Imaging biomarkers in Alzheimer’s disease

This content is intended for health care professionals only for educational and informational purposes and does not substitute for sound medical judgement or clinical decision making in the context of medical treatment

Eisai hhc human health care

PIPN-M3145

Slide outline

Learning Zone

Types of imaging modalities

Neuroimaging findings to support a diagnosis of AD

Modality	Analyte	Abnormality	Pathology
MRI[1]	Regional anatomy	↓ hippocampal volume, temporal and parietal atrophy, and global brain atrophy[2]	Neurodegeneration[1]*
PET	^{18}F-flortaucipir	↑ neocortex and temporal lobe uptake[3]	Brain tauopathy[4,5]
PET	^{11}C-Pittsburgh compound B, ^{18}F ligands	↑ cortical uptake[1]	Brain amyloidosis[1]
PET	^{18}F-fluorodeoxyglucose (FDG)	↓ metabolism in posterior cingulate-precuneus and temporoparietal cortex[1]	Neurodegeneration[1]*

***Neurodegeneration is not specific to the etiology of dementia and findings alone cannot be used to make a diagnosis of AD[5]**
AD, Alzheimer's disease; MRI, magnetic resonance imaging; PET, positron emission tomography

1. Frisoni GB, et al. Neurobiol Aging 2017;52:119-131; 2. Frisoni GB, et al. Nat Rev Neurol 2010;6:67–77; 3. Schöll M, et al. Brain 2017;140:2286–2294; 4. Fleisher AS, et al. JAMA Neurol 2020;77:829–839; 5. Preische O, et al. Nat Med 2019;25:277–283

Learning Zone

Magnetic resonance imaging (MRI) use

MRI: most common scan types

- **High-resolution 3D / volumetric T1-weighted images** – assessment of regional atrophy, namely of the hippocampus and lobes[1]
- **T2-weighted images** – detection of small vascular disease and visual rating of hippocampal atrophy[1,2]
- **FLAIR sequence** – detecting cerebral white matter hyperintensities, ischemic changes, and vascular pathologies[2]
- **Gradient echo / T2* / susceptibility-weighted imaging** – detection of cerebral micro-hemorrhages or microbleeds, and cerebral superficial siderosis[2,3]
- **Diffusion-weighted imaging** – useful in cases of rapid cognitive decline suggestive of Creutzfeldt-Jakob disease and structural changes associated with the disease[2]

3D, three-dimensional; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging

1. Frisoni GB, et al. Nat Rev Neurol 2010;6:67–77; 2. Harper L, et al. J Neurol Neurosurg Psychiatry 2014;85:692–698; 3. Jetty SN, et al. J Clin Imaging Sci 2018;8:36

MRI: steps in detecting signal change

STEP 1: exclude brain pathology that may eventually be amenable to surgical intervention[1]

STEP 2: assess images for signal change utilizing FLAIR/T2 hyperintensity[1]

STEP 3: assess images for signal change utilizing T2* hypointensity to detect CMBs[1]

STEP 4: assess images for cerebral atrophy[1]

STEP 5: regardless of whether atrophy is present or absent, biomarker assessment (CSF or PET imaging) should be considered[1]

*T2 hypointensities may also result from calcification, iron deposits, hemorrhagic metastasis or diffuse axonal injury.

CMB, cerebral microbleed; CSF, cerebrospinal fluid; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; PET, positron emission tomography

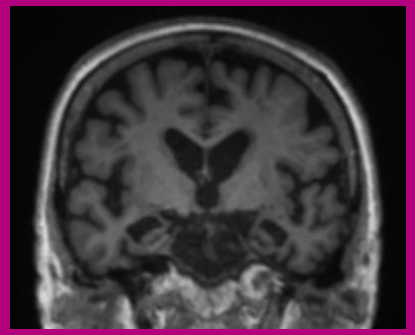
1. Harper L, et al. J Neurol Neurosurg Psychiatry 2014;85:692–698

Assessing atrophy

- Patterns of atrophy on structural imaging are generally indicative of the specific underlying pathology; this is considered a **neurodegenerative marker**
- Findings should be considered in the context of the patient's age and clinical findings

Focal hippocampal atrophy is the most established structural imaging biomarker of AD

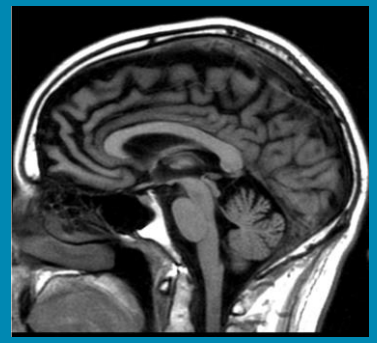
However, focal hippocampal atrophy is also a feature of hippocampal sclerosis and FTLD



Case courtesy of Bruno Di Muzio, Radiopaedia.org, rID: 57096

Focal lobar atrophy

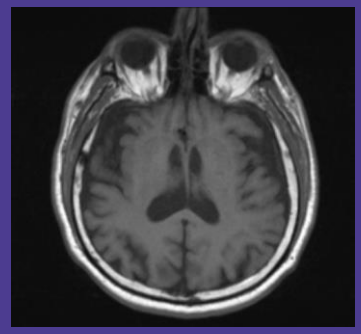
An asymmetric pattern of atrophy (left greater than right or vice versa) or more anterior than posterior atrophy is more suggestive of underlying FTLD pathology than AD



Case courtesy of Frank Gaillard, Radiopaedia.org, rID: 14321

Generalized atrophy

Global volume loss without focal lobar atrophy is a non-specific finding on structural MRI observed in normal aging and dementia; however, symmetric generalized atrophy is more typically observed in AD and DLB



Case courtesy of Gabrielle Matta, Radiopaedia.org, rID: 44422

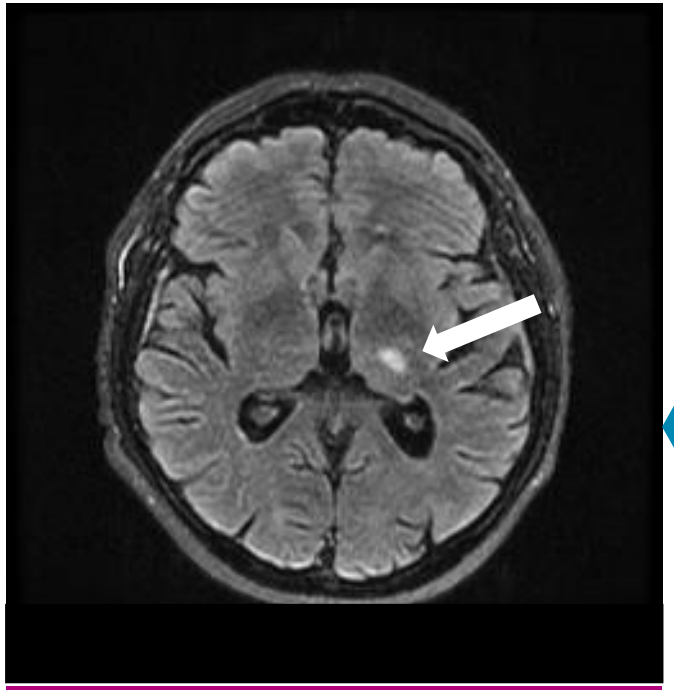
AD, Alzheimer's disease; DLB, dementia with Lewy bodies; FTLD, frontotemporal lobar degeneration; MRI, magnetic resonance imaging

