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Imaging of Alzheimer's Disease: State of the Art

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Outline

- Our patient
- Definition of dementia
- Alzheimer's disease
 - Epidemiology
 - Diagnosis
 - Stages of progression
- Imaging for Alzheimer's
 - Structural
 - Metabolic
 - Molecular



Our patient: history

History of present illness:

- 55-yo man presents with ~2 years of cognitive decline
- Left a high-paying job 5 years ago; no steady job since
- Repeats himself in conversation
- Cannot remember simple tasks
- Low energy, guilt, sadness
- Snores and thrashes at night

Past medical history:

- Obstructive sleep apnea
- von Willebrand's disease

Medications

- B12, fish oil

Family history

- Father: CAD
- Aunt: dementia

Social history

- Highly educated
- No EtOH, drugs

Our patient: exam findings

- General exam: no findings
- Neurologic exam:
 - Constricted affect
 - 25/30 on the MOCA, with 0/5 for delayed recall
 - Slightly increased tone in both arms
 - Otherwise no deficits

MONTREAL COGNITIVE ASSESSMENT (MOCA) Version 7.1 Original Version		NAME:	Education:	Date of birth:	POINTS		
		Sex:		DATE:			
VISUOSPATIAL / EXECUTIVE		Copy cube	Draw CLOCK (Ten past eleven) (3 points)		_ / 5		
NAMING					_ / 3		
MEMORY	Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.	FACE	VELVET	CHURCH	DAISY	RED	No points
		1st trial					
		2nd trial					
ATTENTION	Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [] 2 1 8 5 4 Subject has to repeat them in the backward order [] 7 4 2				_ / 2		
	Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors [] FBACMNAAJKLBAFAKDEAAAJAMOFAA B				_ / 1		
	Serial 7 subtraction starting at 100 [] 93 [] 86 [] 79 [] 72 [] 65 4 or 5 correct subtractions: 3 pts. 2 or 3 correct: 2 pts. 1 correct: 1 pt. 0 correct: 0 pt.				_ / 3		
LANGUAGE	Repeat: I only know that John is the one to help today. [] The cat always hid under the couch when dogs were in the room. []				_ / 2		
	Fluency / Name maximum number of words in one minute that begin with the letter F [] _____ (N ≥ 11 words)				_ / 1		
ABSTRACTION	Similarity between e.g. banana - orange = fruit [] train - bicycle [] watch - ruler				_ / 2		
DELAYED RECALL	Has to recall words WITH NO CUE [] FACE [] VELVET [] CHURCH [] DAISY [] RED []				_ / 5		
Optional	Category cue [] [] [] [] [] Multiple choice cue [] [] [] [] []						
ORIENTATION	[] Date [] Month [] Year [] Day [] Place [] City				_ / 6		
© Z.Nasreddine MD		www.mocatest.org		Normal ≥ 26 / 30	TOTAL _ / 30		
Administered by: _____					Add 1 point if ≤ 12 yr edu		

<<http://www.mocatest.org>>



Our patient: differential diagnosis

Differential diagnosis:

- Depression
- OSA
- Early-onset dementia

6 months later:

- Mood and sleep have improved
- Memory has not

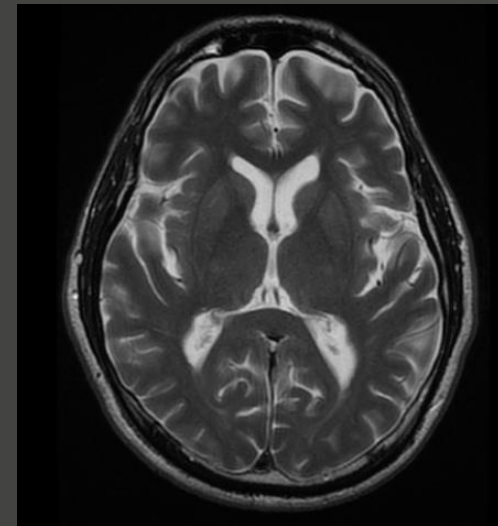
Tests:

- B12: normal
- TSH: normal

Treatment:

- Citalopram
- CPAP

Next test: MRI



Axial T2 MRI: BIDMC PACS

Normal scan

You have seen the clinical presentation of a patient with possible Alzheimer's Disease.

Before returning to the diagnosis, let's continue with a discussion of dementia.



