic biomarkers of AD are Ab imaging and cerebrospinal fluid assay of the amyloid peptide, Ab42.

Markers for neuronal damage or dysfunction are atrophy on MRI, hypometabolism on 18F-FDG PET, and elevation of cerebrospinal fluid tau protein

MRI: the location of atrophy adds specificity for AD and is most prominent in the hippocampi and adjacent entorhinal cortex .



18F-FDG PET: pattern of hypometabolism gives specificity for AD and is found in the lateral and medial posterior (precuneus) parietal cortex, lateral temporal cortex, and posterior cingulate gyrus.



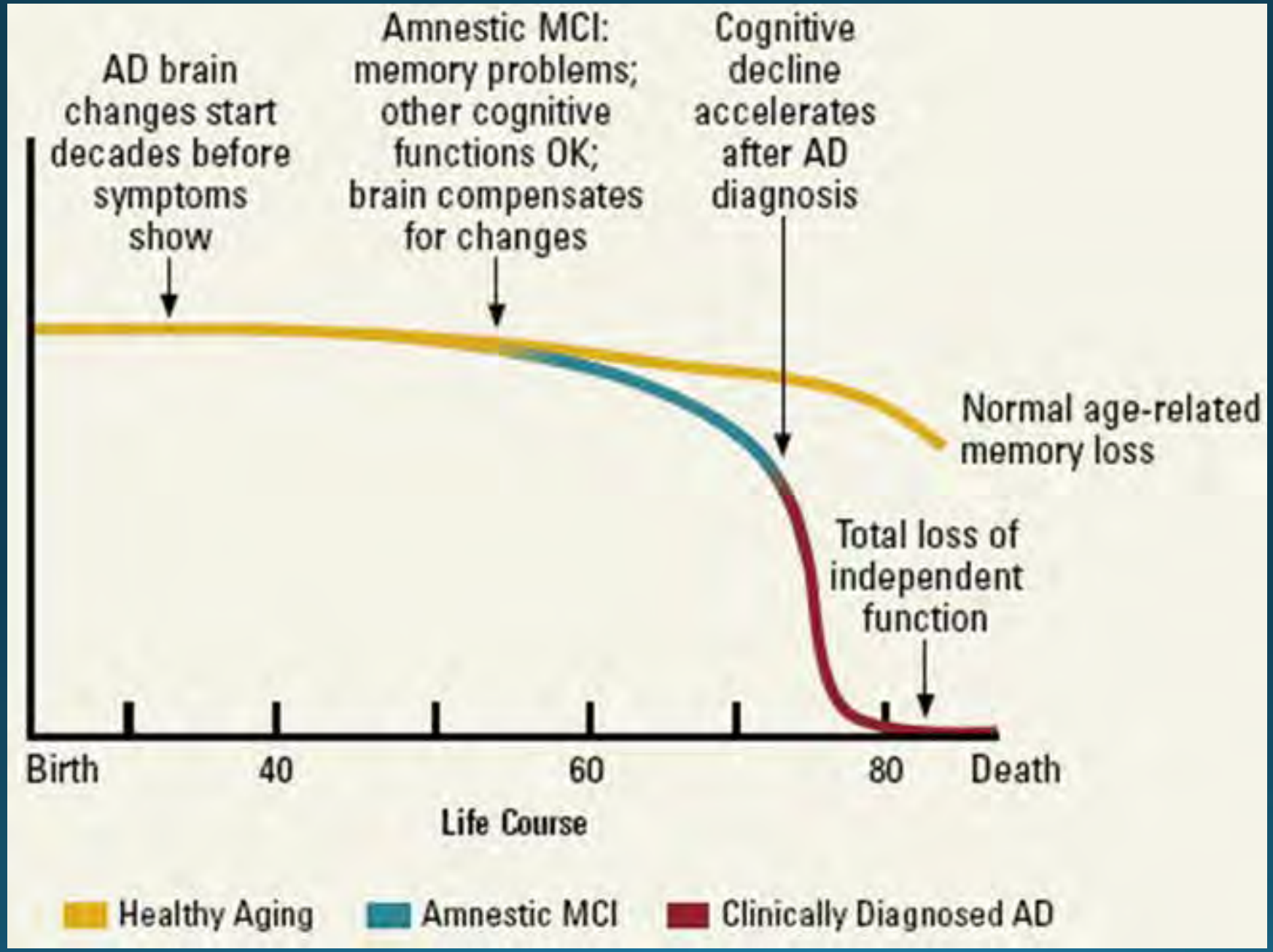
CSF tau and phospho-tau : other reasons, including acute stroke, because they are released into cerebrospinal fluid from damaged neurons.

MCI due to AD

• “high likelihood” when both an amyloid and a neurodegenerative biomarker are positive for AD,

• “intermediate likelihood” if just one biomarker is tested and that is positive,

•MCI “unlikely due to AD” if both amyloid and neurodegenerative biomarkers are negative.


AD brain changes start decades before symptoms show
Amnestic MCI: memory problems; other cognitive functions OK; brain compensates for changes
Cognitive decline accelerates after AD diagnosis
Normal age-related memory loss
Total loss of independent function
Birth
40
60
80
Death
Life Course
Healthy Aging
Amnestic MCI
Clinically Diagnosed AD

AD Pathology in Healthy Elderly

- AD-related neuropathology is also found in about 30% of the asymptomatic elderly population

- a preclinical diagnosis of AD should be restricted to research and therapy trials at this time, because data on the risk of progression to AD for these individuals is insufficient for clinical guidance

- Many persons die with a significant amount of amyloid in the brain but no significant cognitive impairment. Data suggest that amyloid has an essential role in AD but alone does not account for the cognitive decline. Other factors, yet to be fully defined, play an important role in the development of dementia due to AD