Left hand image, Di Muzio B, Alzheimer disease. Case study, Radiopaedia.org (Accessed on 26 Jul 2023) https://doi.org/10.53347/rID-57096. Middle image, Gaillard F, et al. Frontotemporal dementia. Case study, Radiopedia.org. Available from: https://radiopaedia.org/cases/14321 (Accessed 25 July 2023); Matta G, Asymptomatic severe global atrophy. Case study, Radiopaedia.org https://doi.org/10.53347/rID-44422 (Accessed on 25 Jul 2023)

Harper L, et al. J Neurol Neurosurg Psychiatry 2014;85:692–698

Detecting infarction

Lacunar infarct

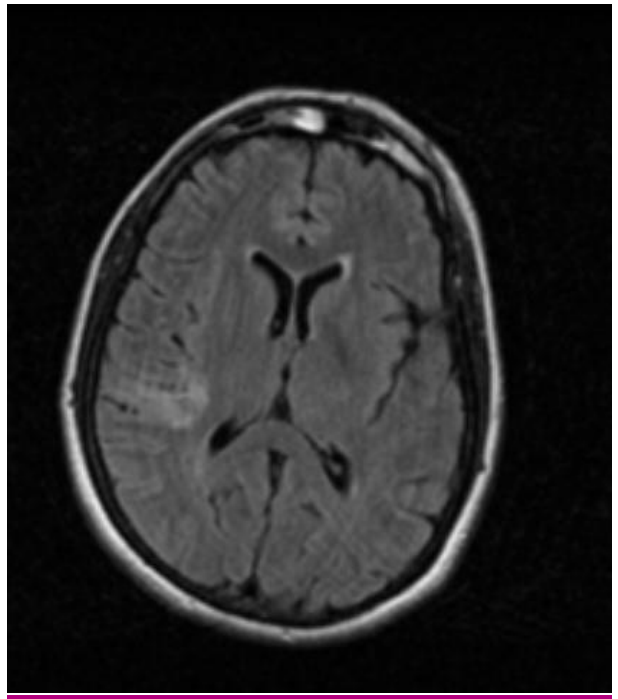


Axial T2-FLAIR MRI shows left thalamic and infarct

Case courtesy of Botz B, Radiopaedia.org, rID: 95543

- Lacunar infarcts occur in deep gray and white matter
- Radiologically 3–20 mm in size; round, oval, or slit-like[1]
- On CT, appear hypodense[2]
- On MRI, hypointense on T1 and hyperintense on T2[1]
- On FLAIR sequences, hypointense with a high signal rim[1]
- Patients with lacunar infarcts develop dementia 4–12 times more frequently than the normal population[3]

Territorial infarct



Axial T2-FLAIR MRI shows acute right middle cerebral artery territory infarct involving right parietal lobe, including the lateral posterior right insular cortex

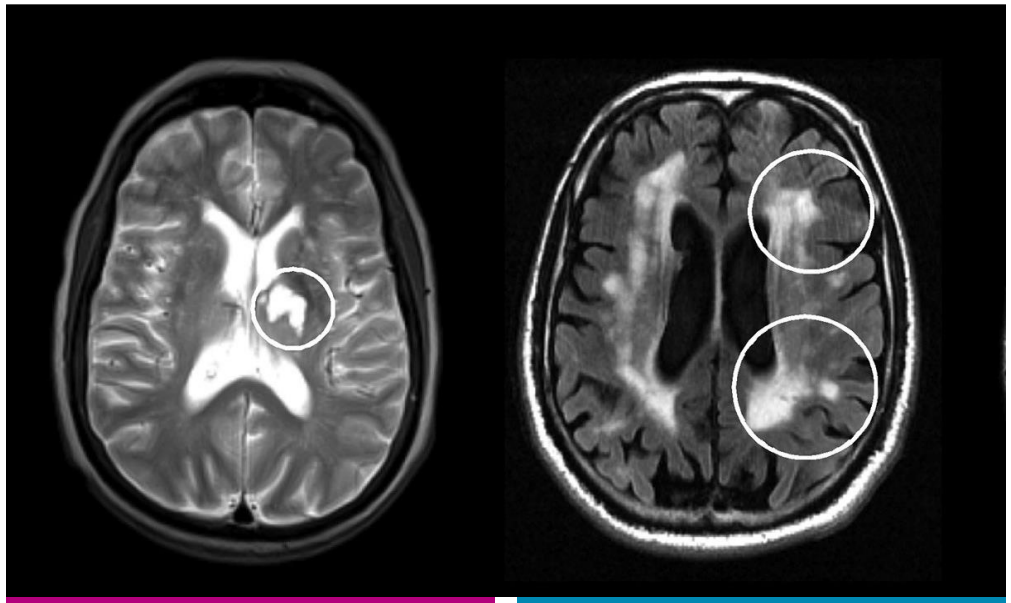
Case courtesy of RMH Core Conditions, Radiopaedia.org, rID: 34112

CT, computed tomography; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging

Image on the left Botz B, Acute lacunar cerebral infarcts. Case study, Radiopaedia.org (Accessed on 25 Jul 2023) https://doi.org/10.53347/rID-95543, and image on the right from Conditions R, Right MCA territory infarct. Case study, Radiopaedia.org (Accessed on 26 Jul 2023) https://doi.org/10.53347/rID-34112