Dementia: definition

DSM-V:

- Decline in ≥ 1 cognitive domain:
 - Learning and memory
 - Language
 - Executive function
 - Attention
 - Perceptual-motor
 - Social cognition
- Interferes with daily living
- Not due to another mental disorder

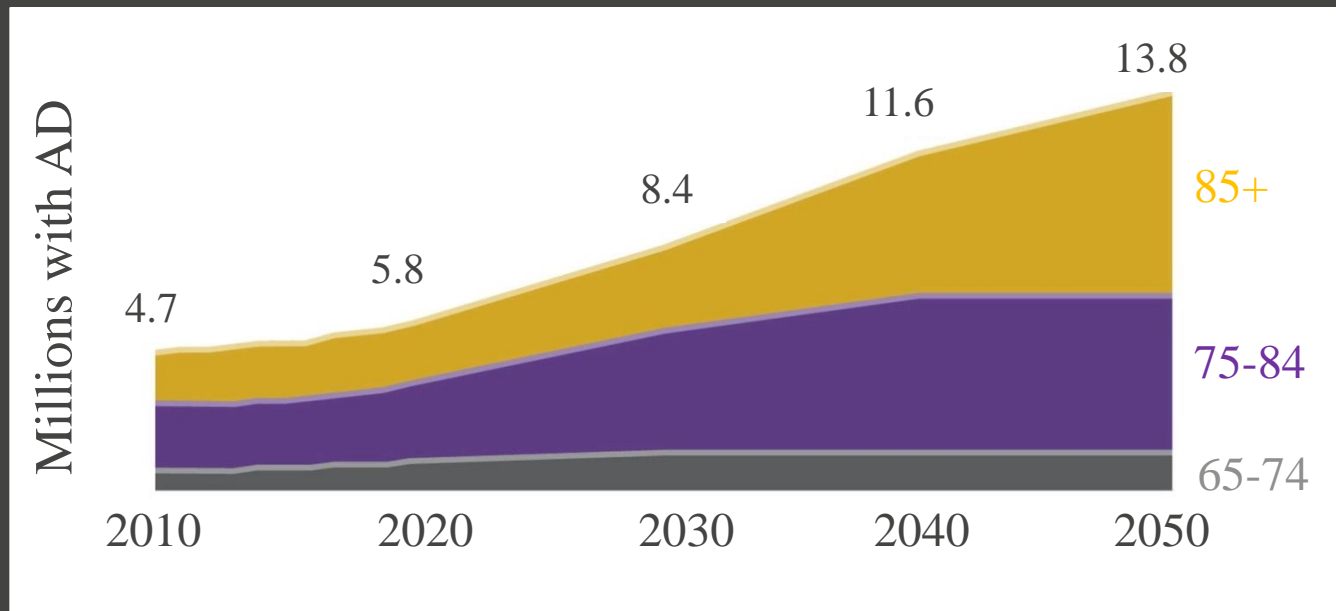
Causes:

- Neurodegenerative
- Vascular
- Neoplastic
- Inflammatory
- Traumatic
- Metabolic
- Infectious
- Epileptic
- Drug-related



Alzheimer's Disease

- 60-80% of all dementia, with 5.2 million patients in the US
- 6th-leading cause of death
- Alone in top 10 without means of prevention or cure
- Annual cost: \$203B directly + \$216B for unpaid caregivers



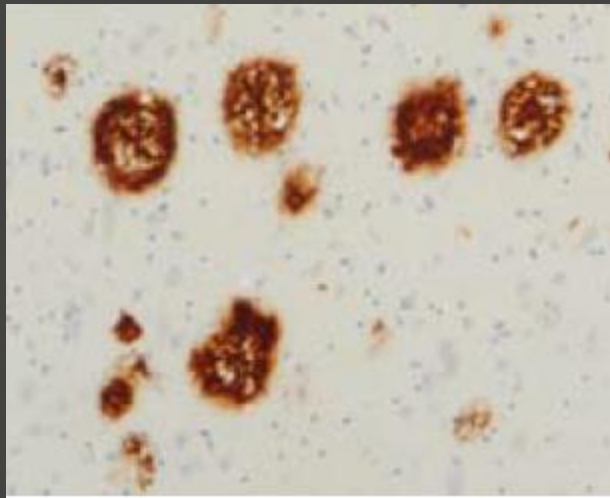
Adapted from Alzheimer's Association, 2013



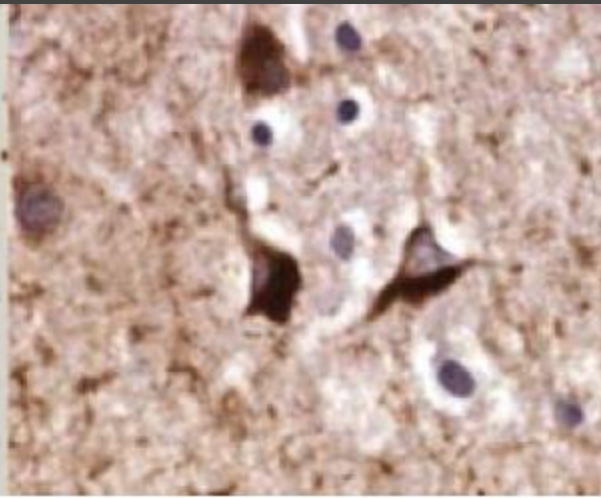
Alzheimer's diagnosis

- Definitive diagnosis is only made at autopsy, with classic findings of amyloid plaques and tau tangles