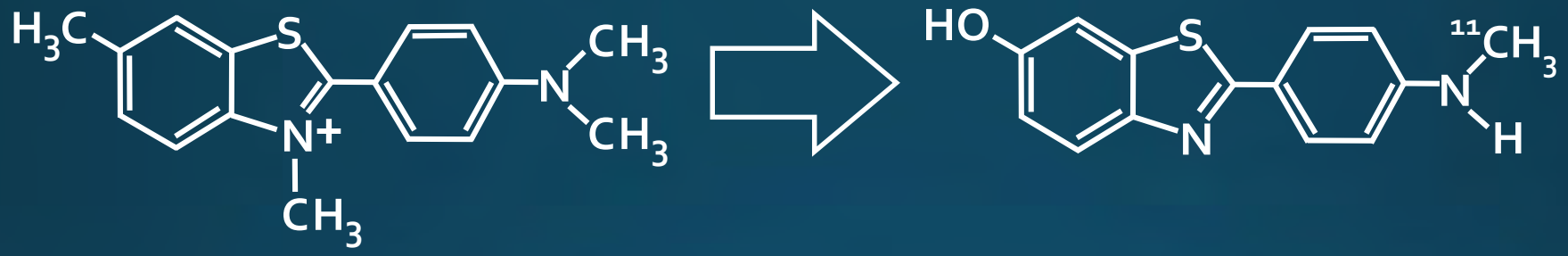
AMYLOID IMAGING

Pittsburgh Compound B (11C-PiB)

11C-PiB : derivative of a fluorescent amyloid dye, thioflavin T: possess high affinity and high specificity for fibrillar Ab

11C-PiB PET studies have shown not only a robust difference in 11C-PiB retention between AD patients and age-matched controls , but also inverse correlations with glucose hypometabolism in some brain regions, as well as decreased cerebrospinal fluid Ab42

Neutral Thioflavin-T Analogues



Thioflavin-T

[^{11}C]PiB

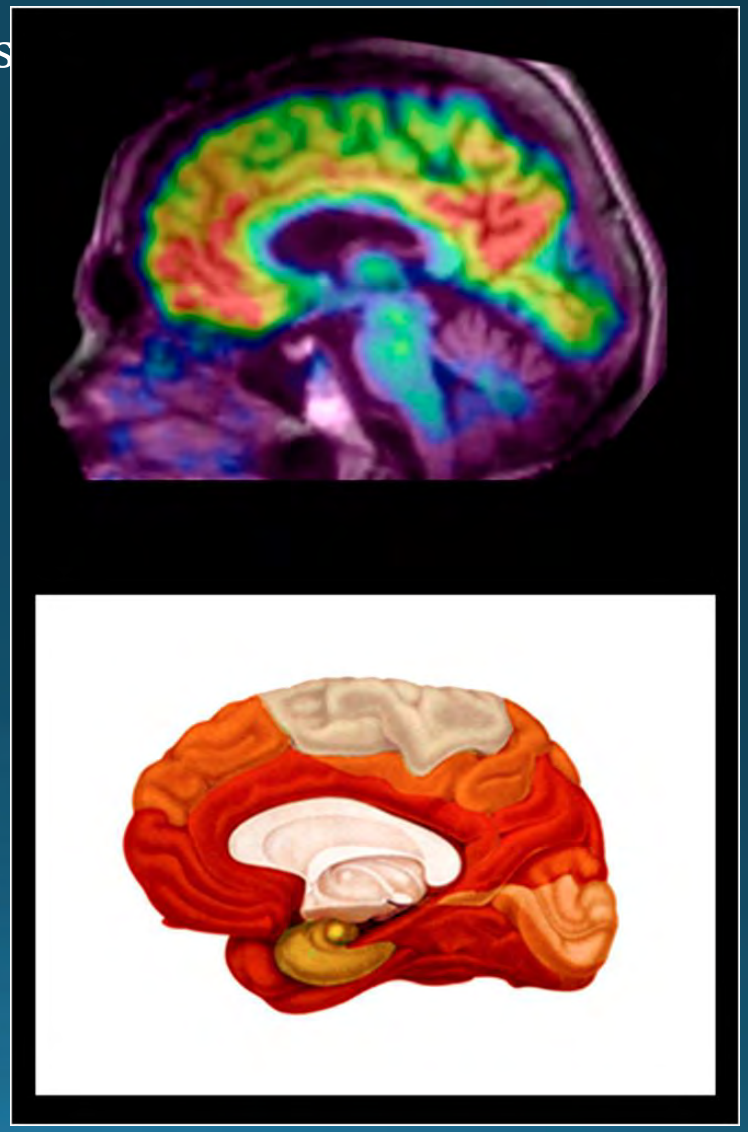
Aβ(1-40) K_i = 300 nM

Aβ(1-40) K_i = 2 nM

11C-PiB in AD

On visual inspection, cortical retention of 11C-PiB is elevated in AD: regional brain binding of 11C-PiB is highest in the frontal cortex, cingulate gyrus, precuneus, striatum, parietal cortex, and lateral temporal cortex. The occipital cortex, sensorimotor cortex, and mesial temporal cortex are usually less affected .

In healthy individuals, a moderate degree of nonspecific uptake is seen in white matter



Reading of 11C-PiB Scans

- cerebellar gray matter as a reference region

- Under most circumstances, the ratio of cortical to cerebellar binding provides a reliable measure of brain amyloid burden

- regions for neocortical SUV ratio usually include only the cortical areas known to accumulate amyloid plaque (frontal, lateral andmedial parietal, and lateral temporal cortex; anterior and posterior cingulate gyrus).

- The scan acquisition time is usually 20 or 30 min.

