Update on Dementia Diagnosis

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Goal

To provide an update on the latest advances on the diagnosis of dementia.

Objectives

- Define “dementia”.
- List the various sub-types of dementia and their relative importance.
- Describe the key features of the main causes of dementia.
- List the latest advances in investigation used in the diagnosis of dementia.

Definition of Dementia

A clinical syndrome characterized by a

progressive decline in higher cognitive functions (memory, behavior, language, visuospatial and executive function)

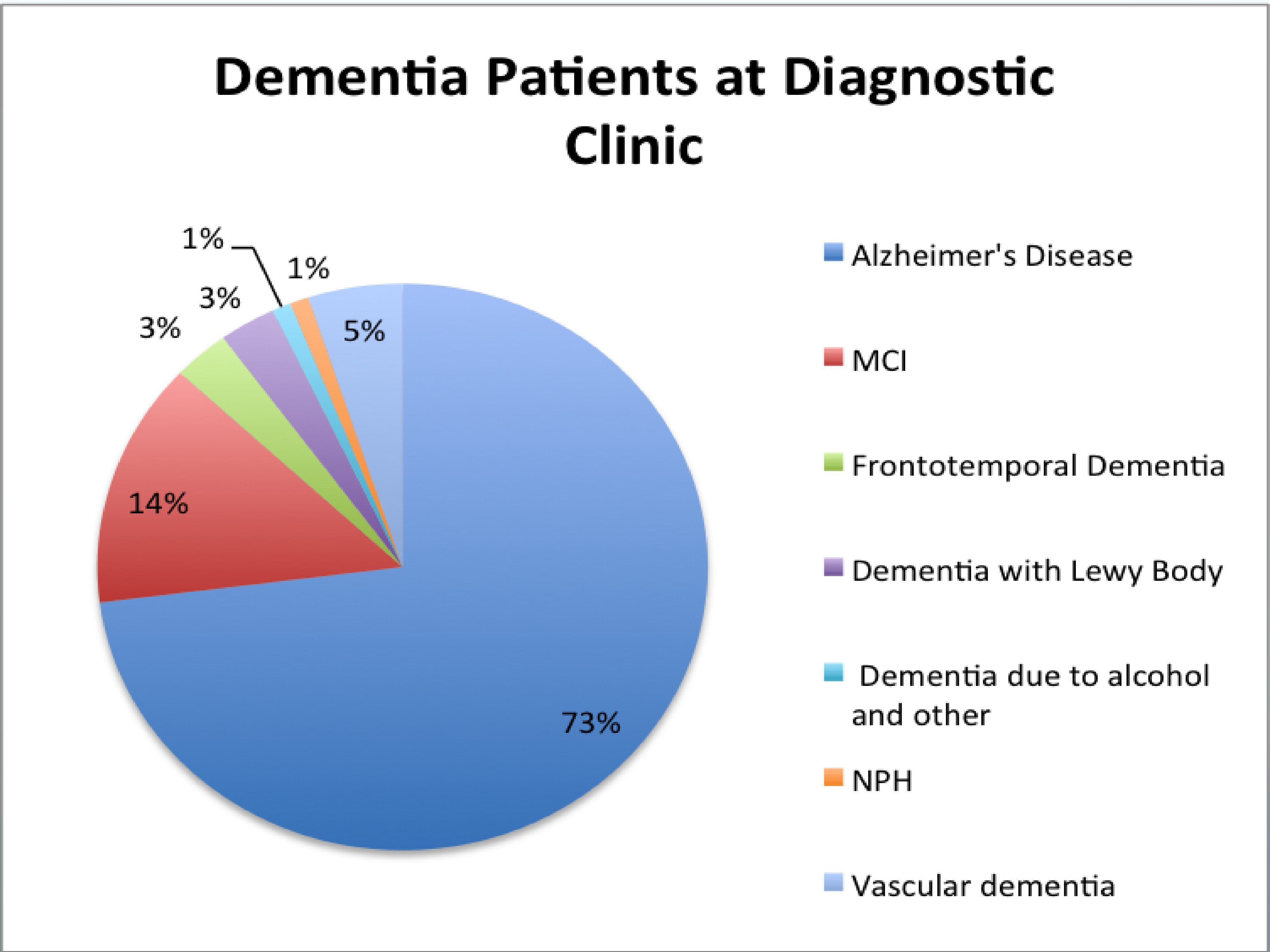
that is severe enough to **negatively impact on activities of daily living.**

Background

- 35.6 million worldwide are affected
- 5.1 million people in Caribbean are over age 60
- 8.1% prevalence of dementia in people over age 60 in Caribbean
- **330, 000 with dementia in Caribbean**
- Almost doubles every 20 years
- 2030: 620, 000 (88% proportionate increase)
- 2050: 1.04 million (215%)

Dementia Prevalence in Barbados

- Barbados Population 278,000 (2010 census)
- Over 65 years: 36,140 (13%)
- **3000 persons have dementia in Barbados**


Dementia Patients at Diagnostic Clinic
1%
1%
3%
3%
5%
14%
73%
Alzheimer's Disease
MCI
Frontotemporal Dementia
Dementia with Lewy Body
Dementia due to alcohol and other
NPH
Vascular dementia

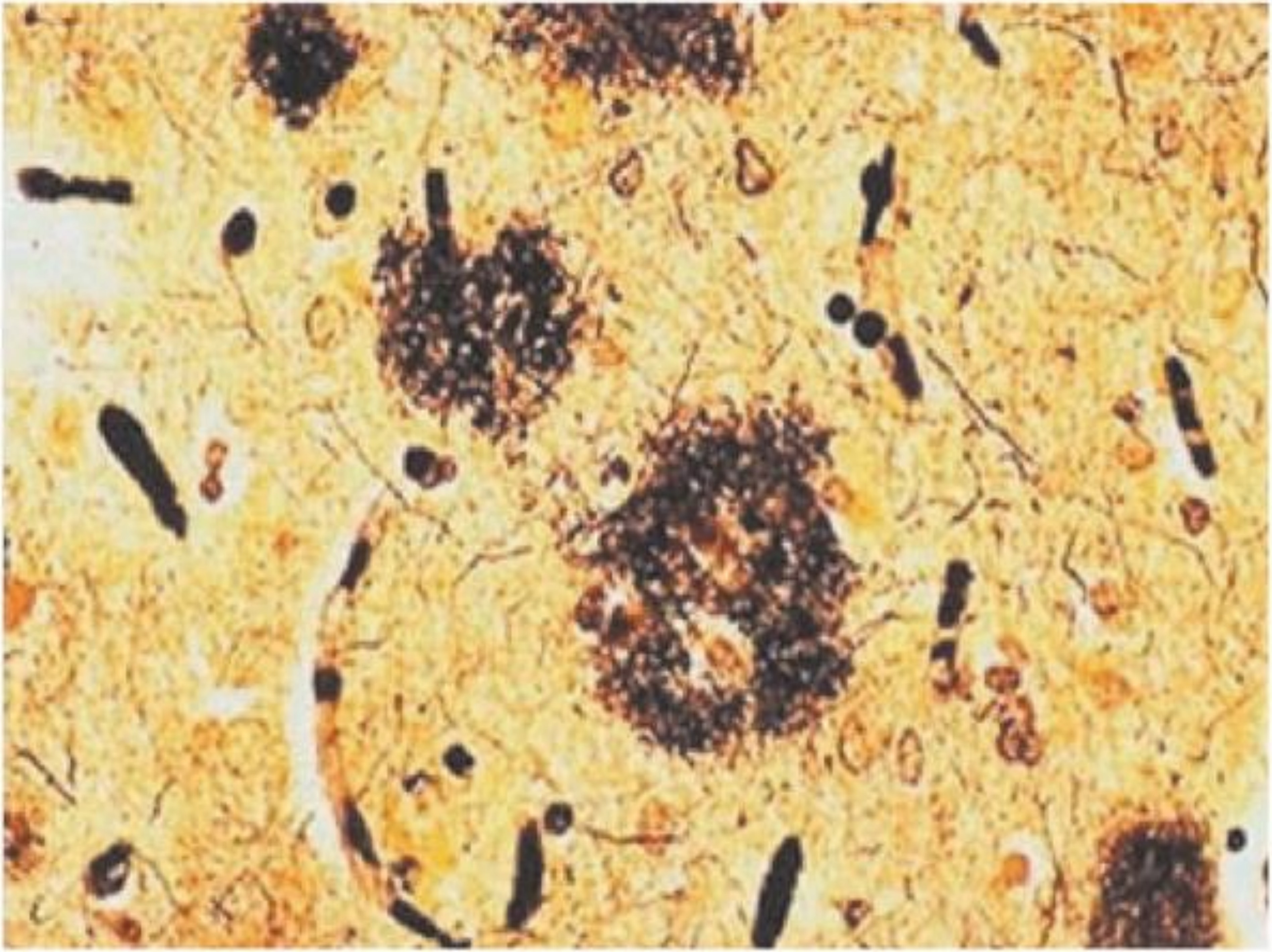
Causes of Dementia

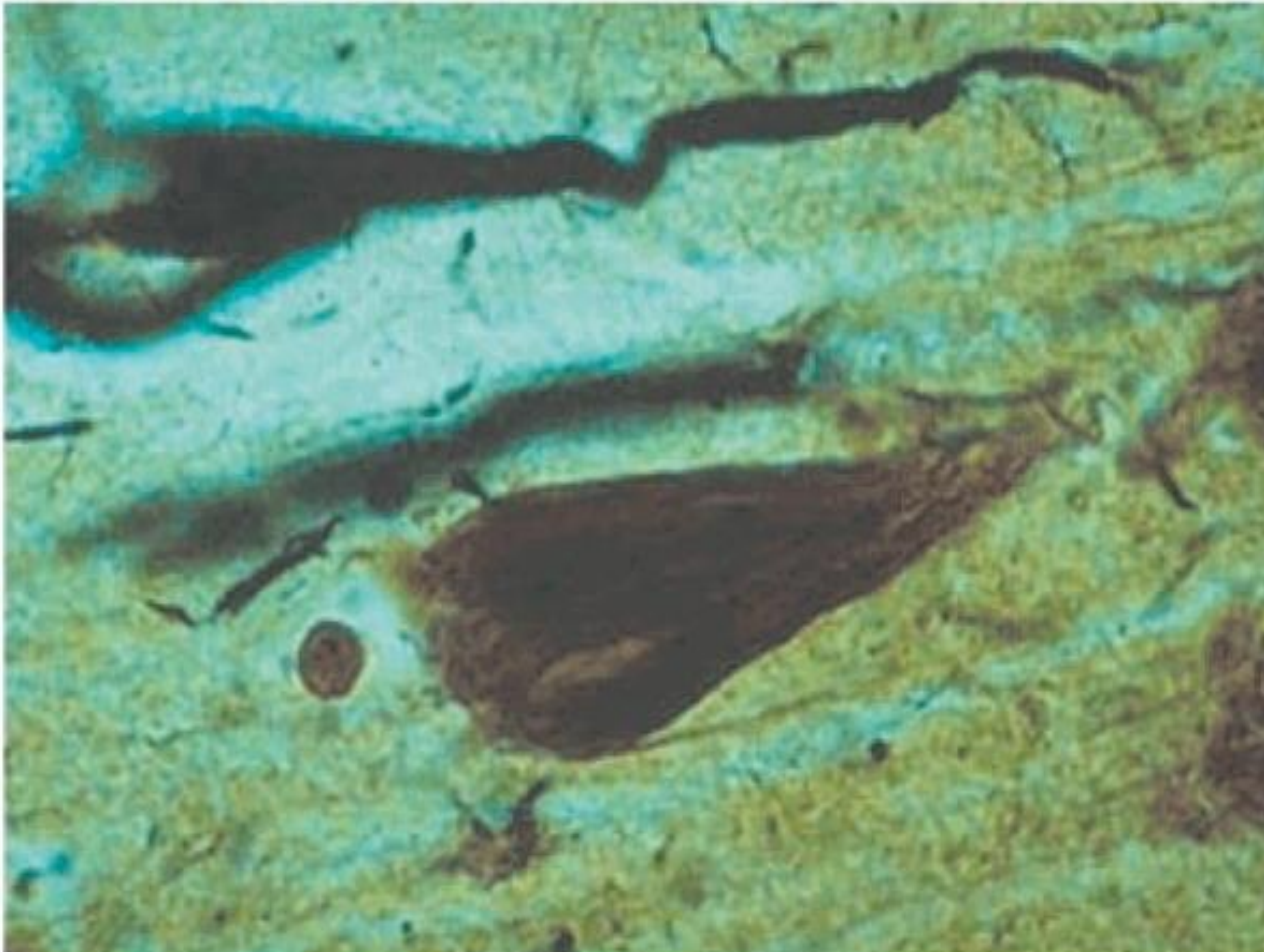
- Primary:
  - **Alzheimer Disease** 70%
  - **Lewy Body Dementias** (5-10%)
    - Dementia with Lewy Bodies
    - Parkinson Disease Dementia
  - **Frontotemporal Dementia** 5%