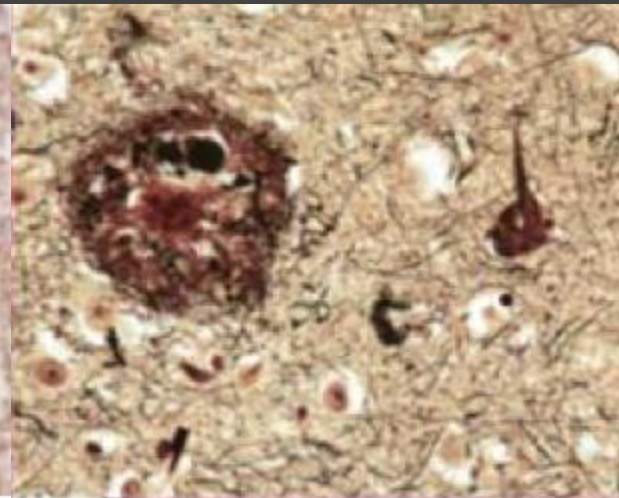
A β plaques



Tau tangles



Both pathologies on
silver stain



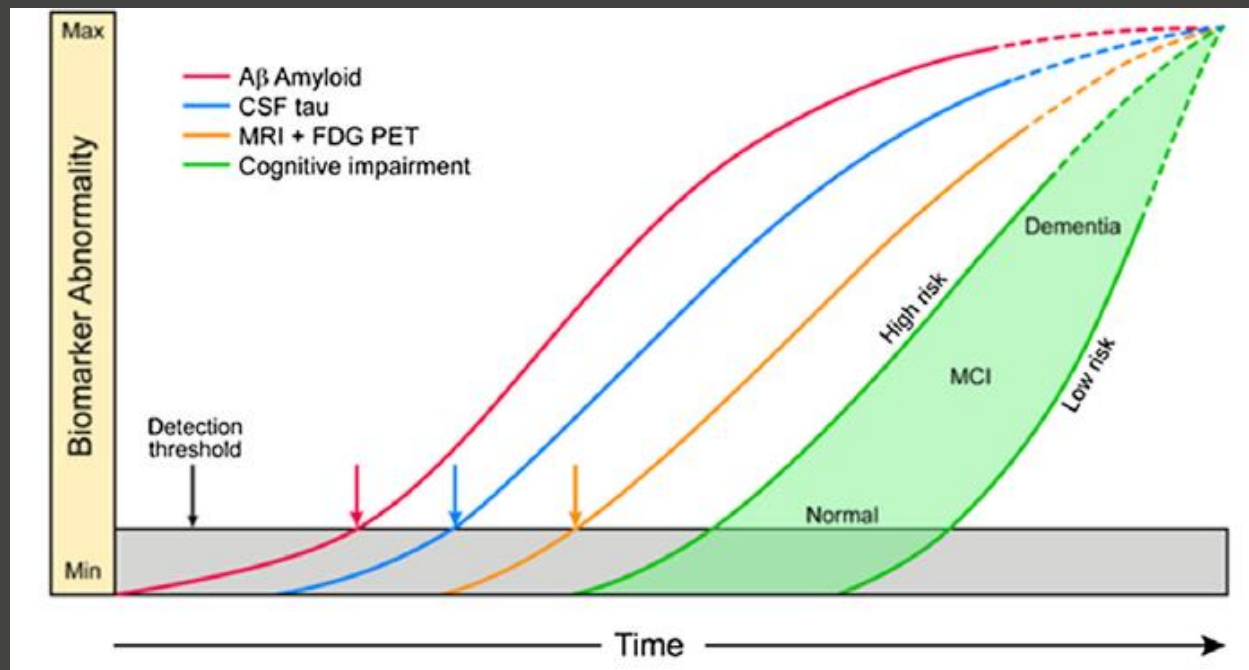
Serrano-Pozo et al., 2011



What is the role for imaging?