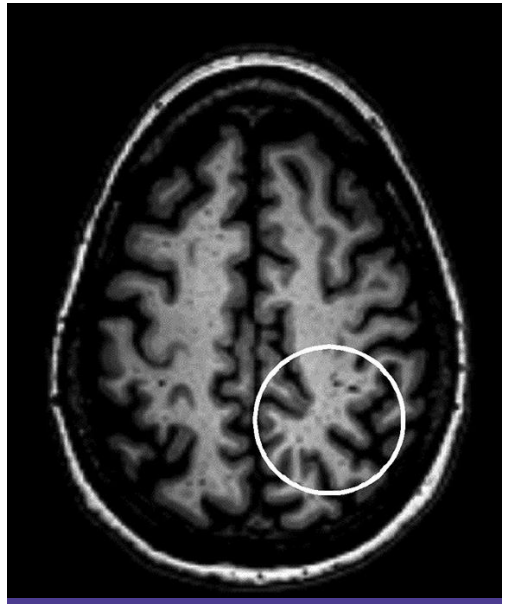
1. Guermazi A, et al. Neuroradiology 2007;49:1–22; 2. Harper L, et al. J Neurol Neurosurg Psychiatry 2014;85:692–698; 3. Loeb C, et al. Stroke 1992;23:1225–1229

Vascular findings associated with cognitive decline



Lacunar infarcts on T2-weighted images

Periventricular white matter lesions and confluent deep white matter lesions on T2 FLAIR



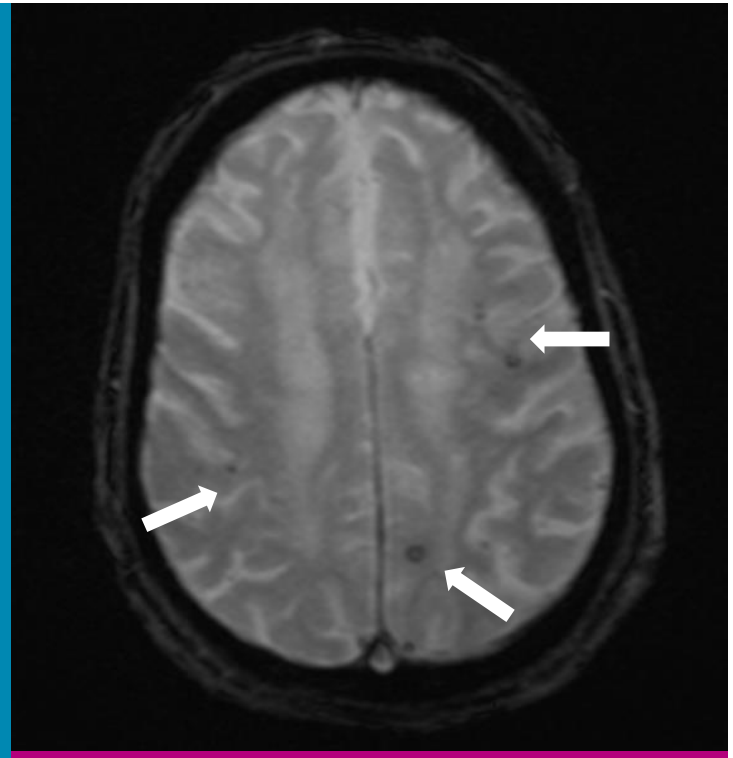
Dilated perivascular spaces on T1-weighted images

FLAIR, fluid-attenuated inversion recovery

Images used with permission from Grajauskas L, et al. Ageing Res Rev 2019;49:67–82

Detecting microbleeds

- **Microbleeds** – focal hypointensities on T2*-weighted or susceptibility-weighted images (SWI) representing hemosiderin deposition from microhemorrhage (less than 1 cm)[1–4]
- Microbleeds appear in approximately 20% of AD cases[5]



SWI image shows punctate hypointense lesions in a cortico-medullary distribution

Case courtesy of Mohamed Abdalla, Radiopaedia.org, rID: 62065

AD, Alzheimer's disease

Image from Abdalla M, Cerebral amyloid angiopathy. Case study, Radiopaedia.org (Accessed on 25 Jul 2023) https://doi.org/10.53347/rID-62065
1. Mortimer AM, et al. Pract Neurol 2013;13:92–103; 2. Harper L, et al. J Neurol Neurosurg Psychiatry 2014;85:692–698; 3. Joseph-Mathurin N, et al. Neurology 2021;96:e1632–e1645; 4. Filippi M, et al. JAMA Neurol. 2022;79(3):291–304;
5. Sepehry AA, et al. AJNR Am J Neuroradiol 2016;37:215–222

Differentiating between dementia etiologies is complex owing to mixed pathologies (1/2)

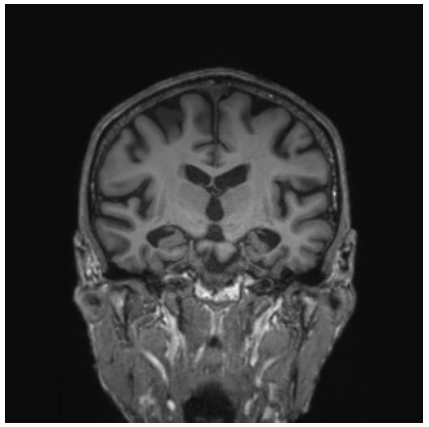
Mixed pathologies are common: over 30% of patients with AD exhibit vascular comorbidity and 80% of DLB cases co-occur with AD.[1,2] Thus, while imaging results can be used to aid diagnosis by highlighting structural changes, they are not diagnostic on their own

MRI findings related to aging and dementia are complex: several pathological processes can impact similar brain structures that mediate cognitive decline; therefore, differential pathologies can further complicate the diagnosis[3]

AD, Alzheimer's disease; DLB, dementia with Lewy bodies; MRI, magnetic resonance imaging

1. Jagtap A, et al. BGM 2015;7:43–56; 2. Karantzoulis S, Galvin JE. Expert Rev Neurother 2011;11:1579–1591; 3. Jagust W, et al. Ann Neurol 2008;63:72–80

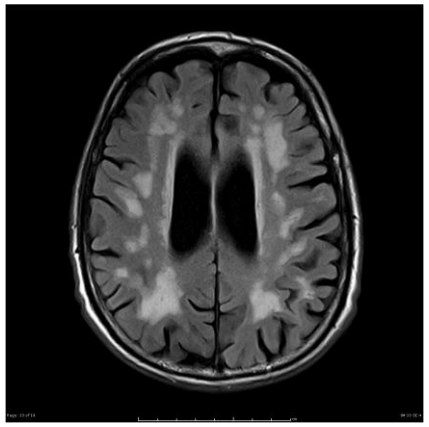
Differentiating between dementia etiologies is complex owing to mixed pathologies (2/2)



Case courtesy of Frank Gaillard, Radiopaedia.org, rID: 92689

MRI (T1)