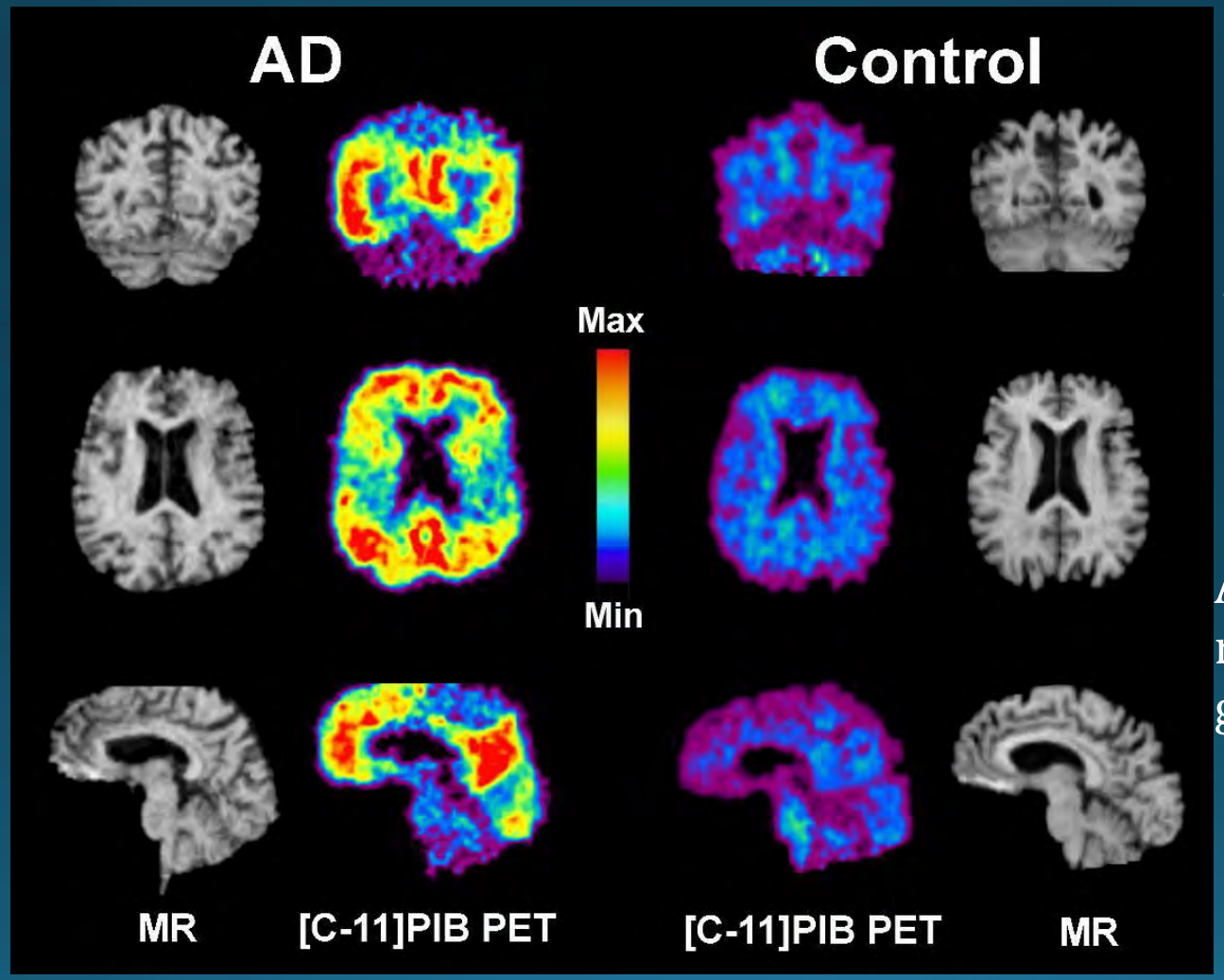
- upper limit of normal binding: usually is between 1.3 and 1.6 for neocortical SUV ratio

- 11C-PiB scans can be reliably interpreted by visual inspection, with binding at least equal to white matter uptake clearly seen in cortex, though usually this binding is clearly in excess of white matter uptake.

[^{11}C]PiB in AD and Control

Appearance in expected gray matter areas

Absence in areas where there is no amyloid



Very little retention

Absence of retention in gray matter

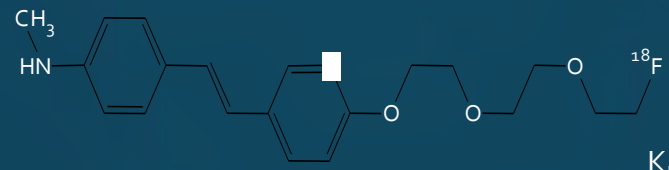
18F-LABELED RADIOPHARMACEUTICALS FOR AMYLOID IMAGING

Clinicians can now choose between three approved PET Aβ imaging tracers:

- Florbetapir (Amyvid)
- Flutemetamol (Vizamyl)
- Florbetaben (Neuraceq)