1. Diagnose
2. Predict and track progression
3. Assess treatment response

Imaging biomarkers can precede cognitive symptoms by many years



Imaging recommendations

The American College of Radiology recommends imaging in patients with possible or probable Alzheimer’s Disease

Radiologic Procedure	Rating	Comments	RRL*
MRI head without contrast	8	This procedure is used in structural evaluation; volumetric determinations are generally not appropriate in routine clinical imaging.	O
MRI head without and with contrast	7	See statement regarding contrast in text under “Anticipated Exceptions.”	O
CT head without contrast	6		☼☼☼
FDG-PET/CT head	6	This procedure may be used as a problem-solving technique in differentiating dementias.	☼☼☼☼
CT head without and with contrast	4		☼☼☼
CT head with contrast	4		☼☼☼
MR spectroscopy head without contrast	3		O
MRI functional (fMRI) head without contrast	2	This procedure is used for research purposes.	O
Tc-99m HMPAO SPECT head	2		☼☼☼☼
Amyloid PET/CT head	2		☼☼☼
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

Wippold et al., 2015

Imaging Modalities

- Structural: brain volume
 - MRI
- Metabolic: brain function
 - FDG-PET
- Molecular: protein accumulation
 - Amyloid
 - Tau



Structural imaging: MRI

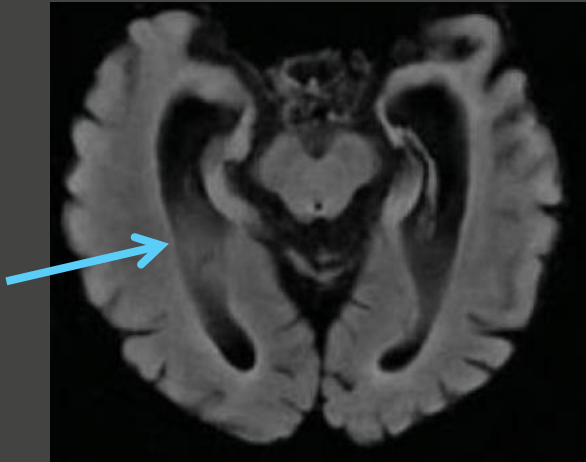
MRI is indicated for two reasons:

- 1) It excludes other causes of cognitive decline, such as stroke, tumor, and demyelinating disease. Our patient had a normal scan, ruling out these possibilities.
- 2) It can strengthen the diagnosis of Alzheimer's Disease by showing a typical pattern of degeneration in the medial temporal lobes. See the next slide for an example.

Structural imaging: MRI

Alzheimer's:

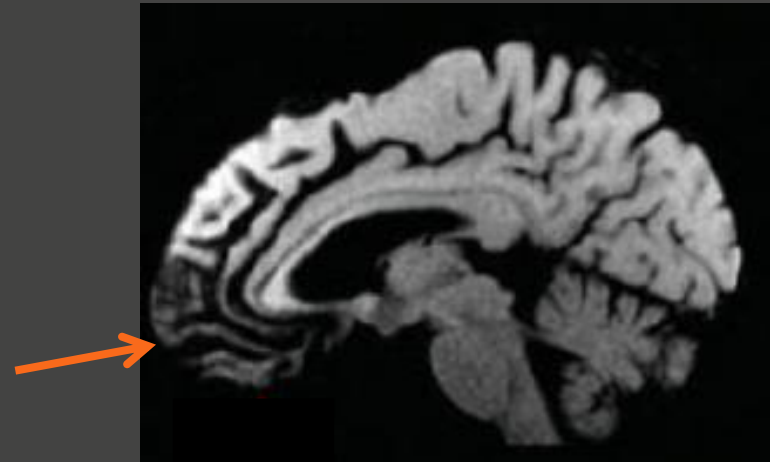
Medial temporal atrophy



*Companion Patient #1: Axial MRI
Risacher & Saykin, 2013*

Frontotemporal dementia:

Frontal atrophy



*Companion Patient #2: Sagittal MRI
Risacher & Saykin, 2013*

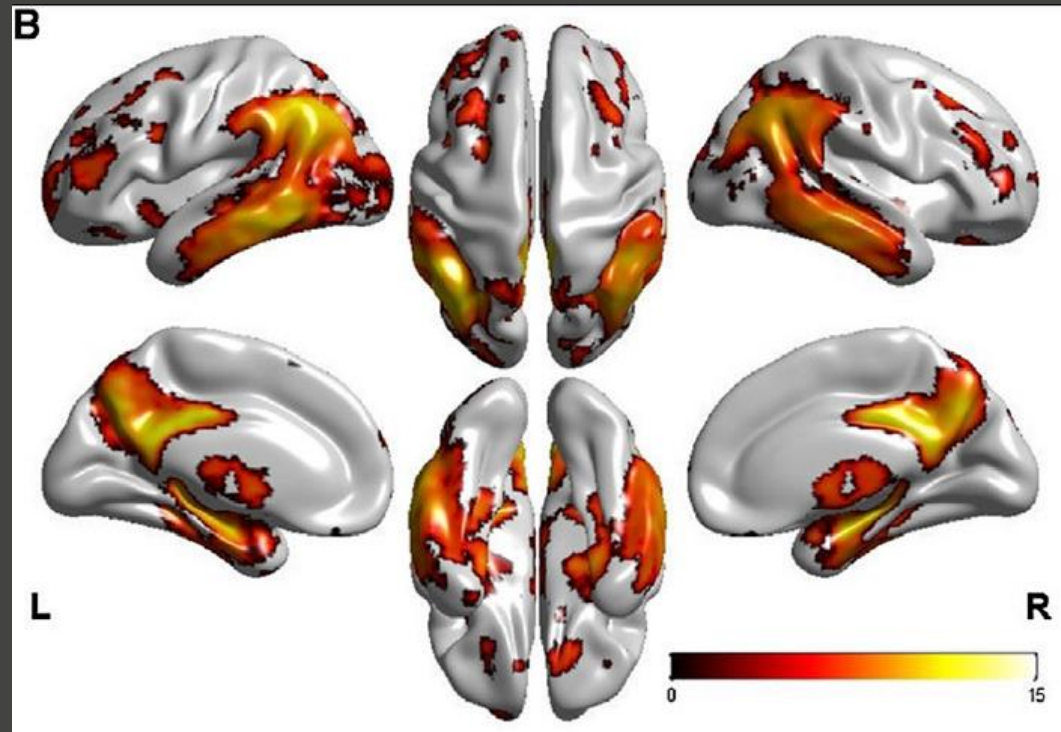
These patterns of atrophy can precede symptoms by ~10 years, and predict progression from MCI to dementia