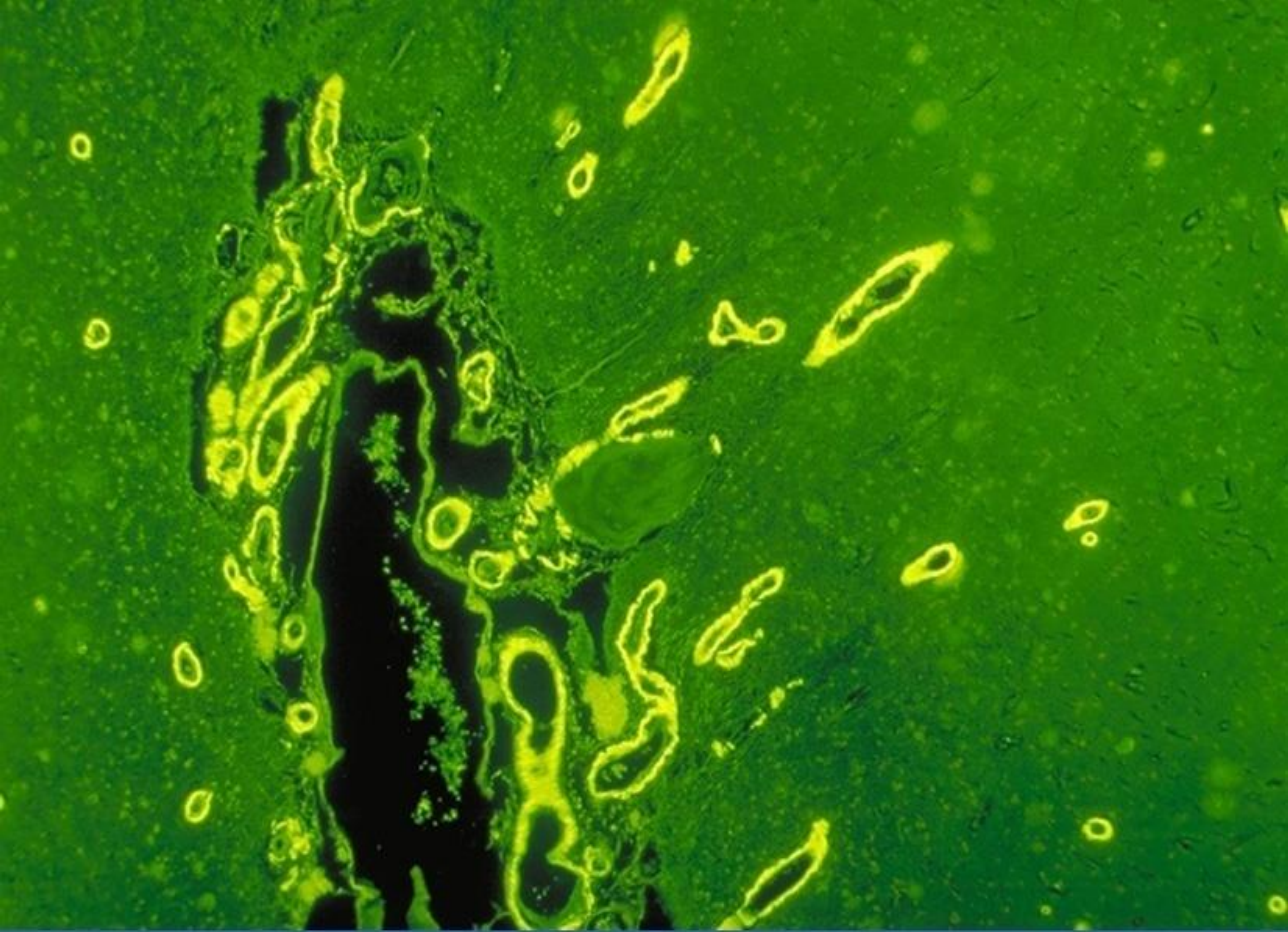
  - Other:
    - Amyotrophic Lateral Sclerosis (ALS)
    - Progressive Supranuclear Palsy (PSP)
    - Multisystem Atrophy (MSA)

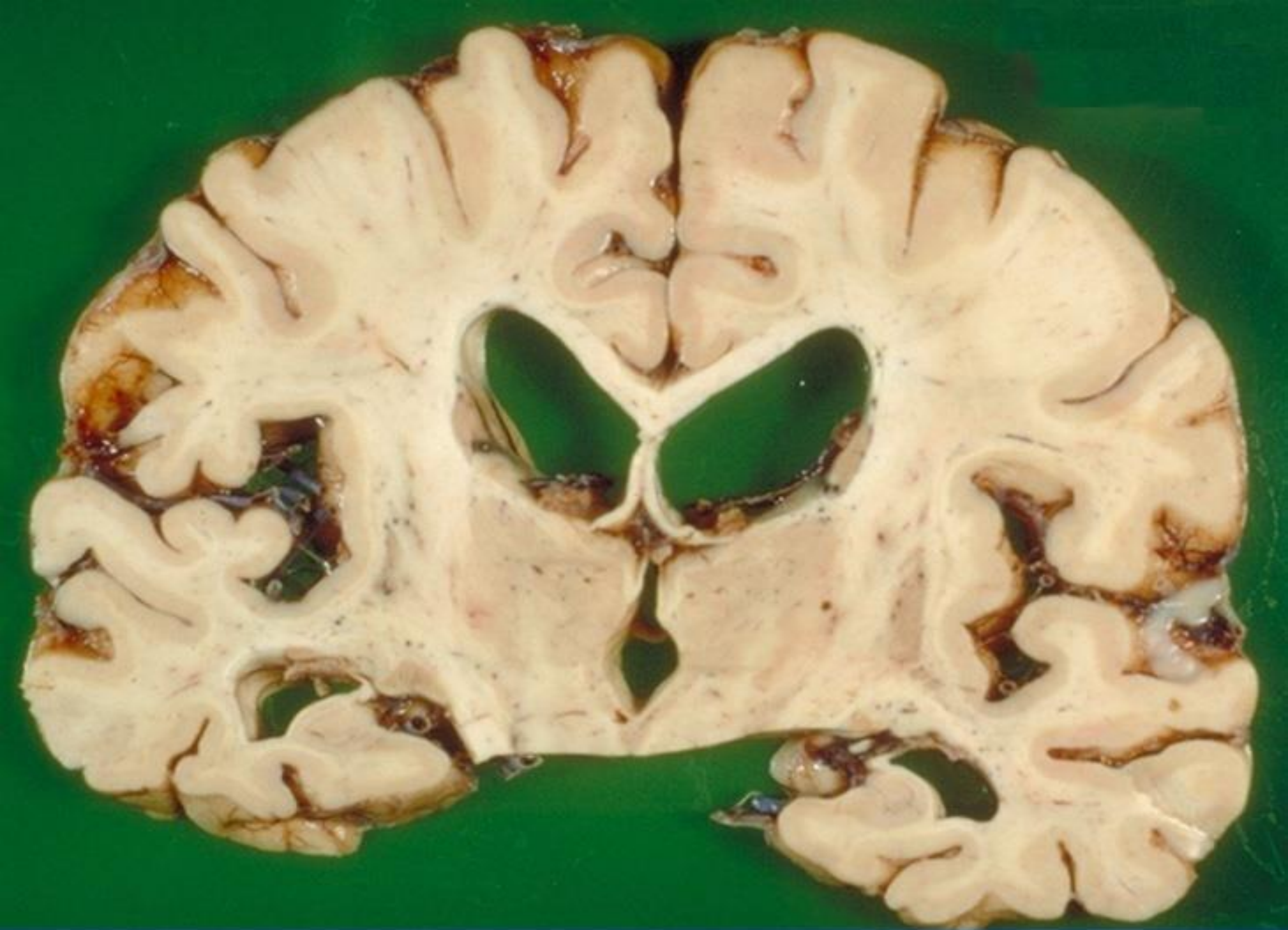
Causes of Dementia

- Secondary:
  - Vascular
    - **Vascular dementia 5-15%**
  - Structural
    - Normal pressure hydrocephalus (NPH)
    - frontal lobe tumors
    - Subdural hematoma
  - Metabolic
    - vit B12 deficiency
    - hypothyroidism
    - renal or hepatic dysfunction
    - hypercalcemia
  - Drugs
    - Alcohol, TCAs; benzodiazepines; narcotics; anti-histamines; anticholingergics
  - Infection
    - HIV/AIDS; neurosyphilis
  - Trauma
    - head injury









Mild Cognitive Impairment (MCI)

- Mild Neurocognitive Impairment
- Cognitive complaint, usually memory: preferably corroborated
- Normal ADLs
- Not demented
- Amnestic MCI most common (single domain)

MCI

- Incidence of 1-2% per year
- 10-15% per year progress to AD (vs 1-2% normal population)
- 80% eventually progress to AD within 6 yrs
  - Not oriented to time
  - MRI evidence of hippocampal atrophy
  - APOEe4 carrier
  - FDG-PET temporoparietal hypometabolism
  - Positive amyloid imaging on PET
  - Increased tau/p-tau and decreased beta amyloid levels in CSF
- Transitional phase (Prodromal AD)
- Not all cases progress, hence not always “very early AD”

Alzheimer’s Disease

- Progressive deficits in:
  - <u>Memory</u>
  - Attention
  - Language
  - Visuospatial perception
  - Executive function
  - Social Comportment (Behavior)
- Progressive deterioration:
  - Instrumental ADLs
  - Basic ADLs