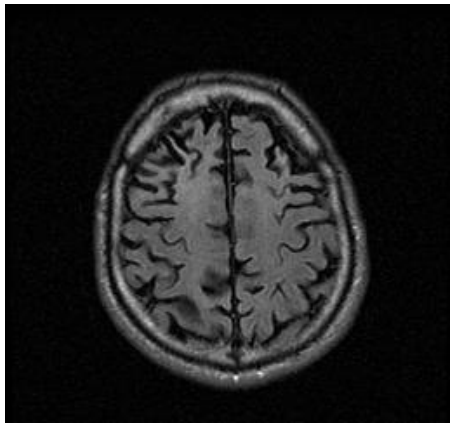
Mild generalized cerebral atrophy in a patient with AD with bilateral hippocampal atrophy



Case courtesy of Frank Gaillard, Radiopaedia.org, rID: 25641

MRI (FLAIR)

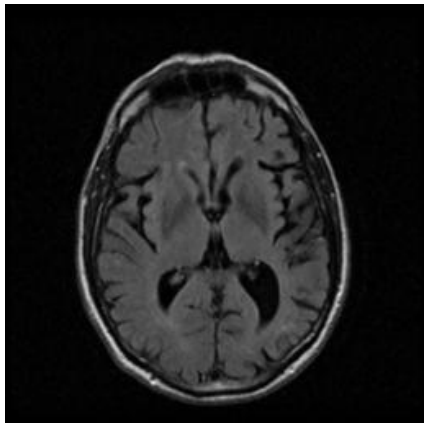
Extensive microvascular damage in vascular cognitive impairment



Case courtesy of Frank Gaillard, Radiopaedia.org, rID: 28163

MRI (FLAIR)

Atrophy much more pronounced in frontal lobes in FTD



Case courtesy of Frank Gaillard, Radiopaedia.org, rID: 28774

MRI (FLAIR)

Non-specific changes in DLB – generalized atrophy with no obvious focal predilection

AD, Alzheimer's disease; DLB, dementia with Lewy bodies; FLAIR, fluid-attenuated inversion recovery; FTD, frontotemporal dementia; MRI, magnetic resonance imaging

Images 1–4, left to right: Gaillard F, Alzheimer disease or LATE. Case study, Radiopaedia.org https://doi.org/10.53347/rID-92689 (Accessed on 25 Jul 2023); Gaillard F, Vascular dementia. Case study, Radiopaedia.org https://doi.org/10.53347/rID-25641 (Accessed on 25 Jul 2023) ; Gaillard F, Frontotemporal dementia. Case study, Radiopaedia.org https://doi.org/10.53347/rID-28163 (Accessed on 25 Jul 2023)

Differentiating between dementia etiologies

Condition	Typical non-specific features observed on MRI
Alzheimer's disease[1]	• Medial temporal lobe atrophy • Parietal atrophy • Ventriculomegaly • Global volume loss
Behavioral frontotemporal lobar degeneration[1]	• Frontal, insula, and anterior temporal atrophy[2] • Medial temporal lobe atrophy; often asymmetry • Global volume loss[3]
Vascular dementia / vascular cognitive impairment[1]	• Cortical and/or lacunar infarcts* • Deep and periventricular white matter T2 hyperintensity / CT hypodensity* • Global volume loss • Mild medial temporal lobe atrophy
Dementia with Lewy bodies[1]	• Global volume loss
Limbic-predominant age-related TDP-43 encephalopathy (LATE)[4]	• Hippocampal atrophy†
Multiple system atrophy[5]	• Atrophy of putamen, middle cerebellar peduncle, pons, and/or cerebellum
Creutzfeldt-Jakob disease[5]	• Cortical diffusion changes; pulvinar sign

*Detecting vascular lesions does not mean the patient has vascular dementia; there is often multiple pathologies
†Hyperintensity in the hippocampal region on a T2 or FLAIR image can help to differentiate between AD etiologies[3]

AD, Alzheimer's disease; CT, computed tomography; FLAIR, fluid-attenuated inversion recovery; LATE, limbic-predominant age-related TDP-43 encephalopathy; MRI, magnetic resonance imaging; TDP-43, TAR DNA-binding protein 43

1. Mortimer AM, et al. Pract Neurol 2013;13:92–103; 2. Seeley WW. Brain Struct Funct 2010;214:465–475; 3. Chan D, et al. Neurology 2001;57:1756–1763; 4. Nelson PT, et al. Brain 2019;142:1503–1527;
5. Frisoni GB, et al. Nat Rev Neurol 2010;6:67–77

Learning Zone

Introduction to amyloid PET

Introduction to amyloid PET

- In-vivo amyloid PET predicts the presence of significant Aβ pathology at autopsy and is considered a surrogate marker of brain amyloid pathology that is required for AD diagnosis[1,2]
- The use of in-vivo tracers helps to establish biomarker relationships with changes in cognition and neurodegeneration, and support a diagnosis[3]
- Increased retention of amyloid radiotracers indicates the presence of fibrillar aggregates of Aβ[3]
  - A positive amyloid PET result alone is not sufficient to diagnose AD, and amyloid PET radiotracers should be combined with other diagnostic tools, such as clinical evaluation and structural imaging, for an accurate diagnosis[3]

Aβ, amyloid beta; AD, Alzheimer's disease; PET, positron emission tomography

1. Clark CM, et al. JAMA 2011;305:275–283; 2. Klunk W. Neurobiol Aging 2011;32:S20–S36; 3. Villemagne VL, et al. Nat Rev Neurol 2018;14:225–236