Metabolic imaging: FDG-PET

FDG-PET tracks glucose metabolism, a proxy for synaptic activity. Medicare will cover this test to distinguish AD vs. FTD.

Decreased
temporal,
parietal, and
posterior
cingulate
uptake in AD



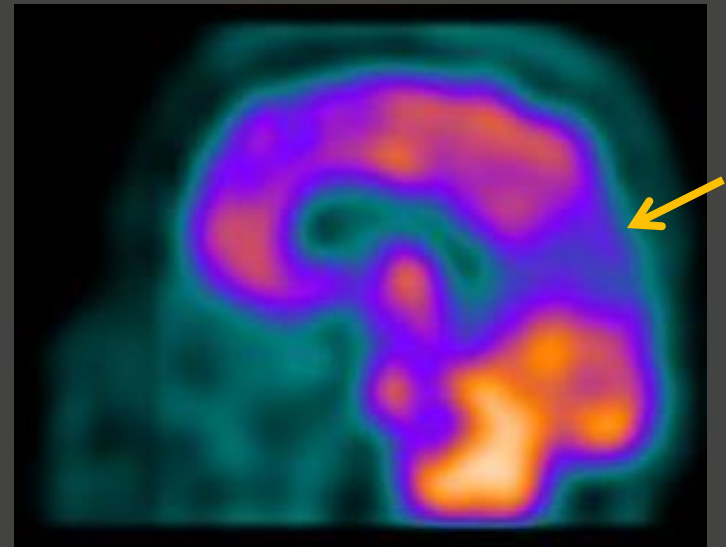
Jack & Holtzman, 2013



Metabolic imaging: less common techniques

- SPECT: radionuclide technique that measures cerebral blood flow
 - Expect **temporo-parietal hypoperfusion** in AD
- fMRI: measures blood flow as patients perform cognitive tasks
- MR spectroscopy: measures metabolite concentrations
 - Expect \downarrow N-acetylaspartate and \uparrow myoinositol, reflecting neuronal injury