Key Features of Non-AD Dementia

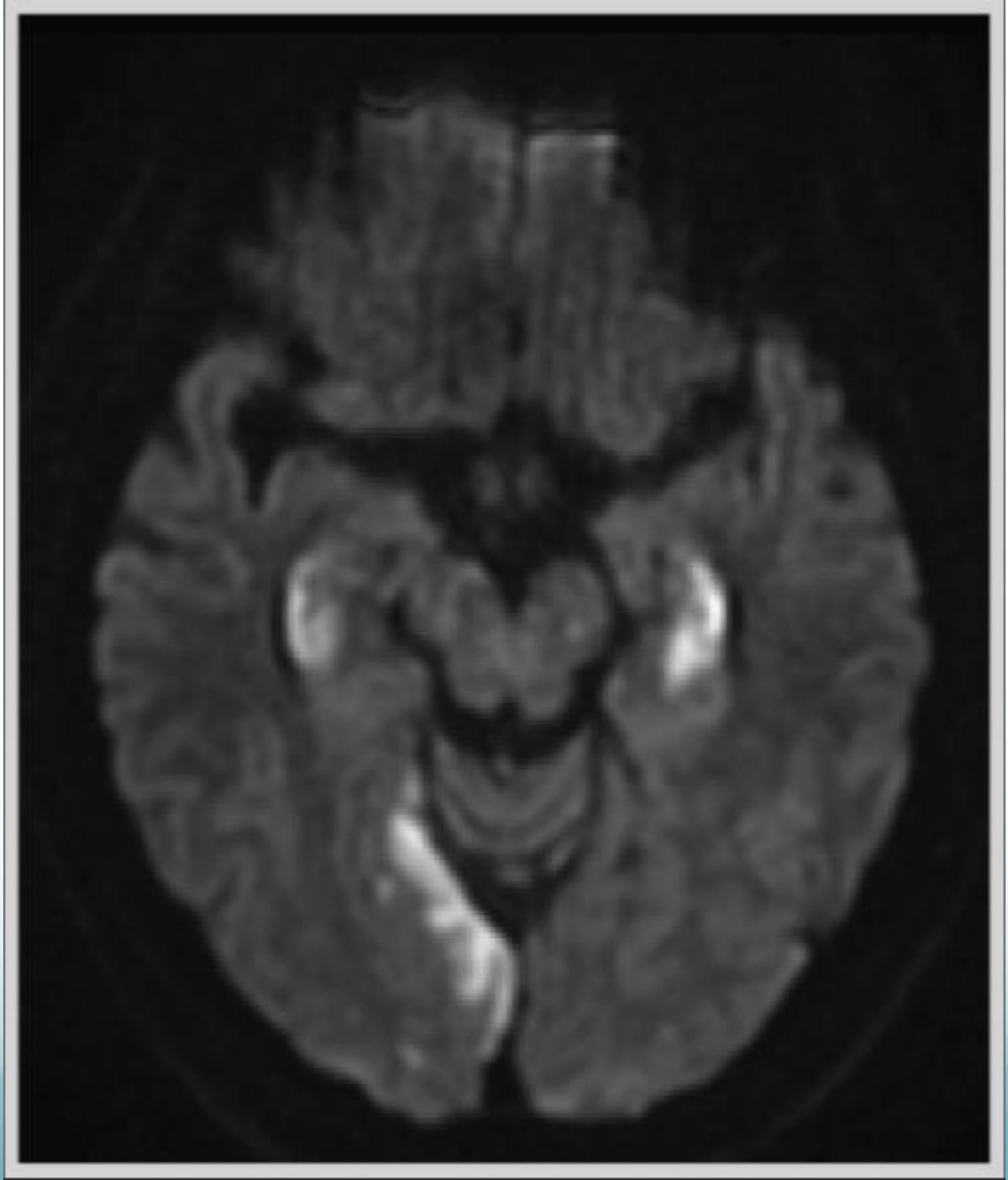
- **Frontotemporal dementia**
  - Age < 60 years
  - Prominent behavioral changes eg disinhibition
  - Prominent language impairment eg aphasia

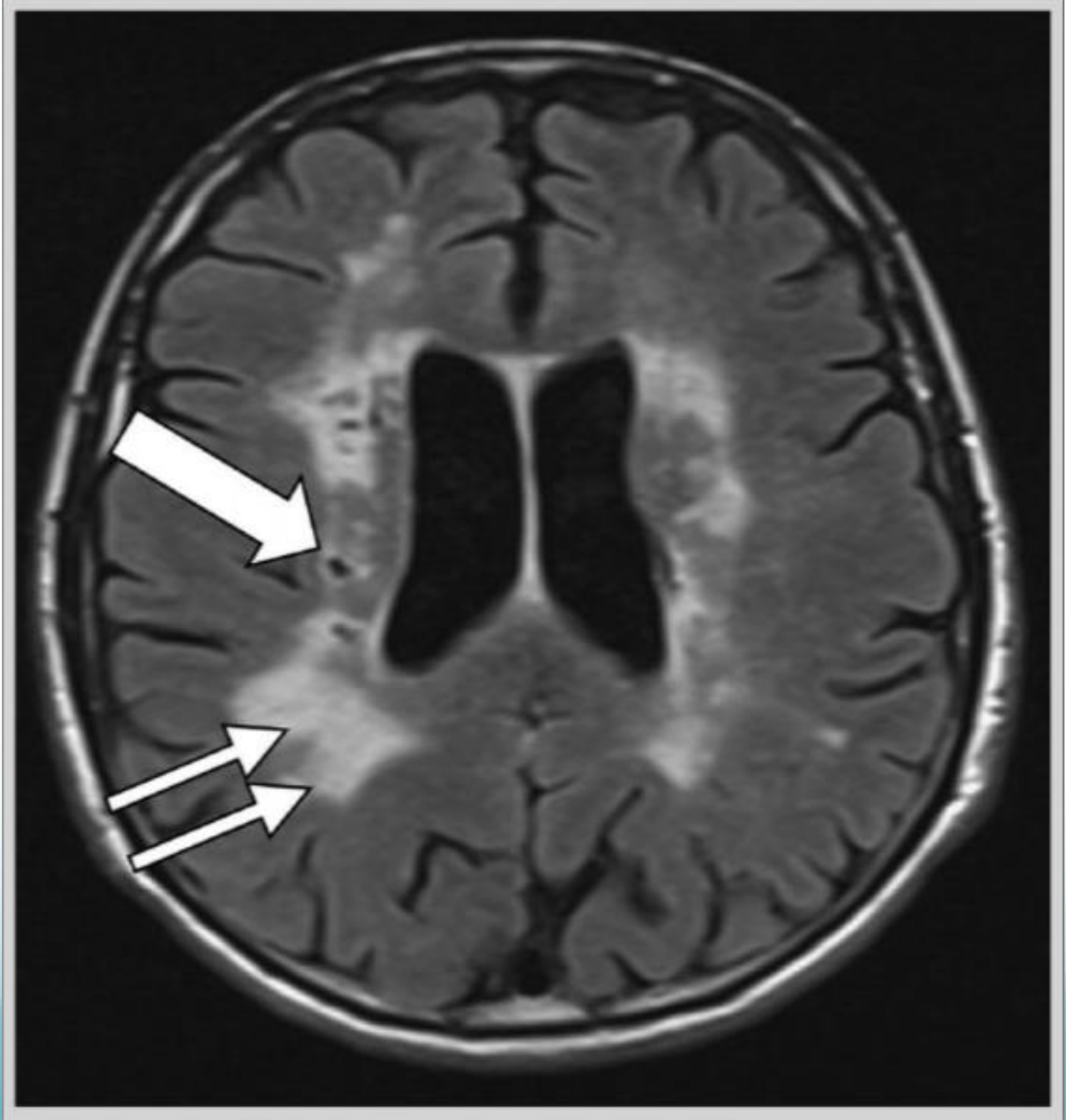
- **Dementia with Lewy Bodies/Parkinson Disease Dementia**
  - Parkinsonism occurs simultaneous/within 1 year of dementia vs >1 yr before dementia
  - Visual hallucinations and fluctuations in mental status are prominent

- **Vascular dementia**
  - Typically stepwise, but may progress insidiously
  - Dysexecutive syndrome
  - Focal neurological findings/history of recurrent strokes.

Vascular Dementia

- **Post-stroke vascular cognitive impairment**
  - Mild
  - Major
- **Non-stroke vascular cognitive impairment**



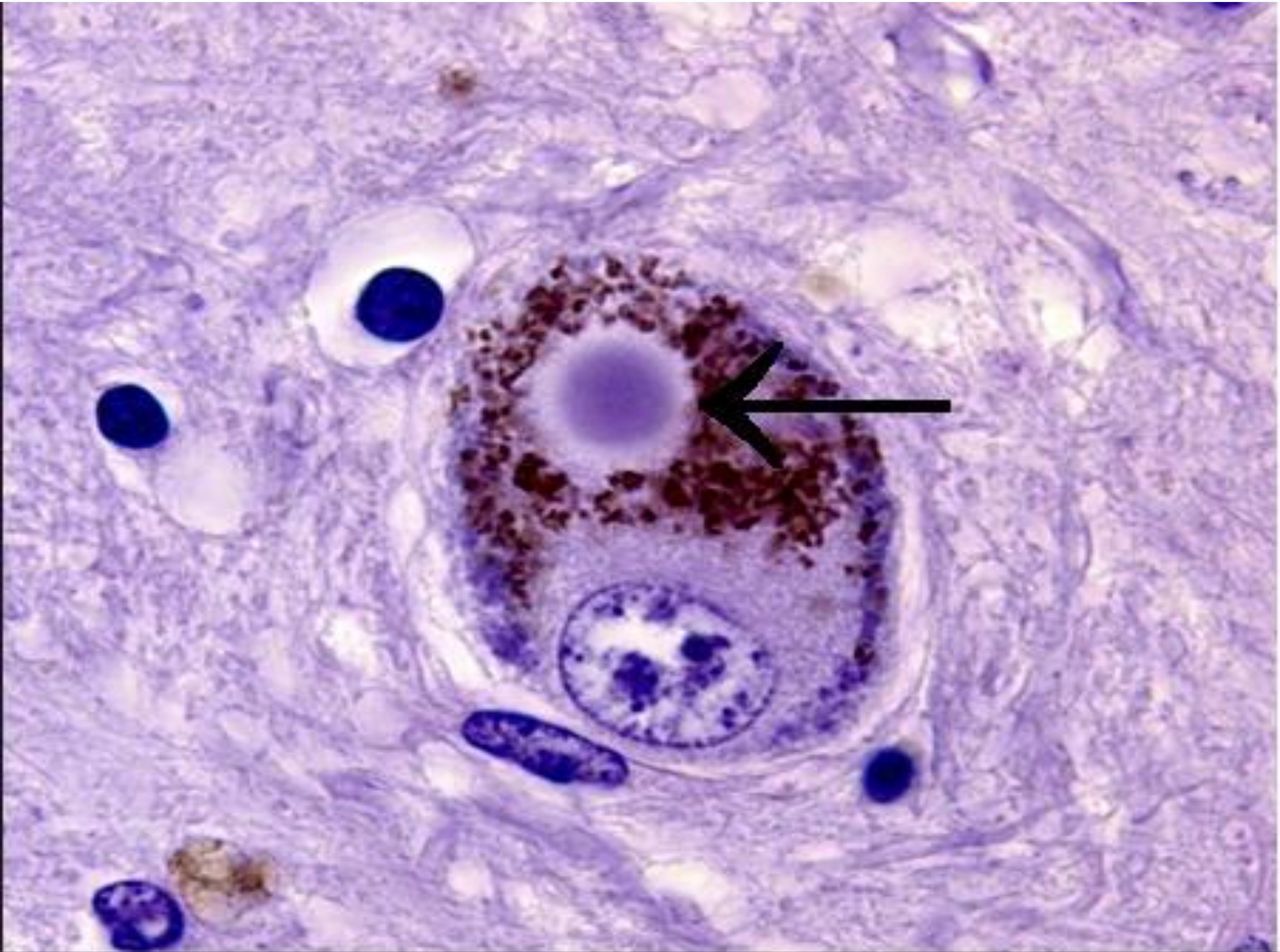


Age Decade	Infarcts		Beginning Confluent or Confluent White Matter Hyperintensities on MRI[b]	Microbleeds[c]	
	≥1 infarct	≥2 infarcts		T2*-Weighted Gradient Recalled Echo (GRE)	Susceptibility-Weighted Imaging (SWI)/ High-Sensitivity Sequence
50–59	5–8%	1–2%	1%	3%	12%
60–69	7–12%	2–3%	1–4%	5–10%	15–17%
70–79	12–23%	3–6%	6–14%	8–16%	30–31%
80+	25–38%	6–9%	19%	18%	40%

MRI = magnetic resonance imaging.
[a] Data are aggregated from multiple population-based studies.
[b] As measured using the Fazekas scale.[13]
[c] As can be seen from the table, susceptibility-weighted imaging (SWI) and other newer, high-sensitivity MRI sequences detect about twice as many microbleeds as older T2*-weighted gradient recalled echo (GRE) sequences.