Approved ^{18}F-Labeled Amyloid Radiotracers

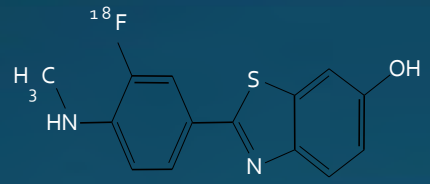
2012



K_D = 3.1 nM
AD brain

[^{18}F]AV-45
florbetapir

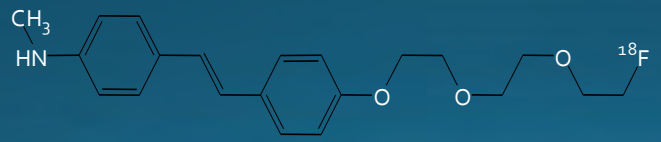
2013



K_D = 2.2 nM
AD brain

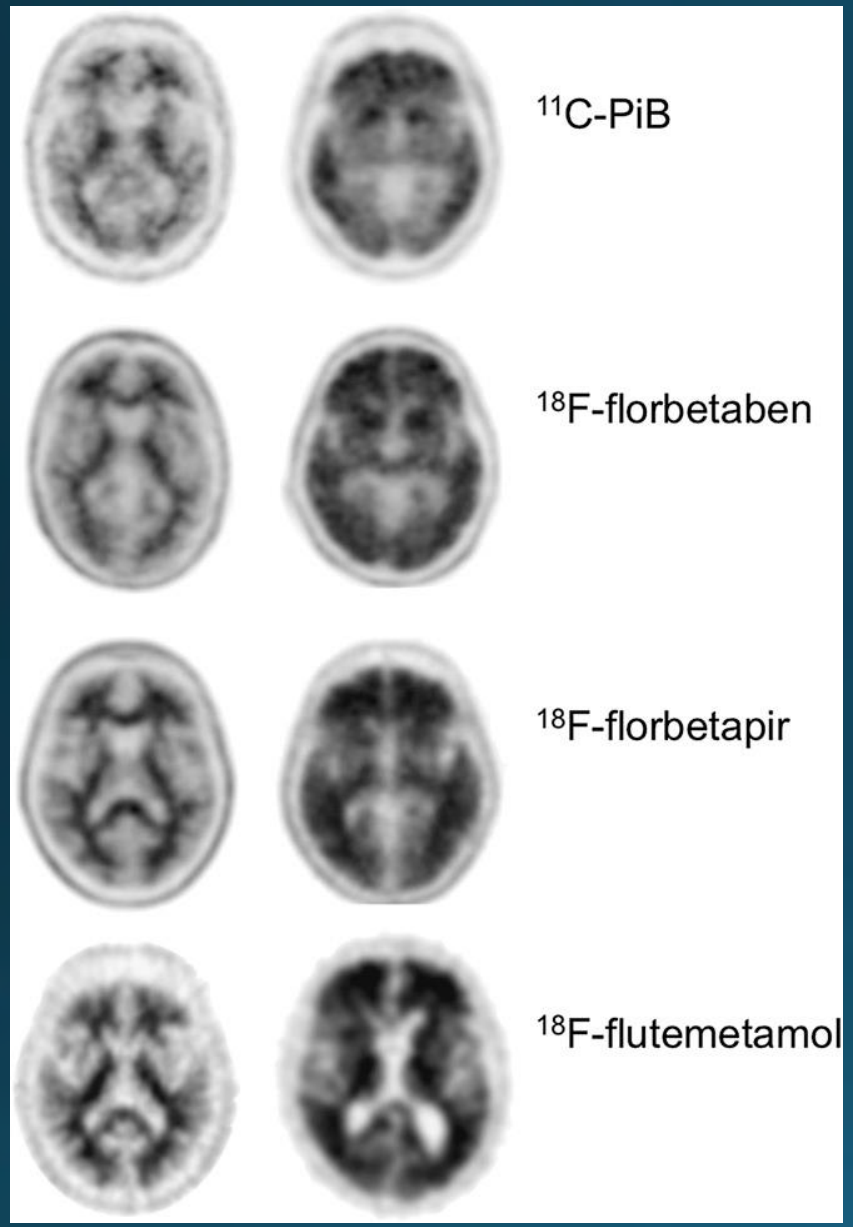
[^{18}F]3′F-PIB / GE-067
flutemetamol

2014



K_D = 6.7 nM
AD brain

[^{18}F]AV-1 / BAY94-9172
florbetaben



Specific criteria for each tracer; online training!

11C-PiB, 18F-florbetaben, 18F-florbetapir, and 18F-flutemetamol images of healthy subjects and AD patients

INDICATIONS AND USAGE

•Amyvid: estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline.

•negative Amyvid scan: sparse to no neuritic plaques and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; reduces the likelihood that a patient's cognitive impairment is due to AD.

•positive Amyvid scan: moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition.

•Amyvid is an adjunct to other diagnostic evaluations.

Limitations of Use:

A positive Amyvid scan does not establish a diagnosis of AD or other cognitive disorder.

•recommended dose for Amyvid is 370 MBq (10 mCi: administered as a single intravenous bolus in a total volume of 10 mL) .

Image Acquisition Guidelines :

•A 10-minute PET image should be acquired starting 30 to 50 minutes after Amyvid intravenous injection.
•Reducing head movement with tape or other flexible head restraints may be employed.
•Image reconstruction should include attenuation correction

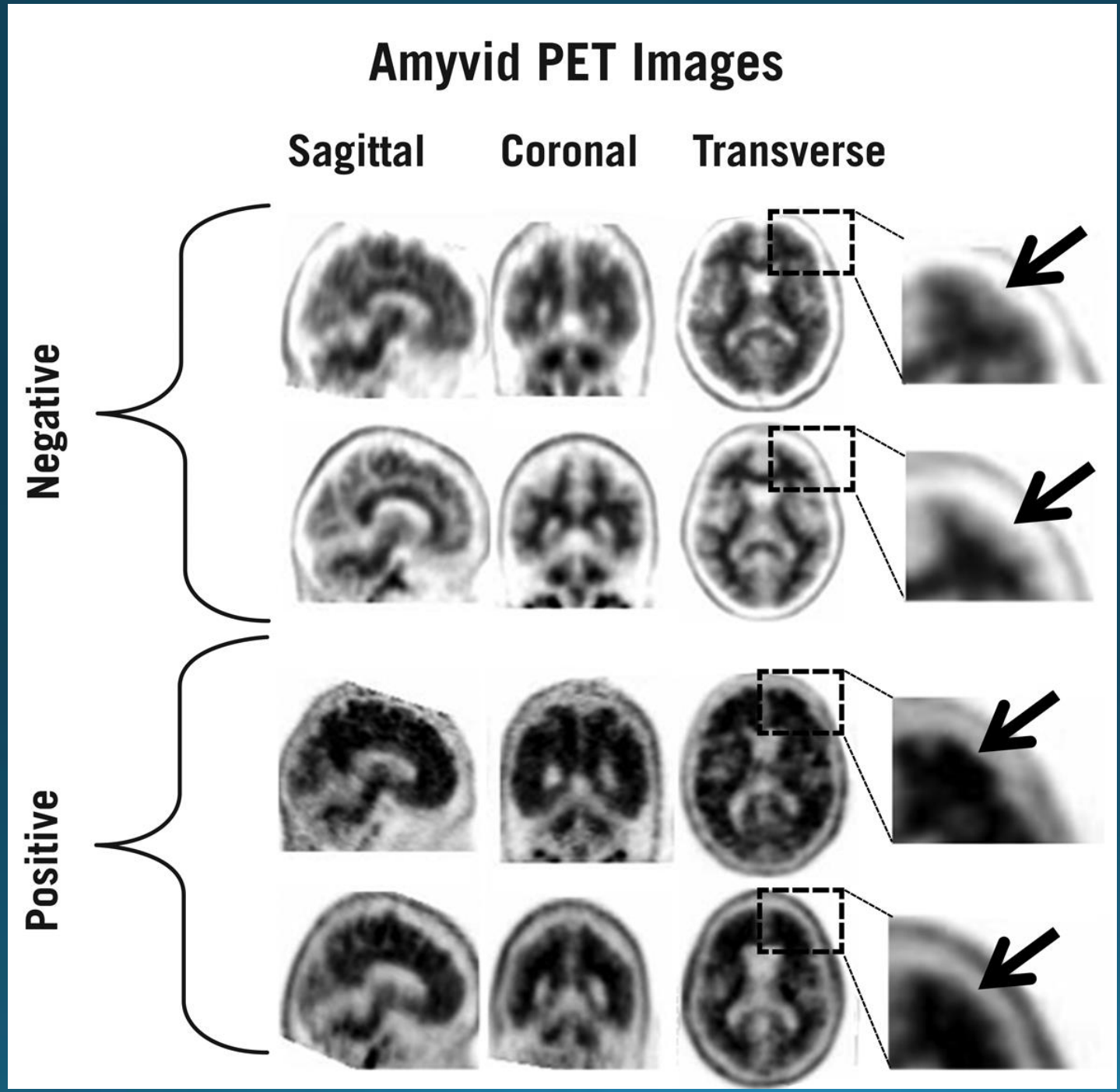
Image Display and Interpretation :