SPECT



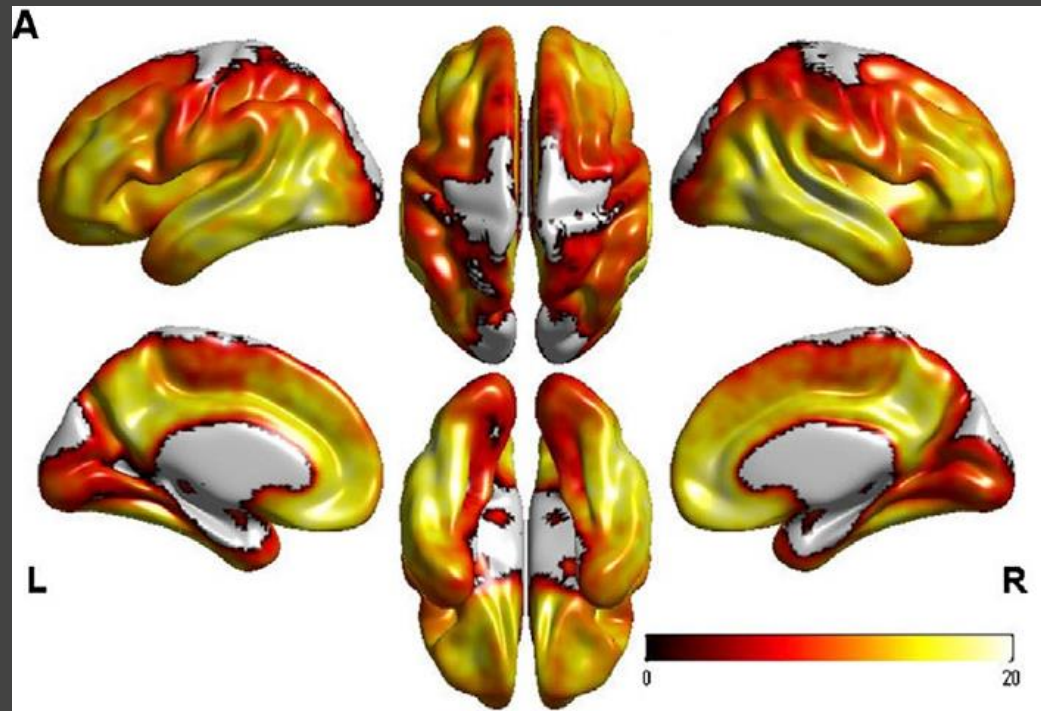
Companion Patient #3: BIDMC PACS



Molecular imaging: amyloid

PET imaging can track amyloid deposition, even before clinical symptoms

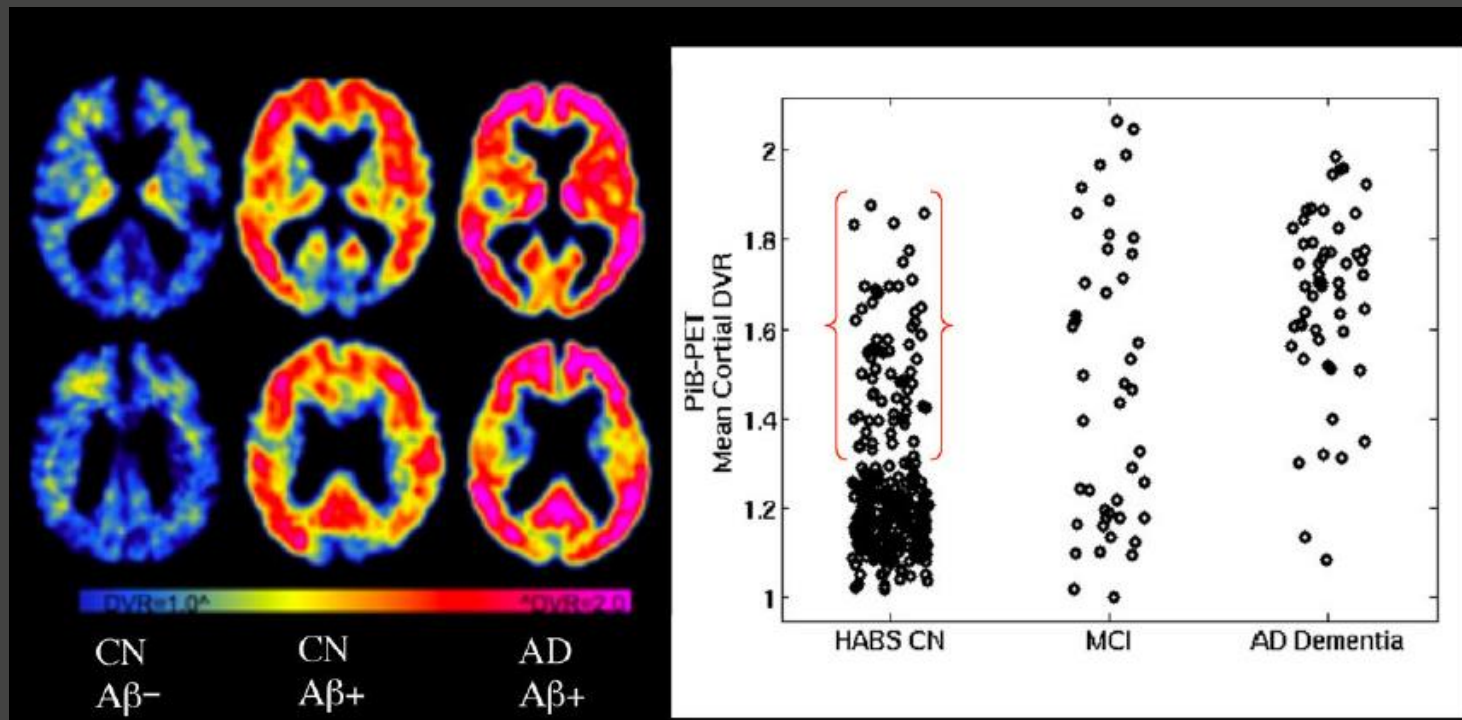
Increased amyloid everywhere but primary sensory & motor cortex, and medial temporal lobe