Lewy Body Dementias

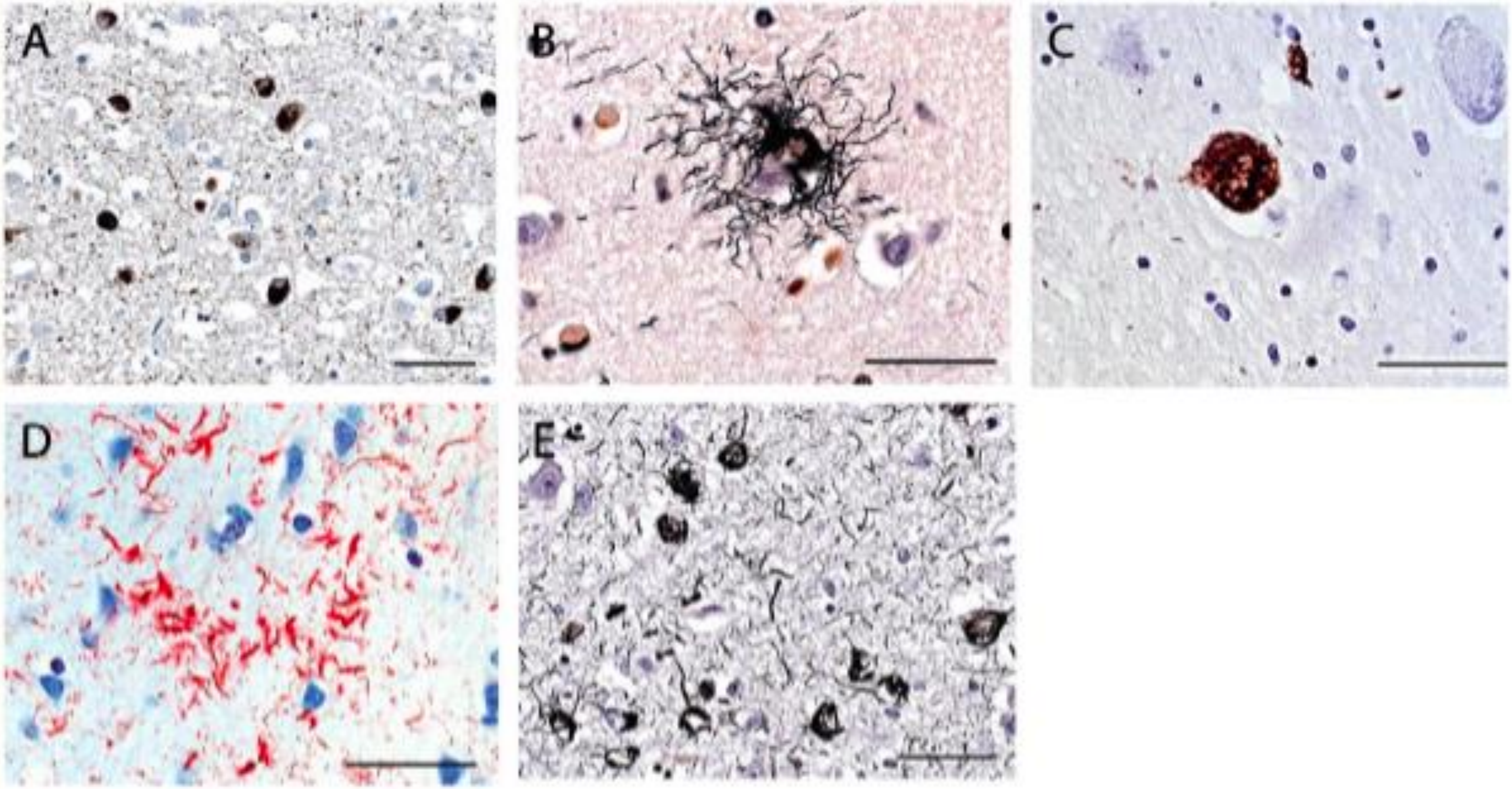
- **Dementia with Lewy Bodies (DLB)**
- **Parkinson Disease Dementia (PDD)**
- "Synucleinopathies"
- DLB:
  - Amyloid deposition in cortex occurs early
  - α-synuclein deposition (Lewy body) ascends from brainstem to cortex
  - Early dementia occurring with parkinsonism or within one year: attention, executive function, visuospatial skill, STM (retrieval-helped with cues)
  - Visual hallucinations
  - Fluctuations in the attention and arousal
  - REM behavioral disorder
  - Autonomic impairment: Constipation; orthostatic hypotension
  - Anosmia



Frontotemporal Dementia

"Tauopathies"

- Behavioral variant of FTD
- Semantic variant primary progressive aphasia (PPA)
- Nonfluent, agrammatic PPA
- FTD associated with motor neuron disease (FTD-MND)
- Progressive supranuclear palsy (PSP)
- Corticobasal Degeneration (CBD)

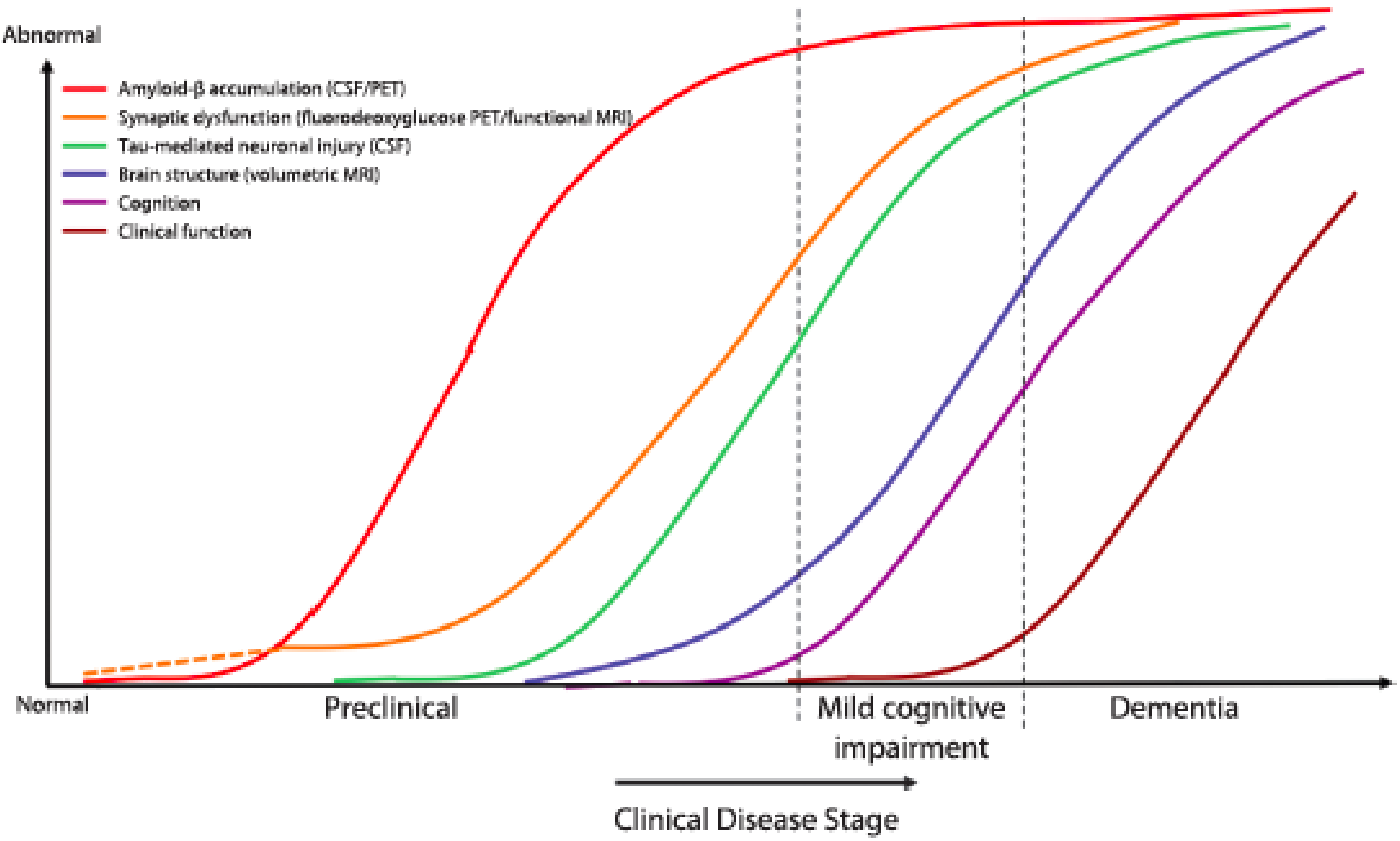

A
B
C
D
E

Frontotemporal Dementia

- 40% autosomal dominant
- Major risk factor
- Mutations to 8 genes
- 3 most common:
  - C9ORF72 expanded repeats
  - GRN mutation
  - MAPT mutation

Atypical AD

- **Frontal variant AD**
  - Behavioral or personality changes marked as compared with memory dysfunction
  - Irritable, impulsive, impatient and disinhibited
  - Executive function markedly affected
- **Posterior cortical atrophy variant of AD**
  - Visuospatial dysfunction prominent
  - Balint's syndrome (simultagnosia, ocular apraxia and ocular ataxia)
  - Gerstmann's syndrome (acalculia, agraphia, R/L disorientation, finger agnosia)
  - Visual agnosia; environmental disorientation
  - Construction, dressing and other ideomotor apraxias early
- **Logopenic variant AD**
  - Aphasia, mainly with anomia and decreased repetition.