• objective of Amyvid image interpretation is to provide an estimate of the brain β-amyloid neuritic plaque density, not to make a clinical diagnosis.

•Image interpretation is performed independently of a patient's clinical features. Images are designated as positive or negative by comparing the radioactivity in cortical gray matter with activity in the adjacent white matter.

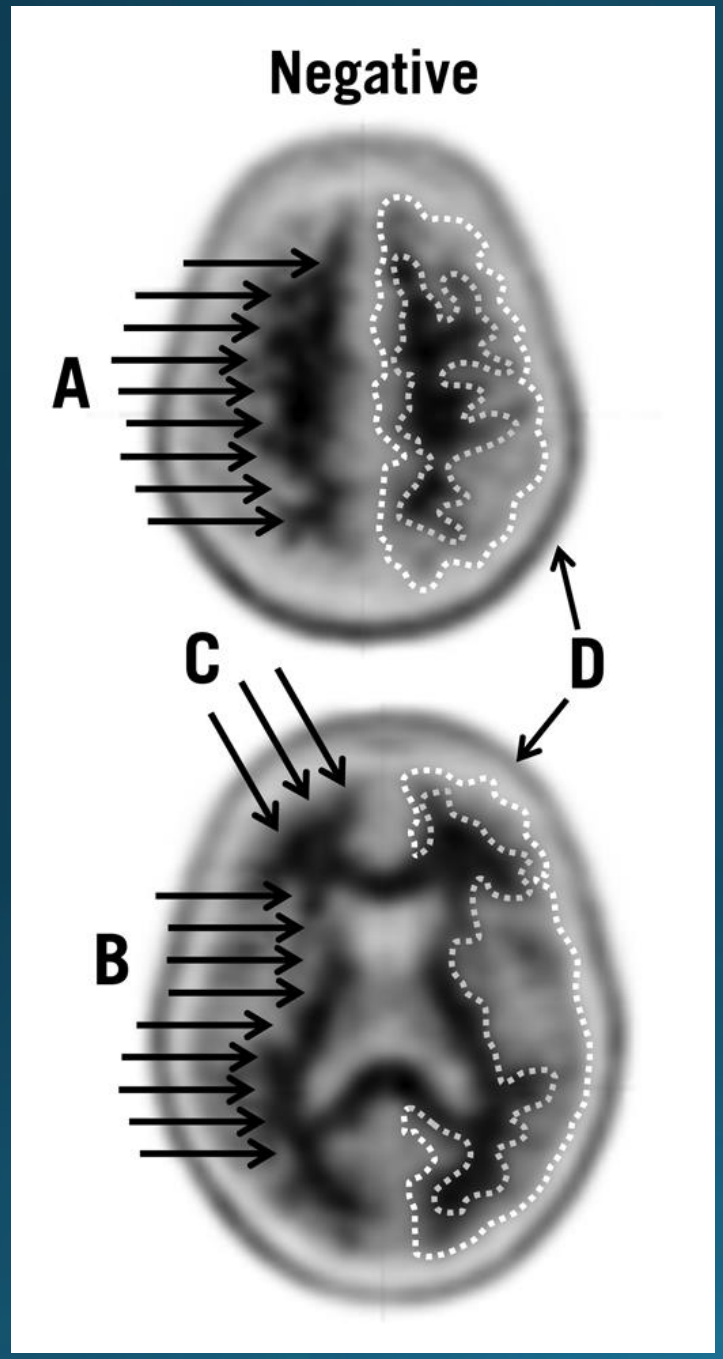
- *Negative scans* show more radioactivity in white matter than in gray matter, creating clear gray-white contrast.

- *Positive scans* show cortical areas with reduction or loss of the normally distinct gray-white contrast. These scans have one or more areas with increased cortical gray matter signal which results in reduced (or absent) gray-white contrast.