Jack & Holtzman, 2013

Molecular imaging: amyloid

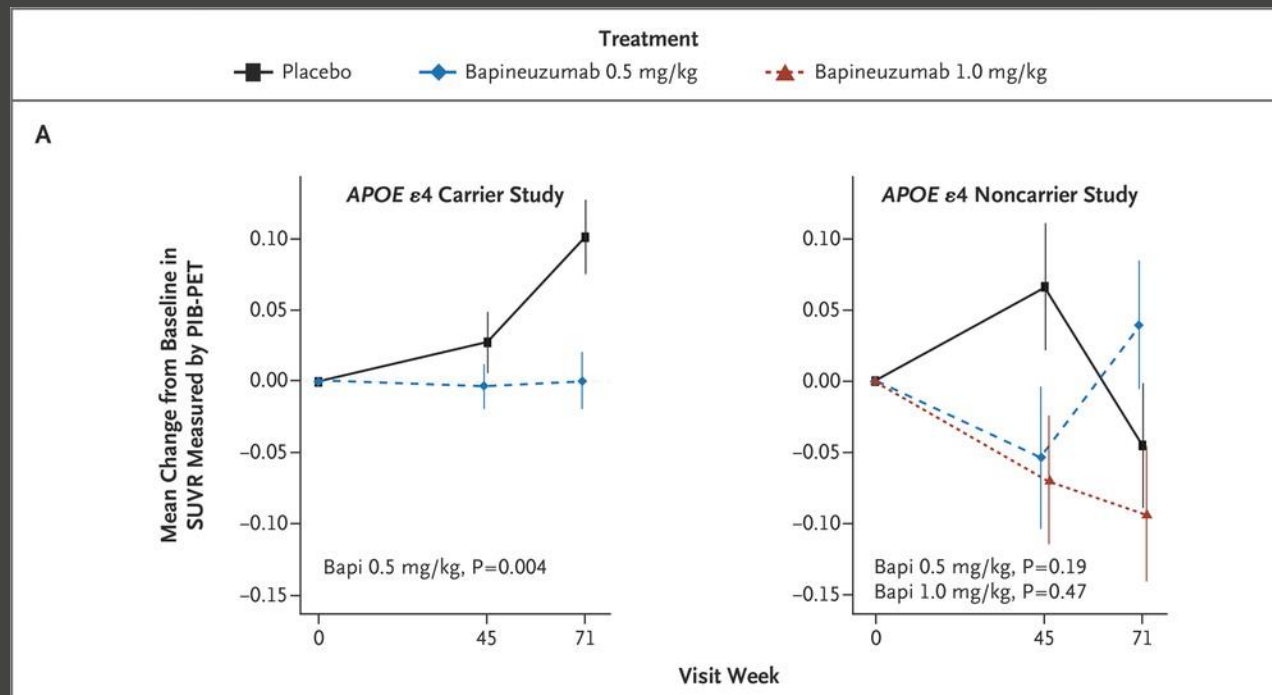
- Amyloid PET has high negative predictive value but low positive predictive value.
- 30% of healthy older adults will have elevated amyloid.





Molecular imaging: amyloid

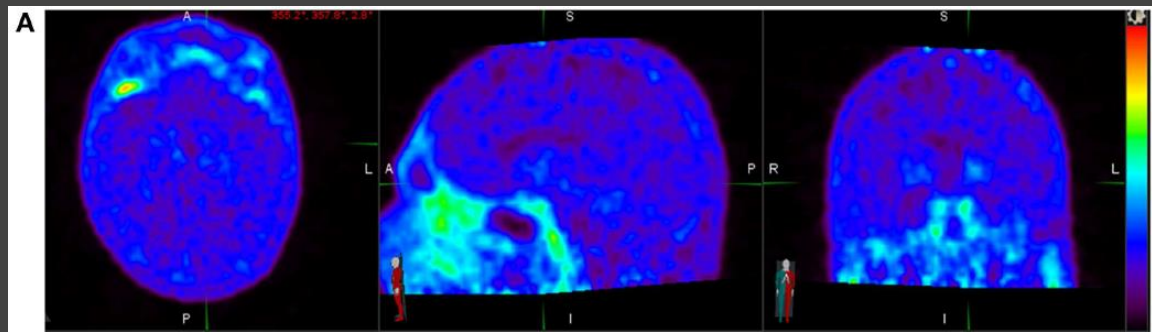
- Amyloid PET is used as a biomarker in drug trials involving anti-amyloid antibodies.
- The antibodies successfully clear amyloid but do not affect clinical outcome.