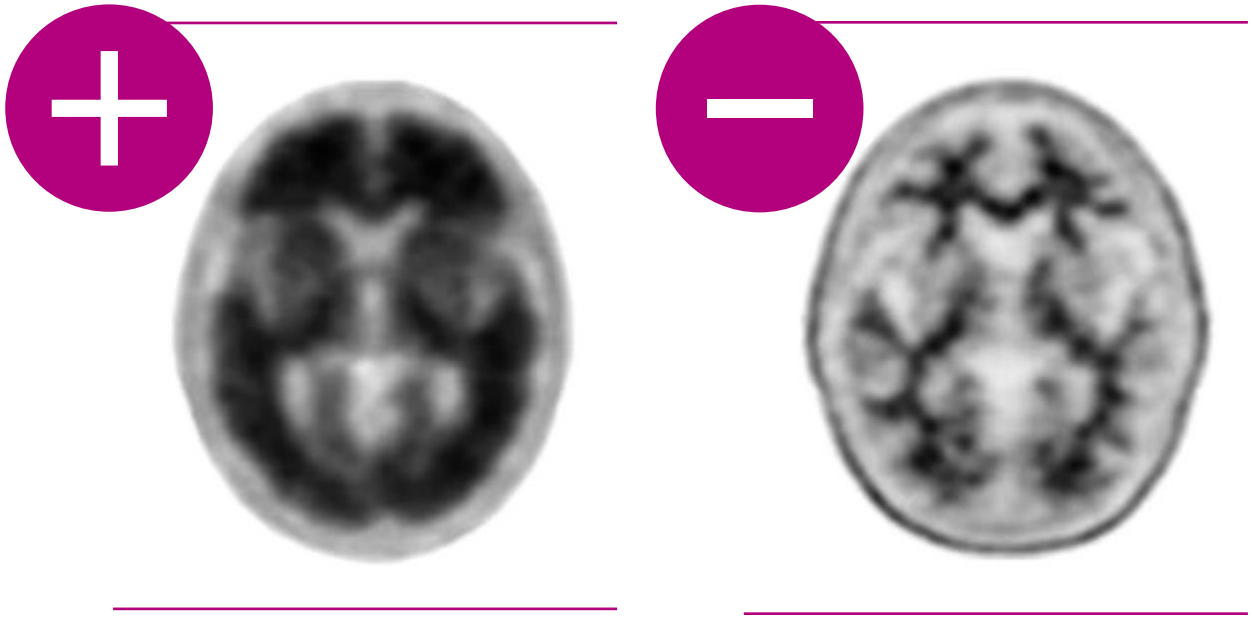
Introduction to amyloid PET tracers[1–3]

- A positive amyloid PET scan using ^{18}F-florbetapir, ^{18}F-florbetaben, or ^{18}F-flutemetamol indicates the presence of moderate-to-frequent amyloid neuritic plaques, but does not independently establish a diagnosis of AD
- All three radiotracers show high non-specific binding in white matter
- Detection of amyloid for all three radiotracers relies on the loss of the normal contrast between white and gray matter due to amyloid accumulation in the cortex
- Specific criteria for a positive scan for each amyloid radiotracer are presented in the package inserts and are reviewed in online training courses provided by the radiotracer manufacturers

AD, Alzheimer's disease; PET, positron emission tomography

1. AMYViD® (^{18}F-florbetapir) highlights of prescribing information. 2012. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202008s000lbl.pdf (Accessed December 17, 2021); 2. Neuraceq® (^{18}F-florbetaben) Highlights of prescribing information. 2014. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204677s000lbl.pdf (Accessed June 12, 2023); 3. VIZAMYL® (^{18}F-flutemetamol) package insert. 2013. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/203137s005lbl.pdf (Accessed June 12, 2023)

Introduction to amyloid PET tracers: ^{18}F-florbetapir (AMYViD®)



Key supportive findings[1]

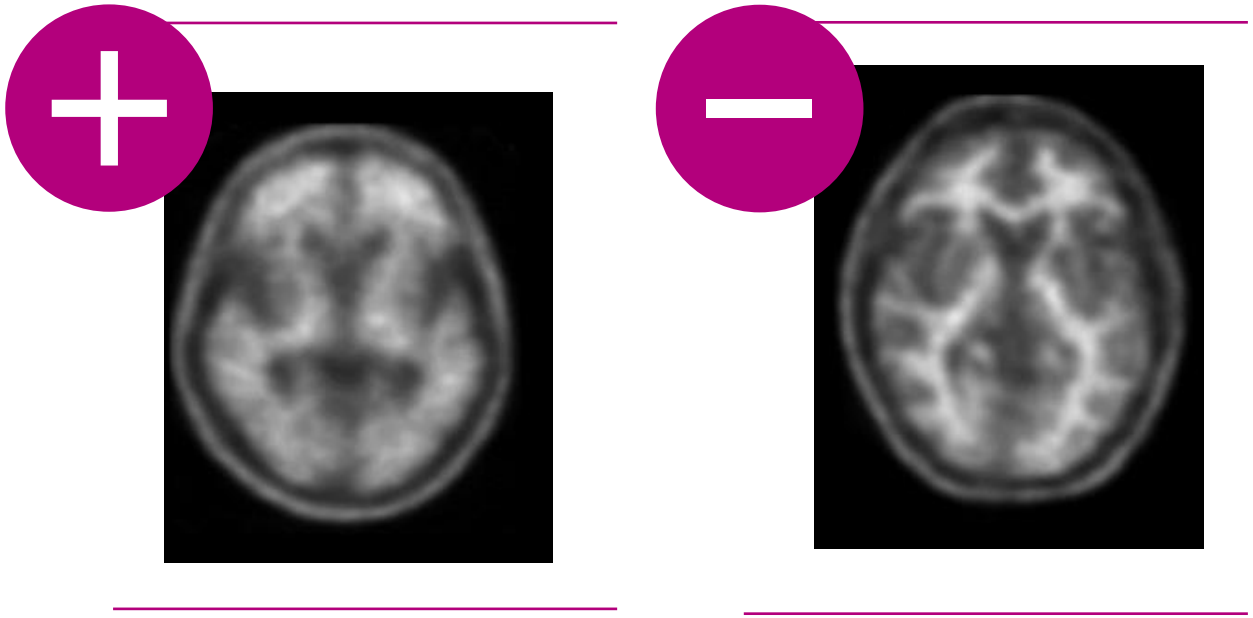
- Binding studies in post-mortem brains showed significant (P<0.0001) correlations between in-vitro ^{18}F-florbetapir binding and Aβ aggregate deposition
- A blinded pivotal study in 59 end-of-life patients resulted in a majority read **sensitivity of 92%** (95% CI 78, 98) and **specificity of 100%** (95% CI 80, 100)

Aβ, amyloid beta; CI, confidence interval; PET, positron emission tomography

This research was originally published in JNMT. Trembath L, et al. J Nucl Med Technol 2015;43:175–184. © SNMMI

1. AMYViD® (^{18}F-florbetapir) summary of product characteristics. 2013. Available from: https://www.ema.europa.eu/documents/product-information/amyvid-epar-product-information_en.pdf (Accessed June 12, 2023)

Introduction to amyloid PET tracers: ^{18}F-florbetaben (Neuraceq®)



Key supportive findings[1]