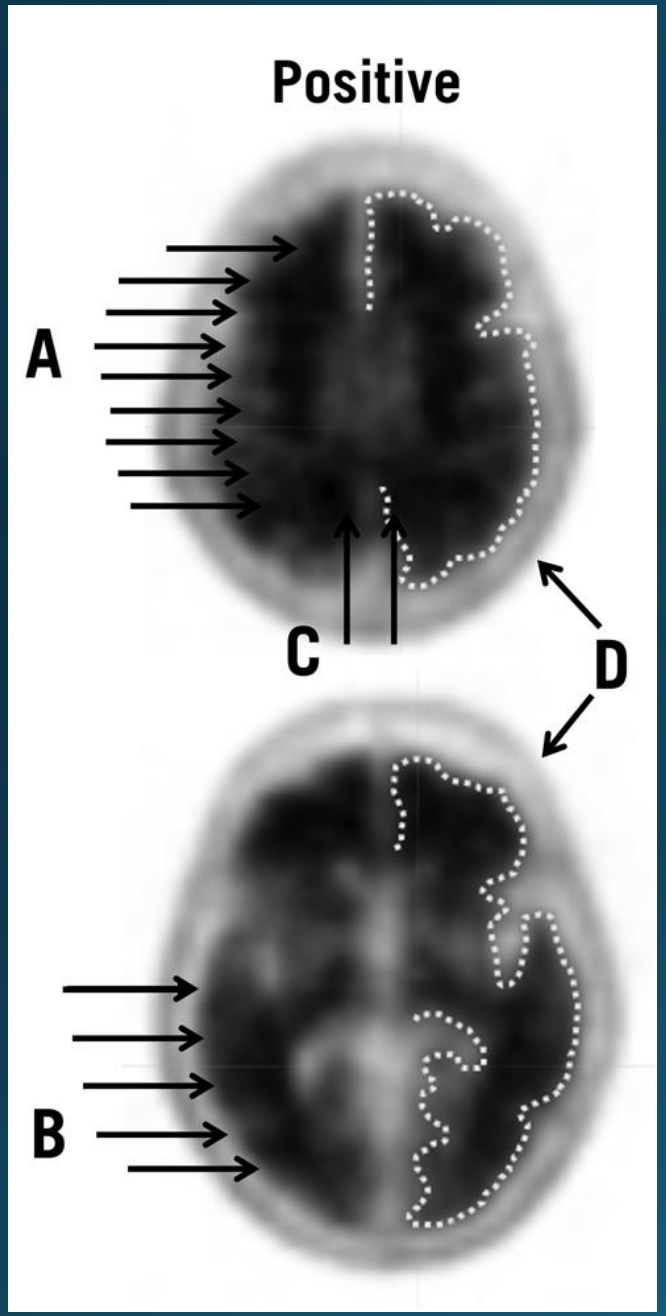
Negative=
Subcortical white matter is more conspicuous than grey matter

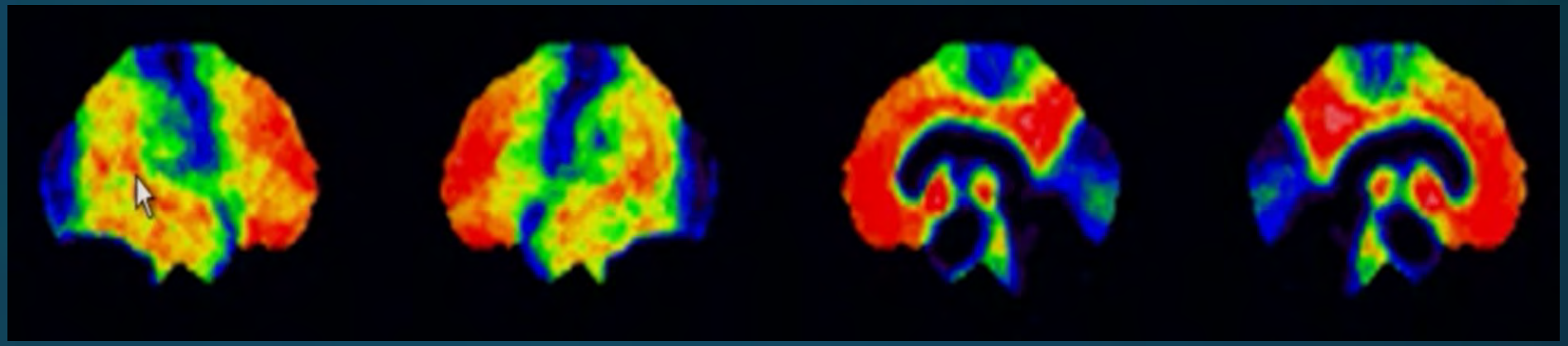
Positive=
cerebral cortex has more uptake than white matter



Typical Negative Scan

A) White matter tracts can be delineated from the frontal lobe to parietal lobe.
B) White matter tracts are clearly identified throughout the occipital / temporal area.
C) Scalloped appearance is seen with “fingers” of white matter in the frontal cortex.
D) Low levels of tracer in scalp or skull that should be distinguished from gray matter uptake by its shape and position.





Typical Positive Scan: pattern of uptake matters

A) White matter tracts are difficult to fully identify as they travel from frontal to parietal lobe.

B) Borders of white matter tracts in occipital/temporal area are lost in places.

C) Increase uptake:

- Intense: *gray matter in posterior cingulate and medial parietal cortex (precuneus)*
- *Frontal cortex including medial aspect*
- Less intense and less frequent: *parietal and temporal neocortex*
- *Relative sparring (very little) : pre and post central gyrus and primary visual cortex.*

Remember: the pattern matters!

Regions most likely and most severely affected: Frontal Ctx, ACingulate Ctx, PCingulate/Precuneus Ctx, Parietotemporal Association Ctx