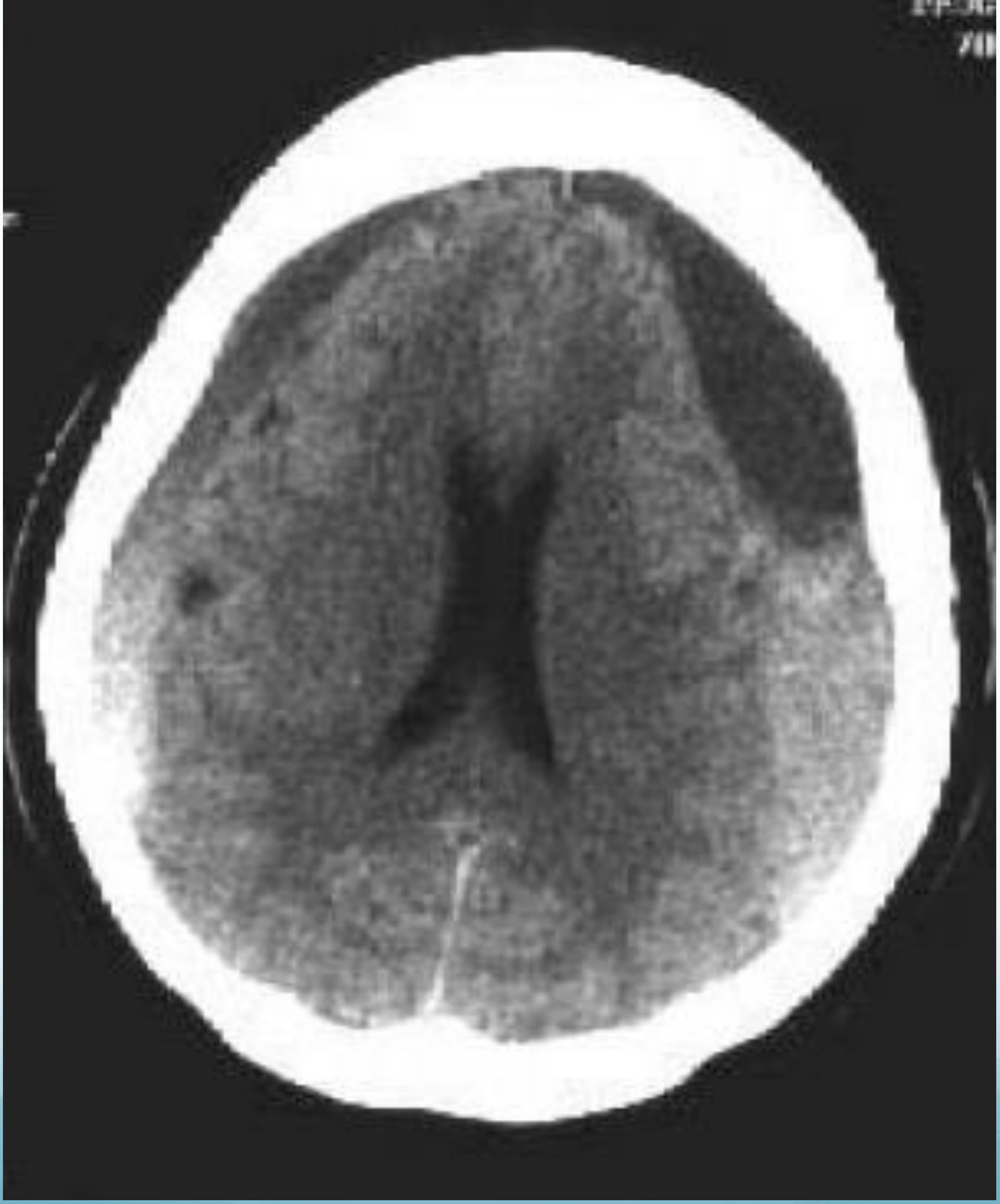

Abnormal
Amyloid-β accumulation (CSF/PET)
Synaptic dysfunction (fluorodeoxyglucose PET/functional MRI)
Tau-mediated neuronal injury (CSF)
Brain structure (volumetric MRI)
Cognition
Clinical function
Normal
Preclinical
Mild cognitive impairment
Dementia
Clinical Disease Stage

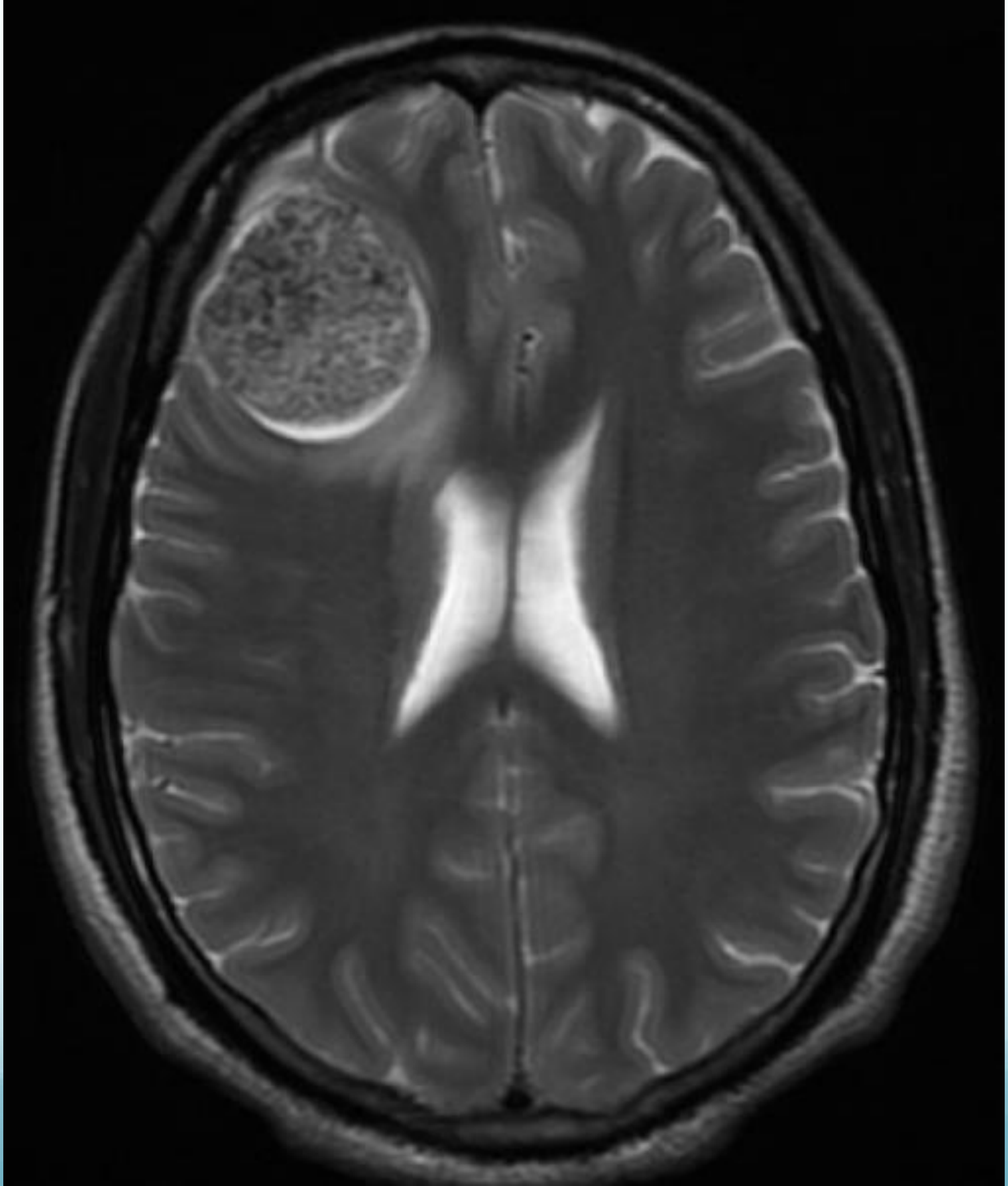
Neurodegenerative Biomarkers

- CSF
  - Decreased levels of amyloid beta
    - Reflects abnormal amyloid beta deposition
  - Increased levels of tau or p-tau
    - Reflects neuronal degeneration
- MRI
  - Mesial temporal lobe/hippocampal atrophy
- FDG-PET
  - Temporal (medial) and parietal (posterior) hypometabolism-AD
  - Frontal hypometabolism-FTD
- Amyloid PET
- Tau PET

Neuroimaging Tests

- **Structural**
  - **CT brain**
    - More available
    - Less expensive
    - Easier to perform on a demented patient
  - **MRI brain**
    - More sensitive for ischemic vascular disease
    - Neurodegenerative biomarker (hippocampal atrophy)
    - Specific diagnoses eg FTD, PSP, MSA.
    - Microhemorrhages in cerebral amyloid angiopathy
  - American Academy of Neurology Guideline recommendation
  - 5% incidence of structural causes of dementia
    - subdural hematoma, frontal lobe tumor, NPH



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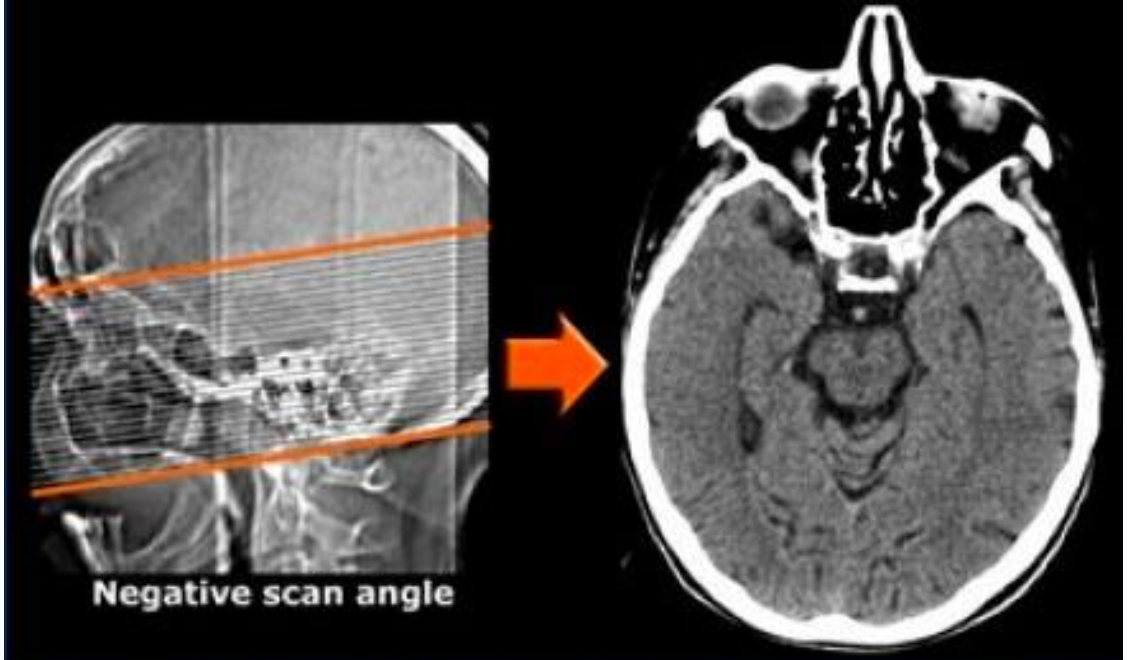
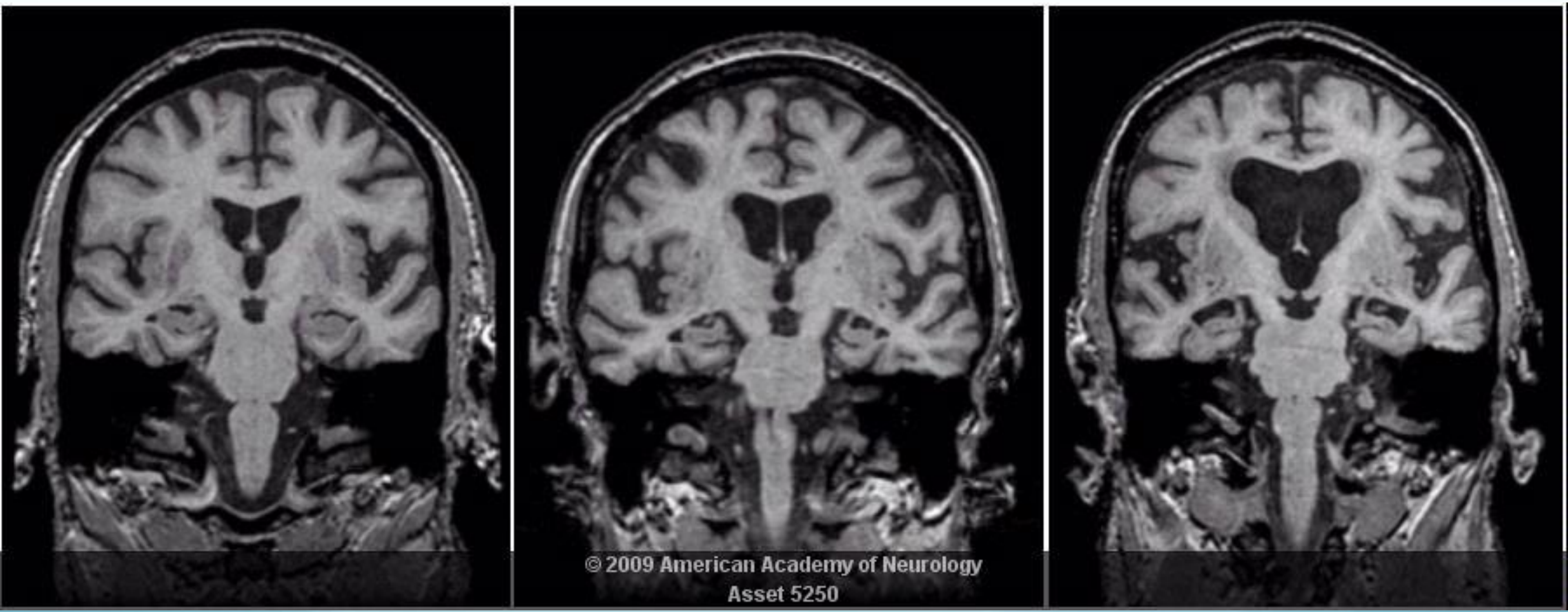