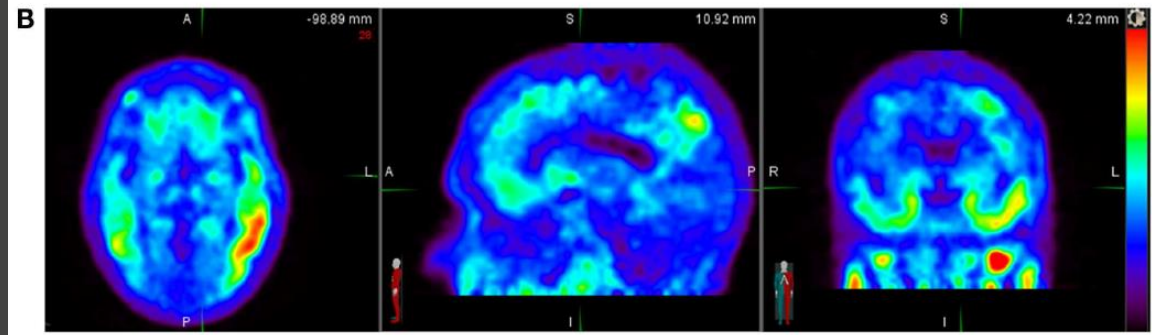
Molecular imaging: tau

PET tracers for tau aggregates are under investigation

Normal



Mild AD:
↑ uptake in
temporal lobes



Companion Patients #4 and #5: James et al., 2015

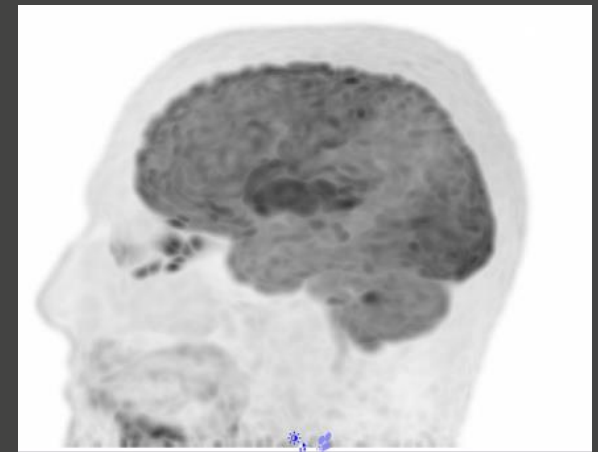
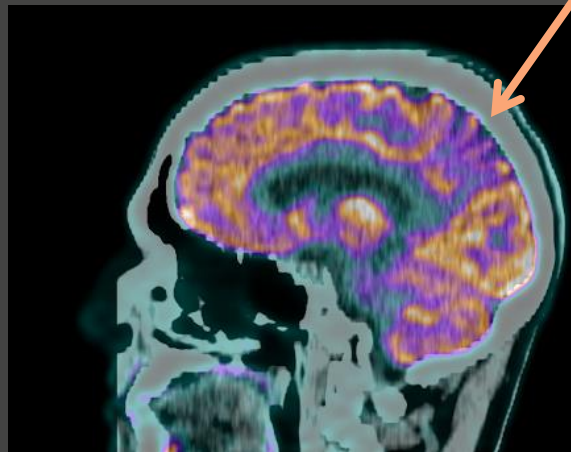
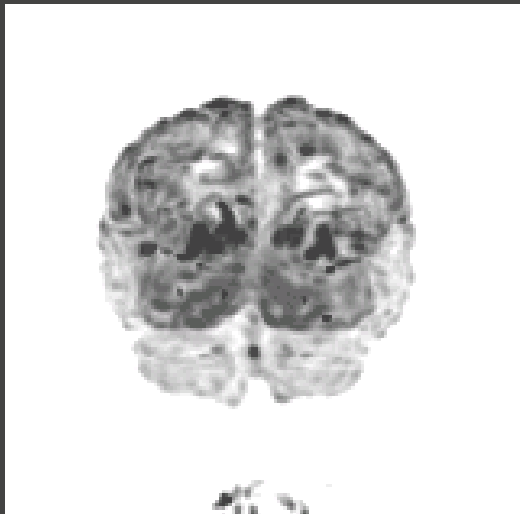


Back to our patient: diagnosis

2 years later:

- Memory deficits persist, but fluctuate between visits
- Spatial skills and orientation remain intact
- Not a classic AD presentation: can imaging clarify?

FDG PET shows **AD-specific hypometabolism**





Our patient: treatment & outcome

- On the basis of the FDG-PET results, along with CSF and genetic testing, our patient was diagnosed with AD.
- He began treatment with donepezil and memantine.
- Although his prognosis is poor, having the diagnosis helped him and his family prepare for the future.
- Imaging was a crucial part of this process.



Summary

- We have followed a patient from his initial presentation to the diagnosis of Alzheimer's Disease.
- We have discussed the definition of dementia, as well as the epidemiology, diagnosis, and stages of progression of Alzheimer's Disease.
- We have reviewed the indications for imaging in Alzheimer's Disease, and seen the classic appearance of AD on structural, metabolic, and molecular imaging, reviewing both standard approaches and the state of the art.



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