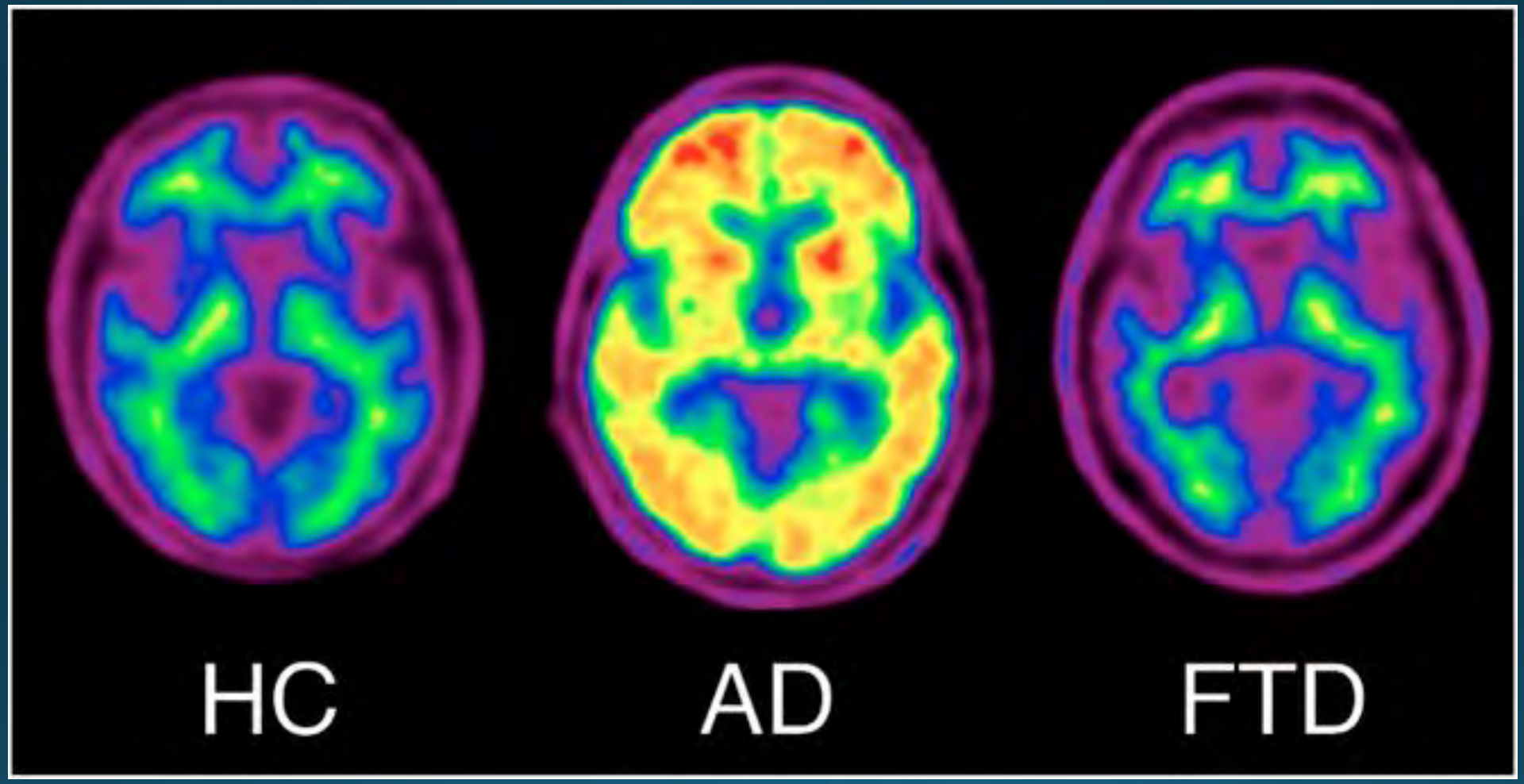
Cerebellar hemispheres cortex is never involved

Some scans may be difficult to interpret due to image noise, atrophy with a thinned cortical ribbon, or image blur.

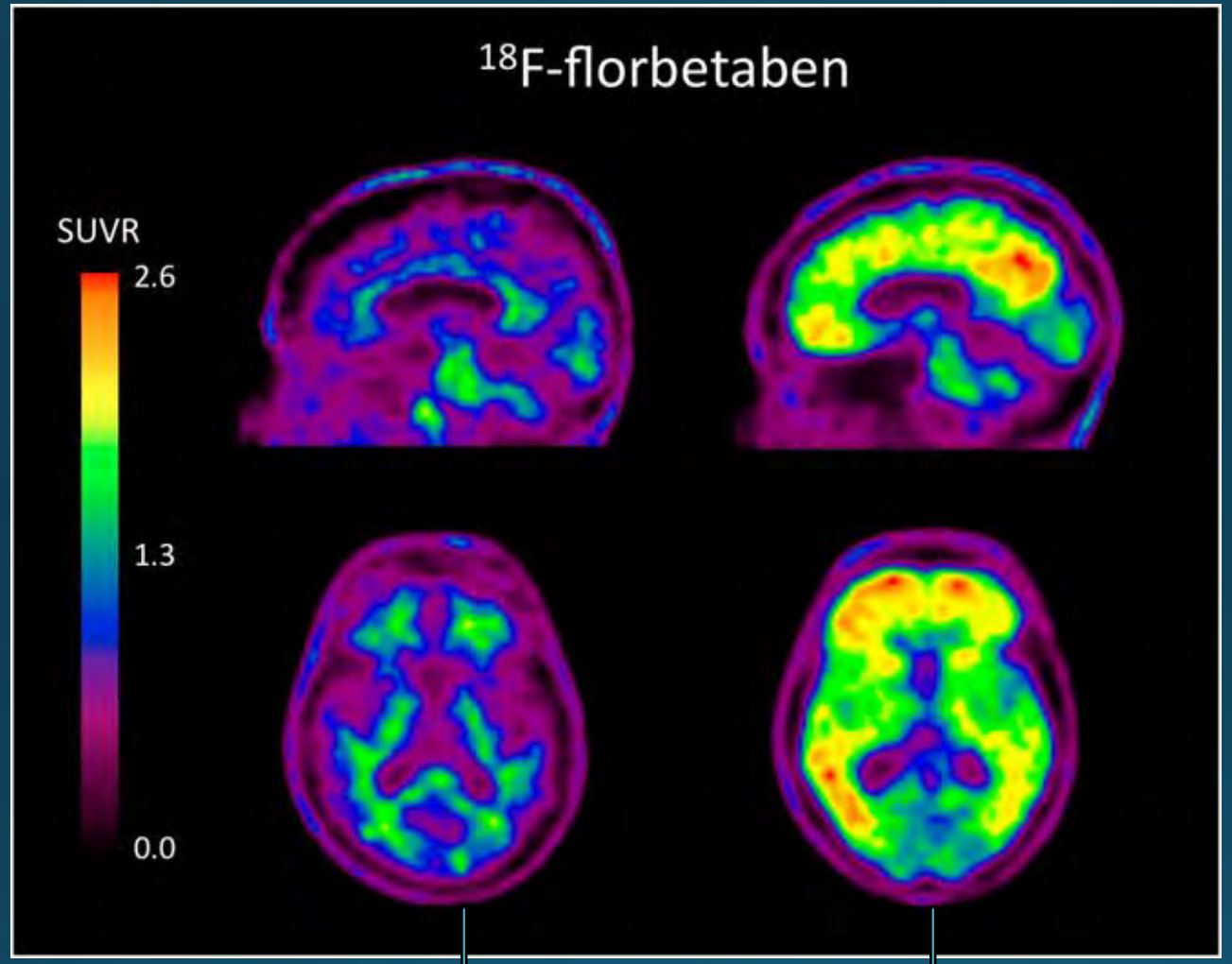
Radiation Dosimetry

- effective dose resulting from a 370 MBq (10 mCi) dose of Amyvid is 7.0 mSv in an adult.