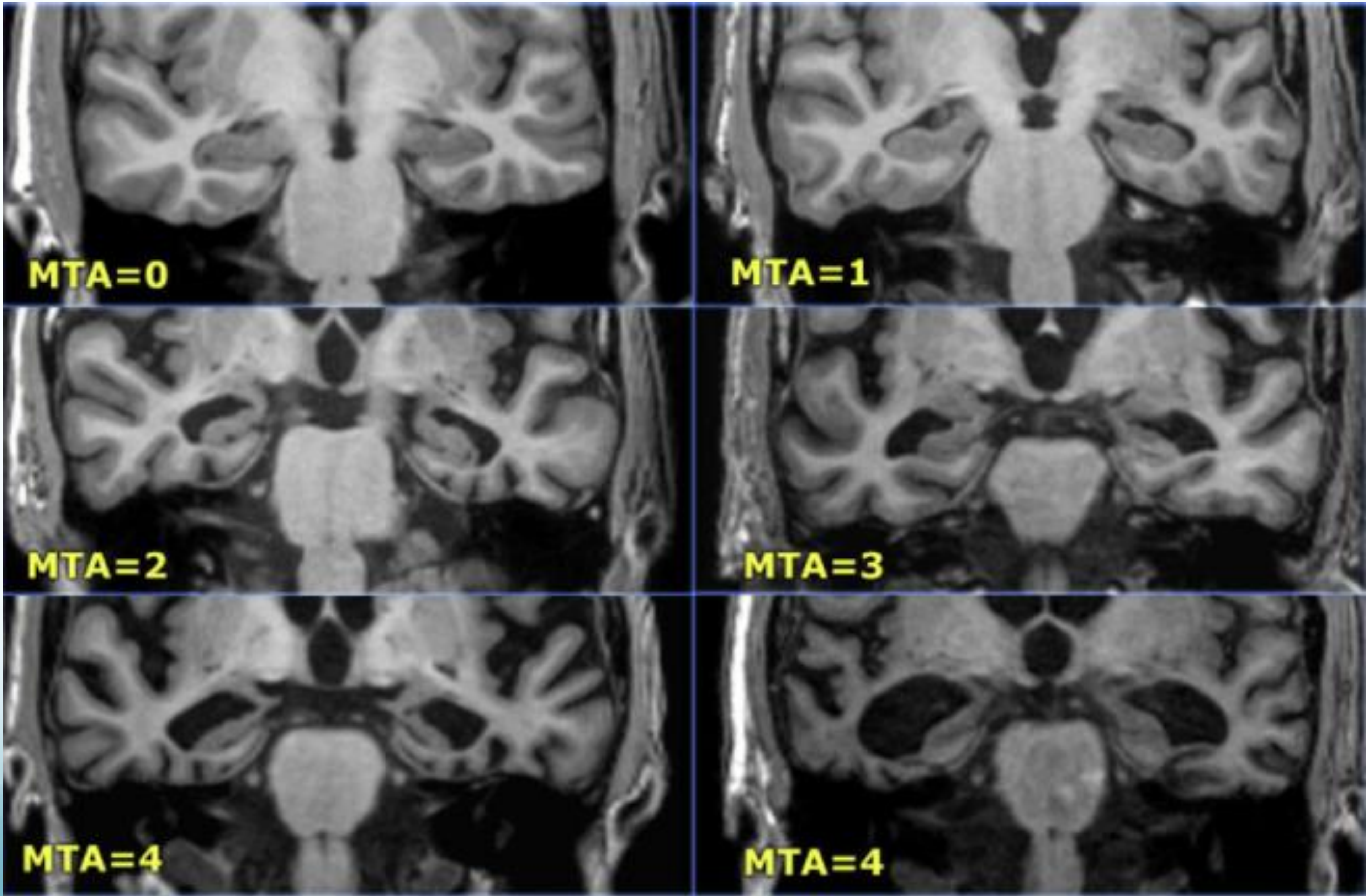
CT with negative scan angle for optimal vizualisation of the hippocampus in the transverse plane

Spiral CT of the brain with coronal reconstructions.

Alzheimer’s Disease

- Coronal MRI scan showing degrees of hippocampal atrophy in normal (left), mild cognitive impairment (middle), and Alzheimer's disease (right) subjects.

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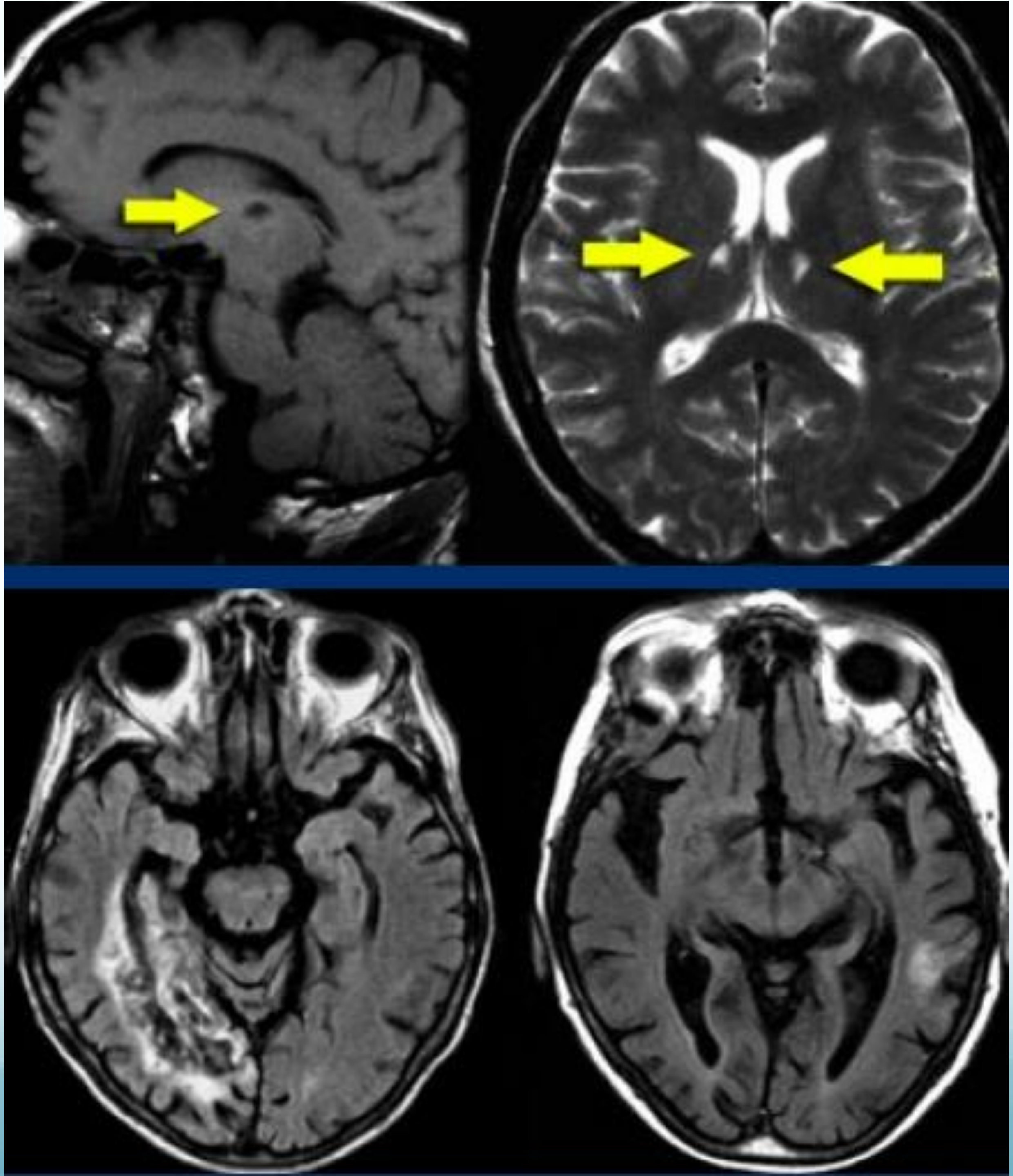