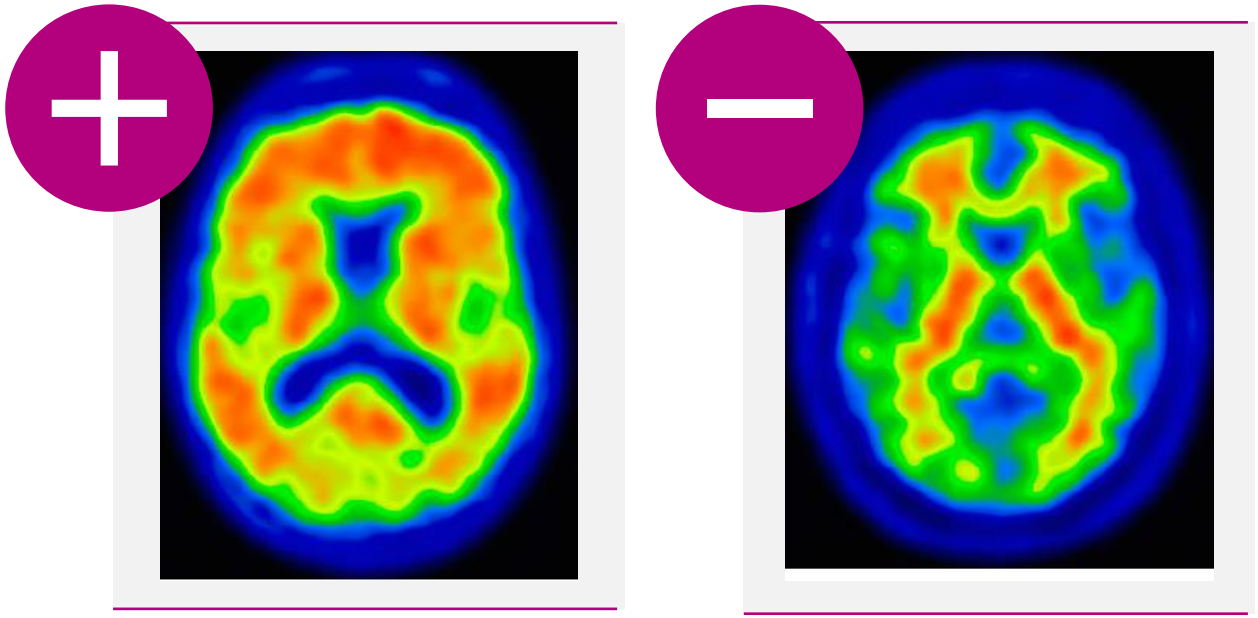
- A blinded pivotal study in 31 end-of-life patients resulted in a sensitivity of 100% (95% CI 80.5, 100) and specificity of 85.7% (95% CI 67.4, 100)
- Comparison of PET scan reading by five blinded, electronically trained readers from 54 subjects with histopathology assessment at autopsy showed **sensitivity of 100%** (95% CI 89.4, 100) and **specificity of 71.4%** (95% CI 52.1, 90.8)

CI, confidence interval; PET, positron emission tomography

Images used with permission from Jovalekic A, et al. Eur J Nucl Med Mol Imaging. 2023 Jun 10. doi: 10.1007/s00259-023-06279-0. Epub ahead of print (CC-BY 4.0: http://creativecommons.org/licenses/by/4.0/).

1. Neuraceq® (^{18}F-florbetaben) summary of product characteristics. 2021. Available from: https://www.ema.europa.eu/documents/product-information/neuraceq-epar-product-information_en.pdf (Accessed June 12, 2023)

Introduction to amyloid PET tracers: ^{18}F-flutemetamol (VIZAMYL®)



Key supportive findings[1]

- A blinded pivotal study in 68 end-of-life patients resulted in a majority read sensitivity of 86% (95% CI 72, 95) and specificity of 92% (95% CI 74, 99)
- Comparison of PET scan reading by five blinded, electronically trained readers from the above 68 patients and an additional 38 (N=106) showed **sensitivity of 91%** (95% CI 82, 96) and **specificity of 90%** (95% CI 74, 98)

CI, confidence interval; PET, positron emission tomography

This research was originally published in JNMT. Mantel E, Williams J. J Nucl Med Technol 2019;47:203–209. © SNMMI

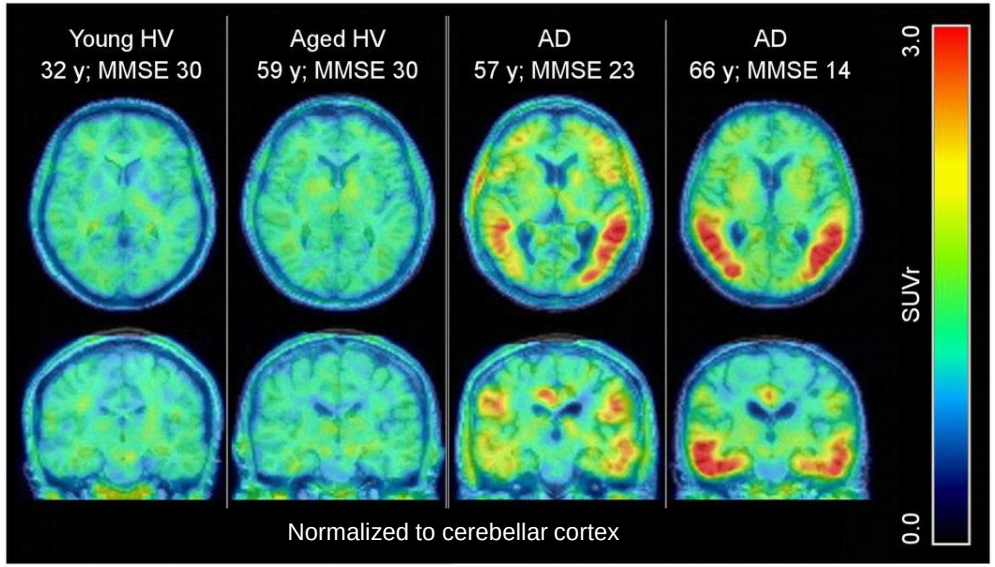
1. VIZAMYL® (^{18}F-flutemetamol) summary of product characteristics. 2017. Available from: https://www.ema.europa.eu/documents/product-information/vizamyl-epar-product-information_en.pdf (Accessed June 12, 2023)

Learning Zone

Introduction to tau PET

Introduction to tau PET

- **^{18}F-flortaucipir (^{18}F-AV-1451) has been approved by the FDA[1]**
- Increased retention of tau tracers is indicative of the presence of neurofibrillary tangles[2]
- Other tau radiotracers of interest include, but are not limited to:*
  - ^{18}F-MK-6240[3–5]
  - ^{18}F-RO-948[4,5]
  - ^{18}F-PI-2620[5]
  - ^{18}F-GTP1[5]
  - ^{3}H-JNJ-067[4]



^{18}F-flortaucipir SUVR images (80–100 min) superimposed onto subject's MRI in transaxial (top row) and coronal (bottom row) views[6]