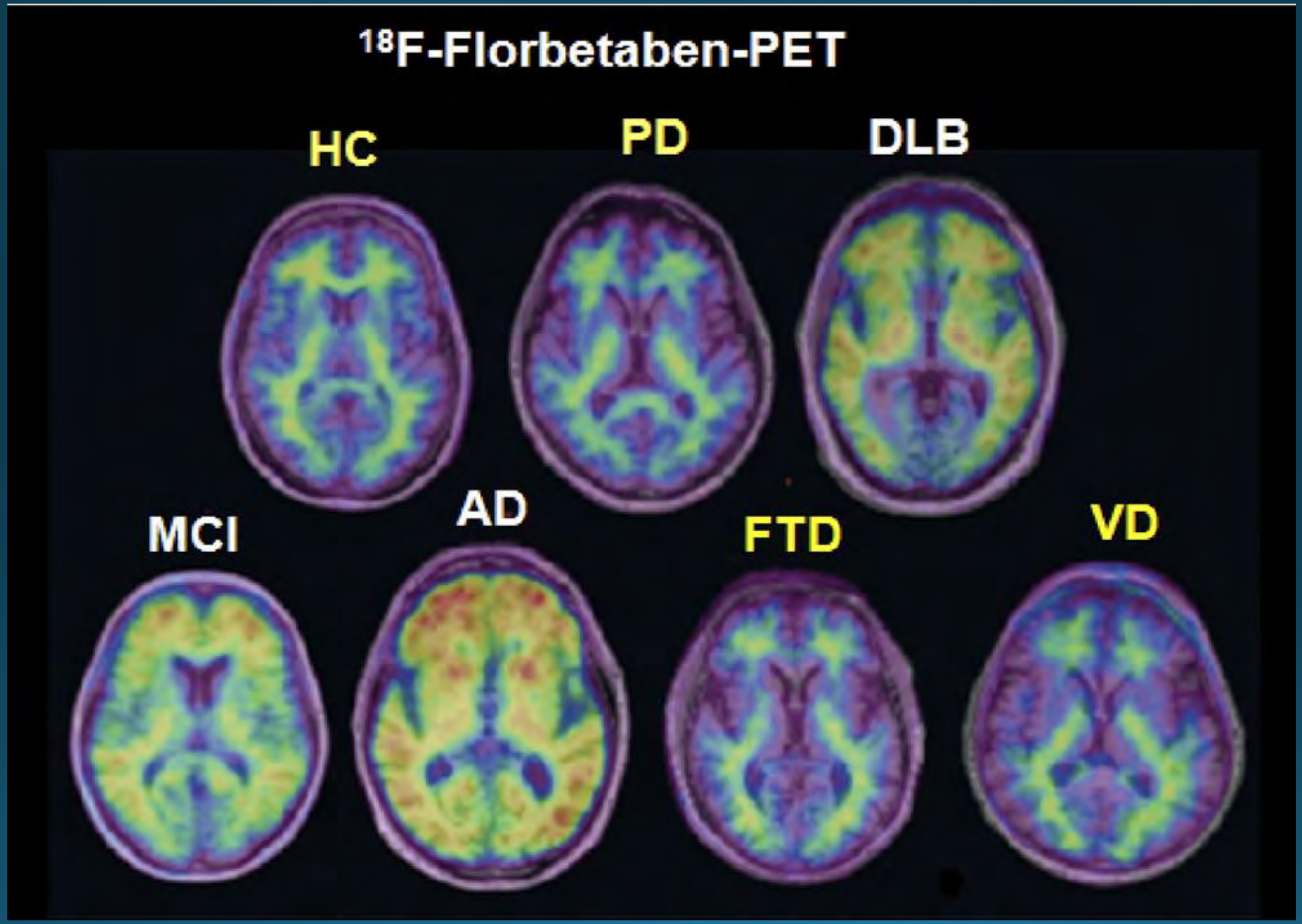
- total radiation exposure from Amyvid administration and subsequent scan on a PET/CT scanner is estimated to be 9 mSv.



18F-florbetaben PET images of healthy aging (HC), AD, and frontotemporal dementia (FTD).



18F-florbetaben images of 2 elderly subjects with MCI


^{18}F-Florbetaben-PET
HC
PD
DLB
MCI
AD
FTD
VD

Accuracy of Amyloid Imaging

- accuracy of amyloid imaging for AD should be over 90% for patients under the age of 70 y, about 85% for patients in their 70s, and 75%–80% for those over 80 y
- Amyloid plaques are not present in frontotemporal dementia. Several studies have shown that amyloid imaging distinguishes clinically diagnosed frontotemporal dementia from AD with high accuracy.
- full potential value of amyloid imaging awaits the development of an effective therapy to slow, halt, or reverse the disease process. Such a therapy will be most beneficial when given early, before dementia has developed. Biomarkers such as amyloid imaging make development of these therapies feasible

Summary:

1. Estimate β-amyloid neuritic plaque density in patients who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline.

2. Negative Amyvid scan: sparse to no neuritic plaques and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; reduces the likelihood that a patient's cognitive impairment is due to AD.

3. Positive scan: moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition.

4. An adjunct to other diagnostic evaluations.

Suggested Articles

1. Eisenmenger LB, Huo EJ, Hoffman JM, et. al. Advances in PET Imaging of Degenerative, Cerebrovascular, and Traumatic Causes of Dementia., Semin Nucl Med. 2016 Jan;46(1):57-87. doi: 10.1053/j.semnuclmed.2015.09.003. Review.
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5. Henriksen G, Yousefi BH, Drzezga A, et. al. Development and evaluation of compounds for imaging of beta-amyloid plaque by means of positron emission tomography., Eur J Nucl Med Mol Imaging. 2008 Mar;35 Suppl 1:S75-81. doi: 10.1007/s00259-007-0705-x. Review.
6. Victor-Villemagne V, Ong K, Mulligan R, et al. 18F-Florbetaben-PET imaging in the differential diagnosis of dementia. J Nucl Med 51(Suppl 2):1786, 2010
7. Johnson KA, Minoshima S, Bohnen NI, et. al. Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association., Alzheimers Dement. 2013 Jan;9(1):e-1-16.