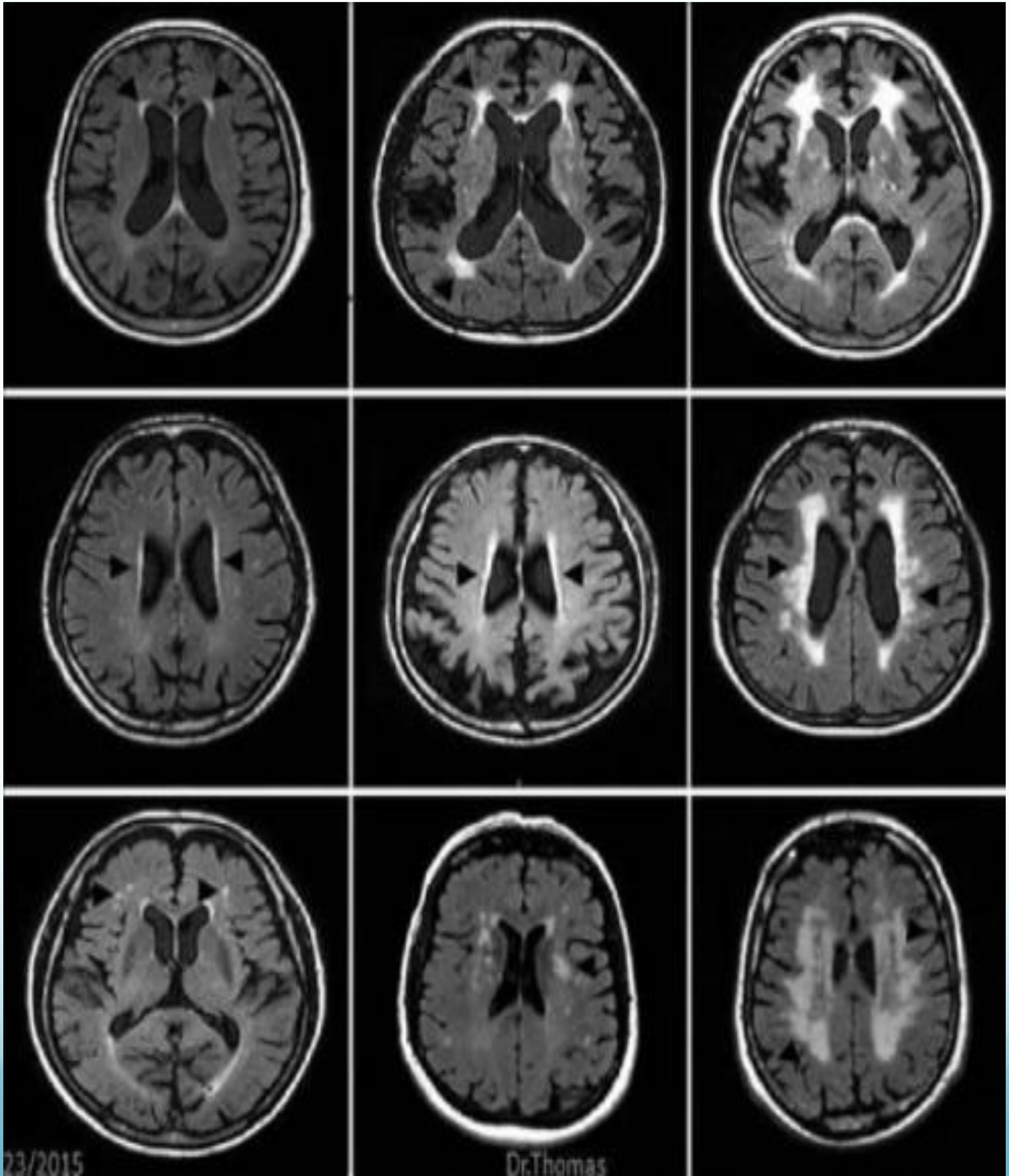
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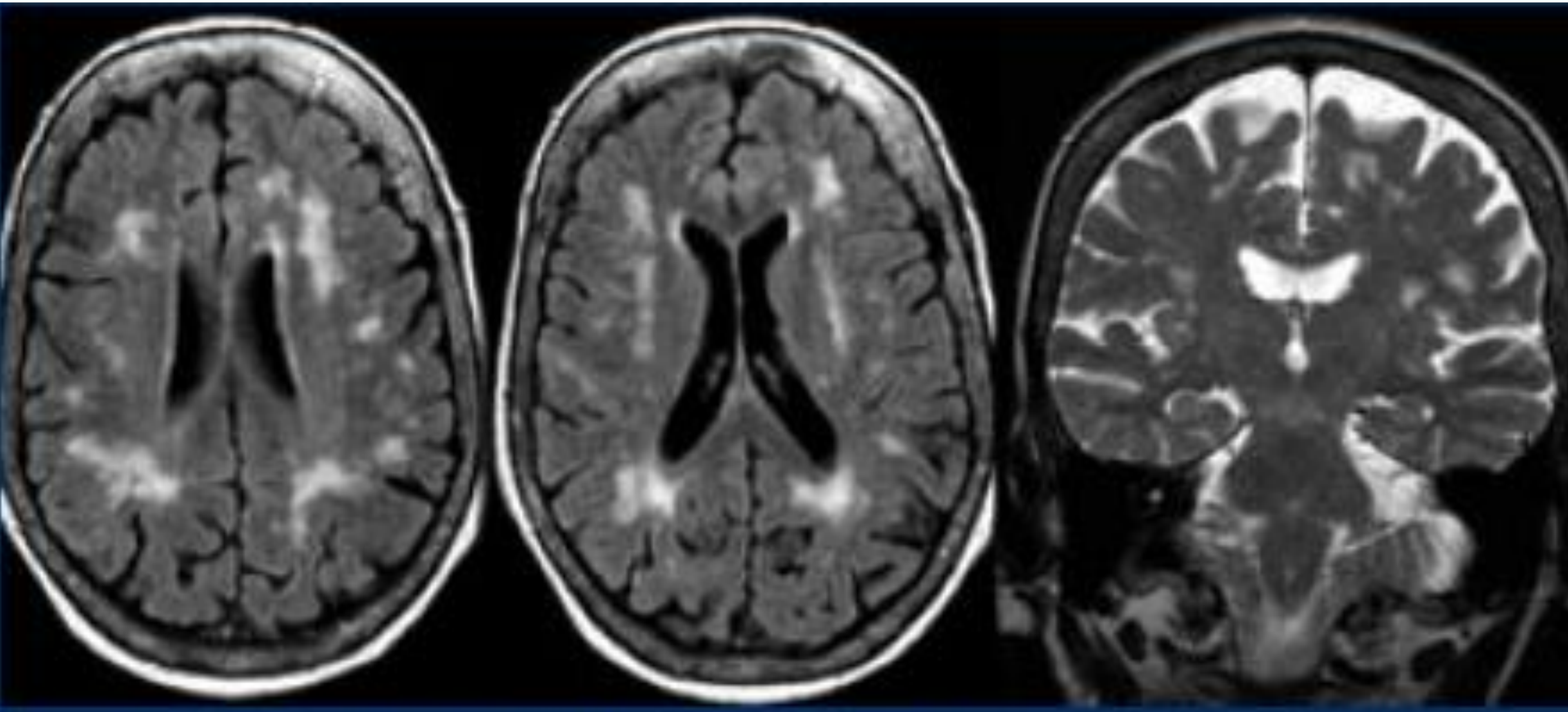
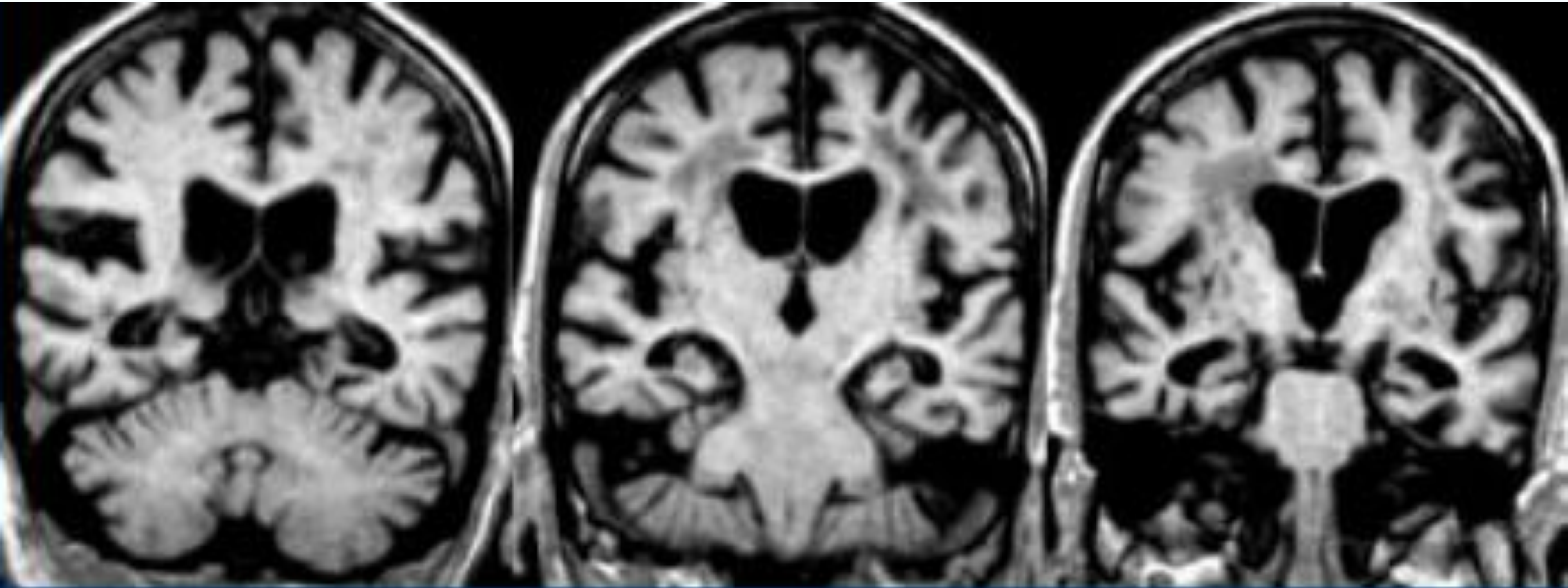
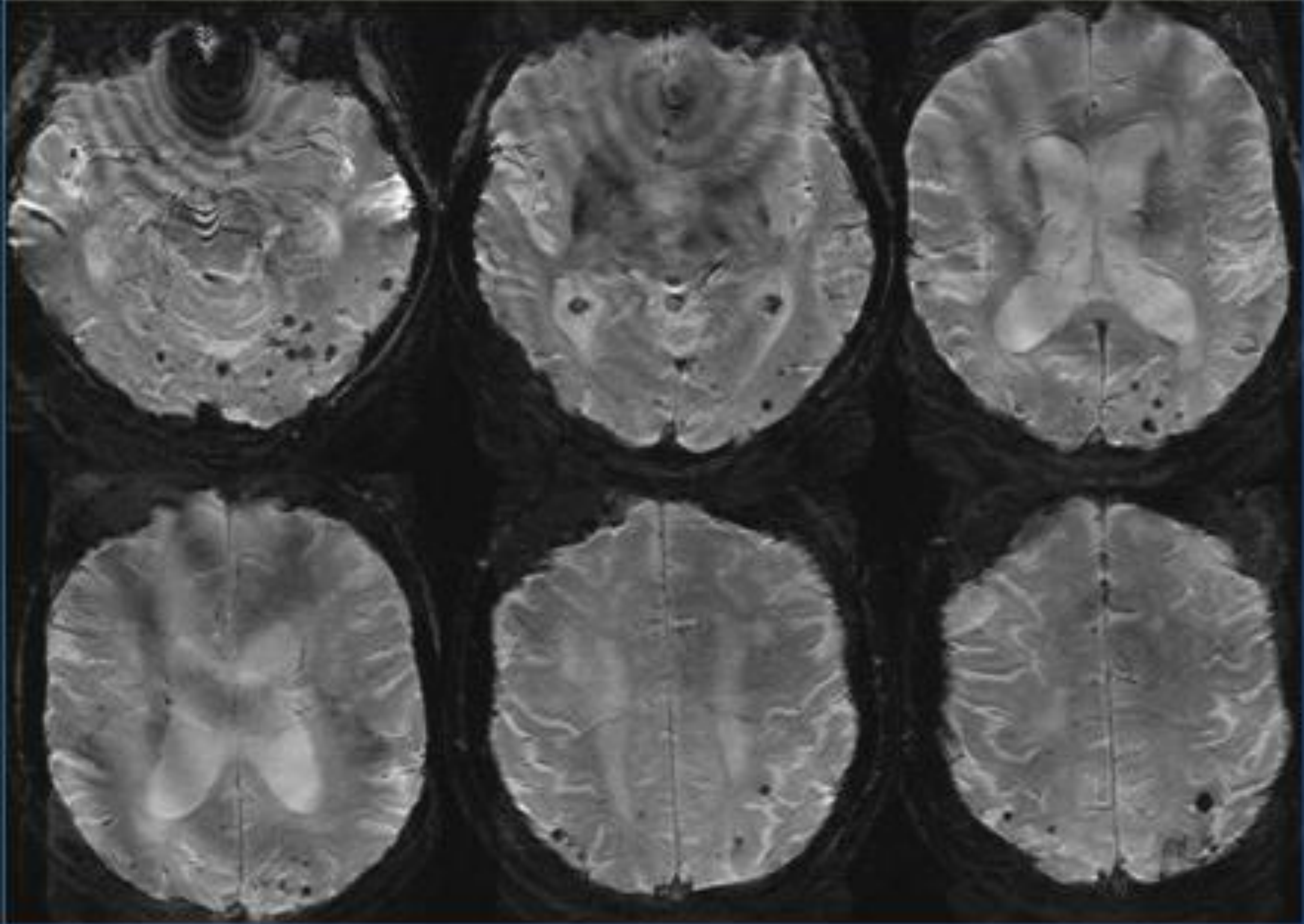
Dr.Thomas