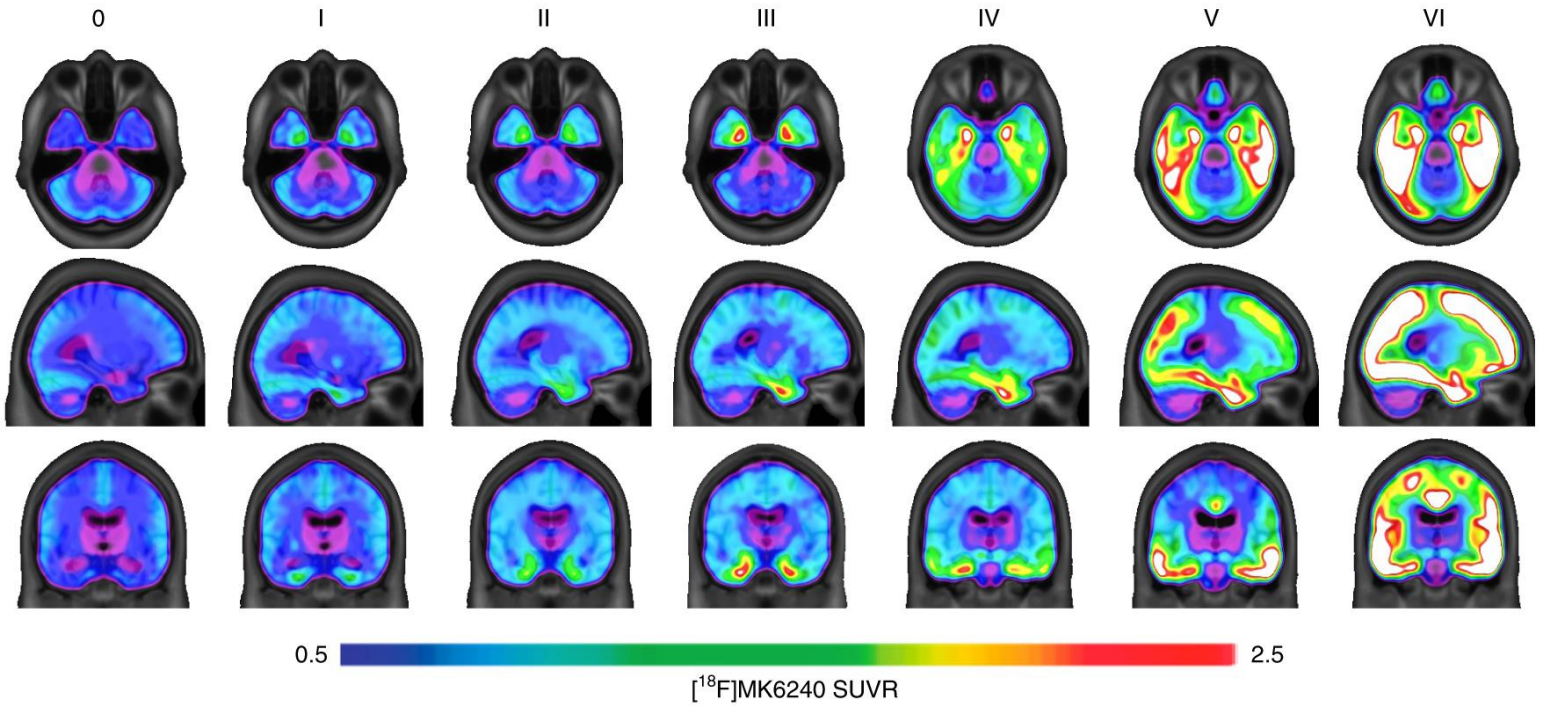
*These tracers are not yet approved for clinical use

AD, Alzheimer's disease; FDA, Food and Drug Administration; HV, healthy volunteer; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; PET, positron emission tomography; SUVR, standardized uptake value ratio

Image used with permission from: Barret O, et al. J Nucl Med 2017;58:1124–1131

1. FDA. Press release. May 28, 2020. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-image-tau-pathology-patients-being-evaluated-alzheimers-disease (Accessed June 12, 2023);
2. Gordon BA, et al. Brain 2019;142:1063–1076; 3. Lohith TG, et al. J Nucl Med 2019;60:107–114; 4. Yap SY, et al. Brain 2021;144:2284–2290; 5. Leuzy A, et al. Mol Psychiatry 2019;24:1112–1134; 6. Barret O, et al. J Nucl Med 2017;58:1124–1131

Tau PET shows regional distribution of elevated brain tau



Braak staging

Stage 0: no detectable tangle accumulation.

Stage I: tangles limited to the transentorhinal cortex

Stage II: tangles spread into the neighboring hippocampus

Stage III and IV: tangle burden increased in these earlier stage regions and appear in the temporal neocortex.

Stage V: extended involvement in association cortices in stage V and extended into the primary sensory areas by **stage VI**

AD, Alzheimer's disease; PET, positron emission tomography

1. Therriault J, et al. Nat Aging. 2022;2(6):526–535

First-generation tau PET tracers: ^{18}F-flortaucipir (1/2)

- ^{18}F-flortaucipir is one of the most widely used tracers[1]
  - It has high selectivity for PHF-tau over Aβ,[2] and binding correlates with CSF p-tau levels[3]
  - It has been validated in autopsy as a reliable biomarker to detect advanced AD pathology **(Braak Stages V and VI)**[1,4]

AD, Alzheimer's disease; CSF, cerebrospinal fluid; PET, positron emission tomography; PHF, paired helical filament; p-tau, phosphorylated-tau

1. Soleimani-Meigooni DN, et al. Brain 2020;143:3477–3494; 2. Brosch JR, et al. Neurotherapeutics 2017;14:62–68; 3. Zhao Q, et al. Front Neurol 2019;10:486; 4. Fleisher AS, et al. JAMA Neurol 2020;77:829–839

First-generation tau PET tracers: ^{18}F-flortaucipir (2/2)

- ^{18}F-flortaucipir has off-target binding to choroid plexus, basal ganglia, neuromelanin and melanin-containing cells (substantia nigra, pigmented cells in the eye, leptomeninges), and to areas of hemorrhage[1,2]

PET, positron emission tomography

1. Leuzy A, et al. Mol Psychiatry 2019;24:1112–1134; 2. Brosch JR, et al. Neurotherapeutics 2017;14:62–68

Other tau PET tracers

Other tau PET tracers[1,2]

- ^{18}F-RO-948
- ^{18}F-MK-6240
- ^{18}F-PI-2620
- ^{18}F-GTP1
- ^{18}F-JNJ-067

- **Tau PET tracers other than flortaucipir** have been developed; these are still being researched and are not yet approved for routine clinical use
  - In general, the newer tau PET tracers have lower off-target binding compared to first-generation tracers (eg ^{18}F-flortaucipir) and have a high contrast between normal brains and areas with tau deposition; they may prove more sensitive for detection at low levels of tau[2]
  - Although off-target binding is low,[1,2] such binding is nevertheless present and can complicate routine clinical applications[2]

PET, positron emission tomography

1. Leuzy A, et al. JAMA Neurol 2020;77:955–965; 2. Yap SY, et al. Brain 2021;144:2284–2290

Desirable characteristics of tau imaging agents

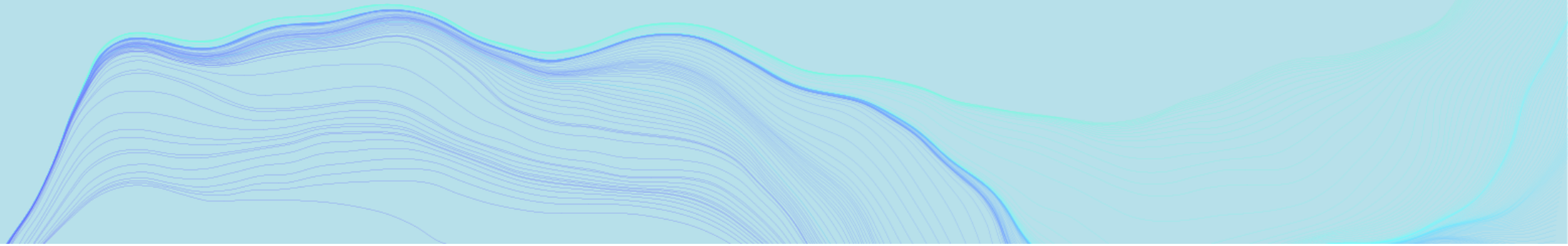
- High binding affinity for PHF-tau[1]
- High level of selectivity for PHF-tau (>20-fold selectivity needed) over Aβ[1]
- Low non-specific binding[2]
- Long half-life (^{18}F ligands have a longer half-life than ^{11}C ligands)[1,2]
- High blood-brain barrier permeability[1]
- Very low metabolism[1]

Aβ, amyloid beta; PHF, paired helical fragment

1. Brosch JR, et al. Neurotherapeutics 2017;14:62–68; 2. Dickstein LP, et al. Eur J Nucl Med Mol Imaging. 2011;38:352–357.

Learning Zone

Introduction to FDG PET



Brain ^{18}FDG PET examination

- FDG is a glucose analog, and its uptake in the brain reveals patterns of metabolism[1]
- Brain FDG PET is useful in the evaluation of suspected neurodegenerative disease and can aid in the specific diagnosis of dementia[1]
- FDG PET is primarily indicative of synaptic activity,[1] with preclinical studies showing that its uptake correlates with the synaptic protein synaptophysin[2]
- A normal brain FDG PET scan has high negative predictive value; patients with a negative result have a decreased likelihood of receiving an AD diagnosis within 5 years[3]

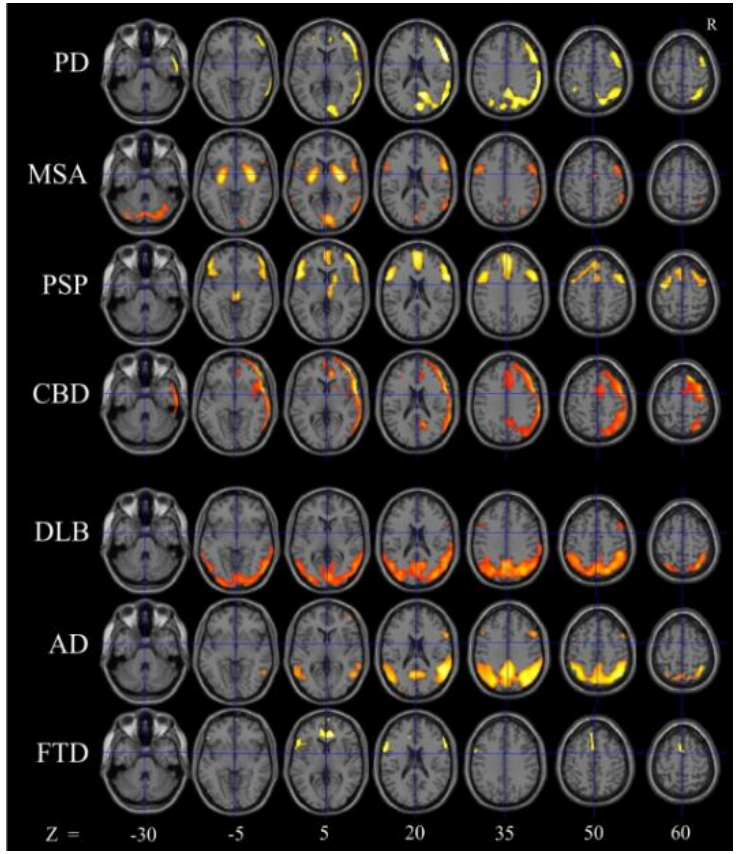
AD, Alzheimer's disease; FDG, fluorodeoxyglucose; PET, positron emission tomography

1. Johnson KA, et al. Cold Spring Harb Perspect Med 2012;2:a006213; 2. Rocher AB, et al. Neuroimage 2003;20:1894–1898; 3. Jagust W, et al. Neurology 2007;69:871–877

Regional pattern of neurodegeneration across different dementia etiologies

FDG PET as a neuroimaging marker is not specific to a particular dementia etiology, but **rather an identifier of regional neurodegeneration**[1]

- **Although there is some variability and overlap, each disease has a typical regional pattern of hypometabolism caused by the typical regional pattern of neurodegeneration**



AD, Alzheimer's disease; CBD, corticobasal degeneration; DLB, dementia with Lewy bodies; FDG PET, fluorodeoxyglucose positron emission tomography; FTD, frontotemporal dementia; PD, Parkinson's disease; PSP, progressive supranuclear palsy; SMA, sensorimotor area and middle temporal gyrus

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1. Teune LK. Francesco Signorelli and Domenico Chirchiglia, IntechOpen, 2013. DOI: 10.5772/56505.
Available from: https://www.intechopen.com/books/functional-brain-mapping-and-the-endeavor-to-understand-the-working-brain/fdg-pet-imaging-in-neurodegenerative-brain-diseases (Accessed June 12, 2023)

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