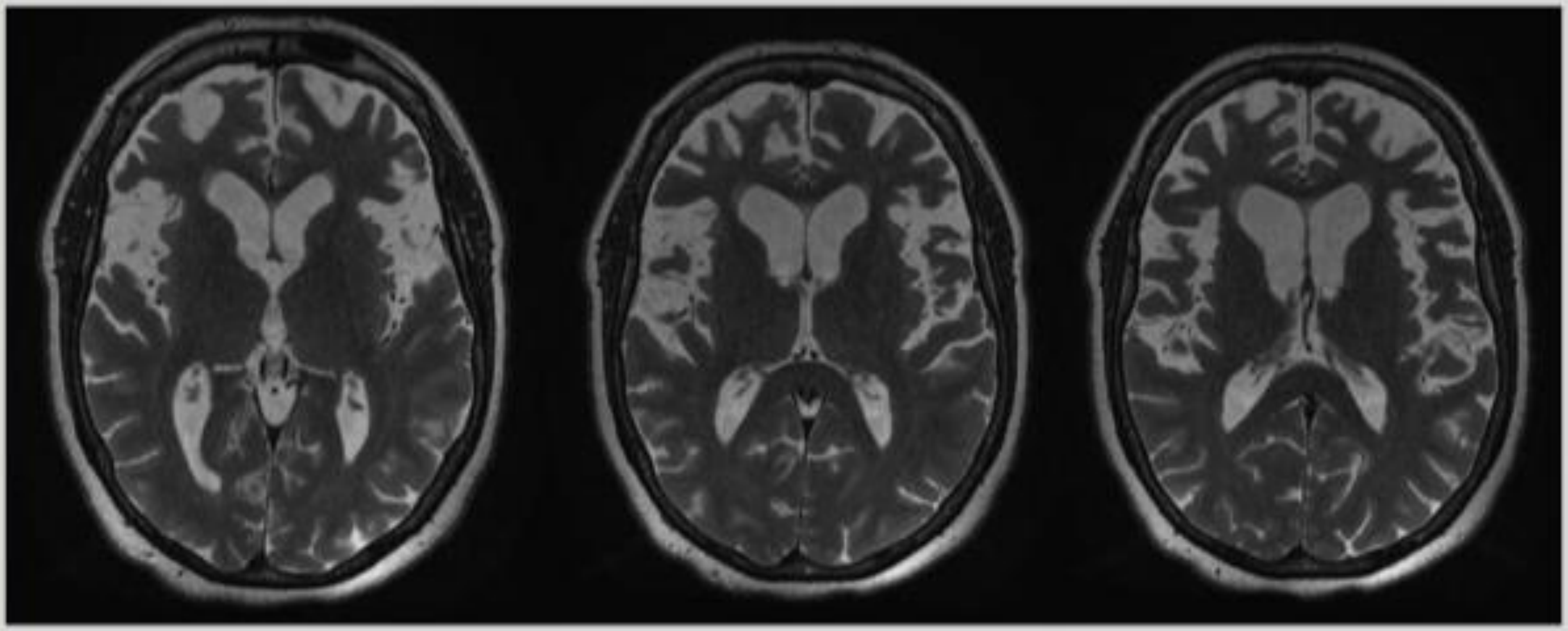


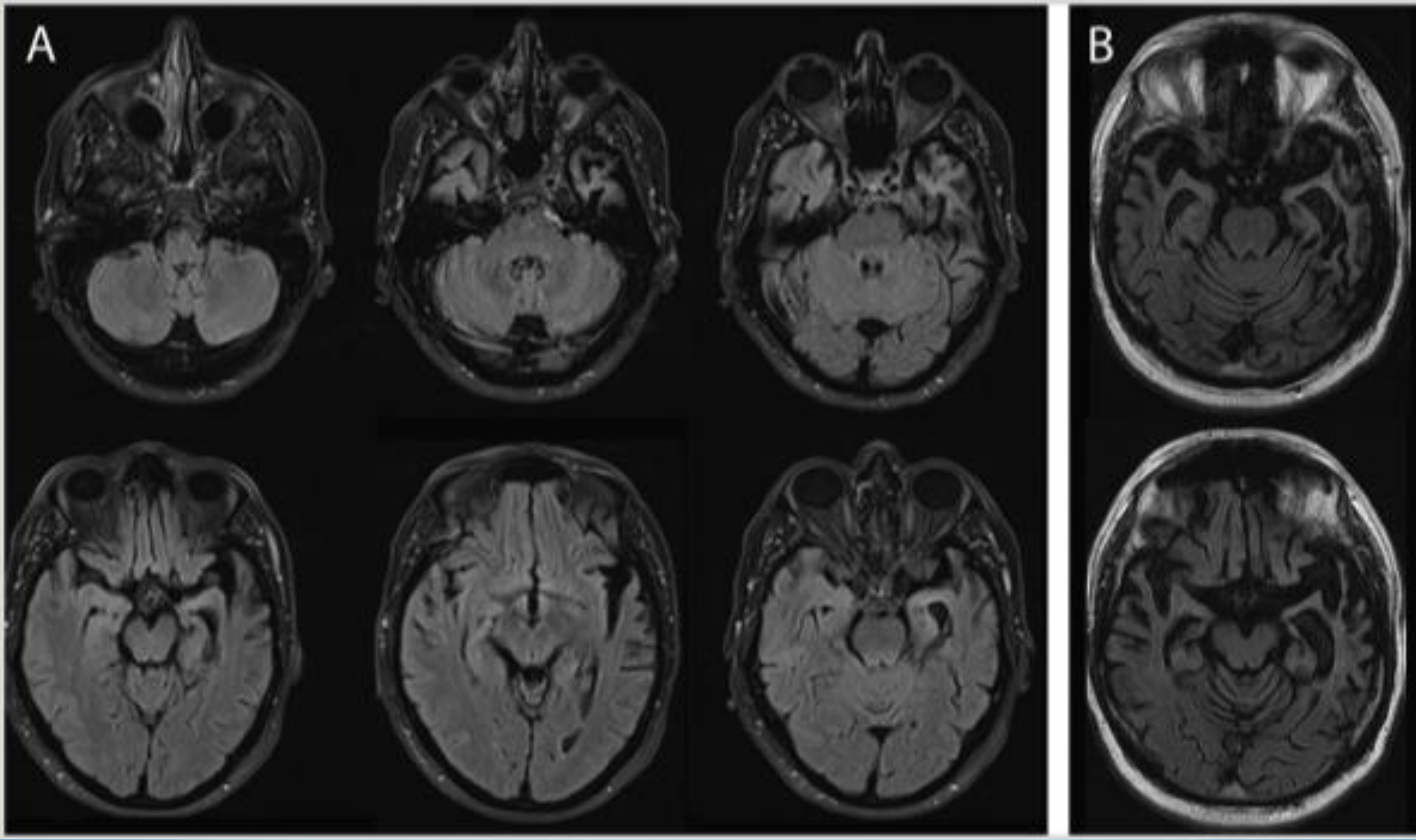
Vascular dementia, no medial temporal lobe atrophy.

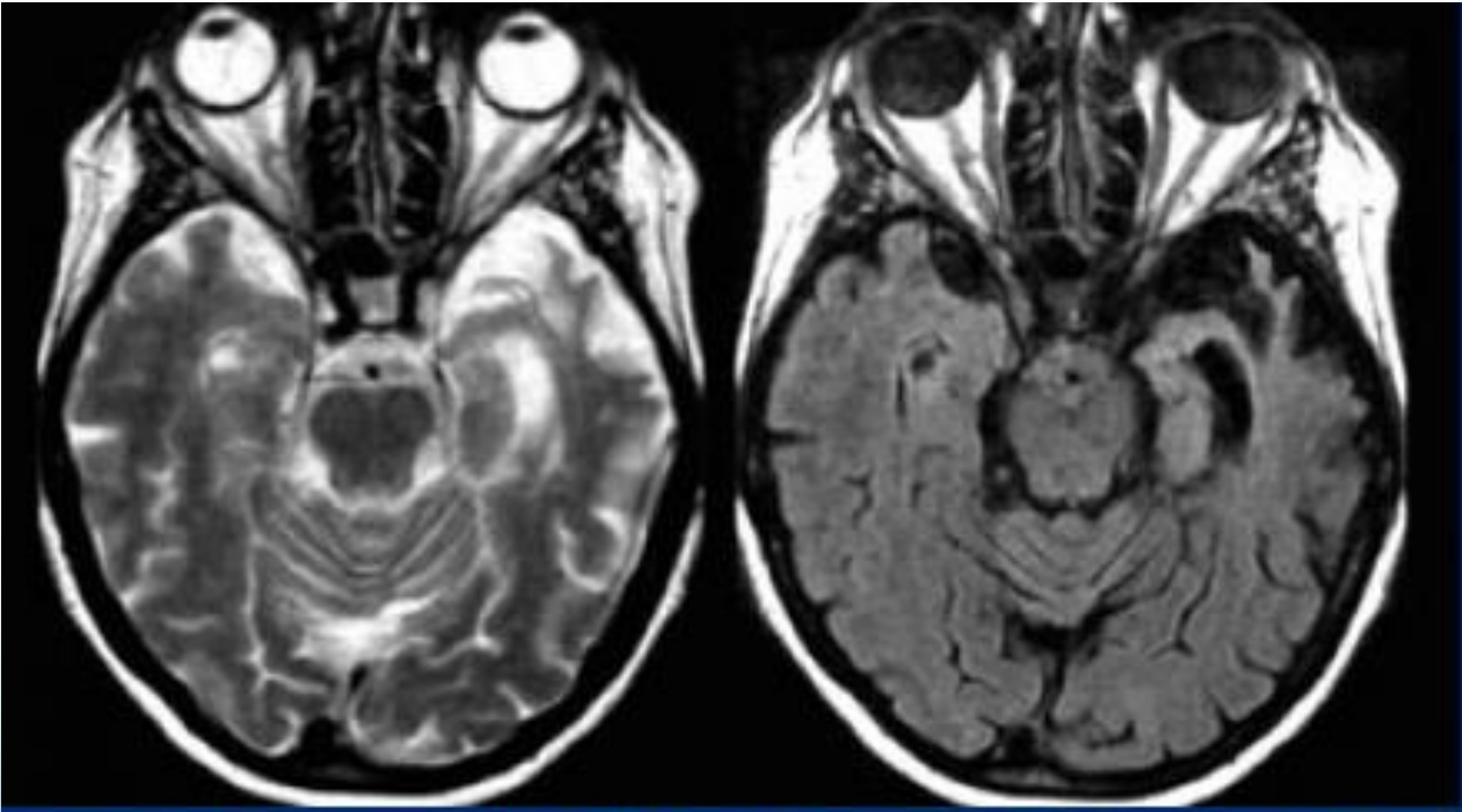




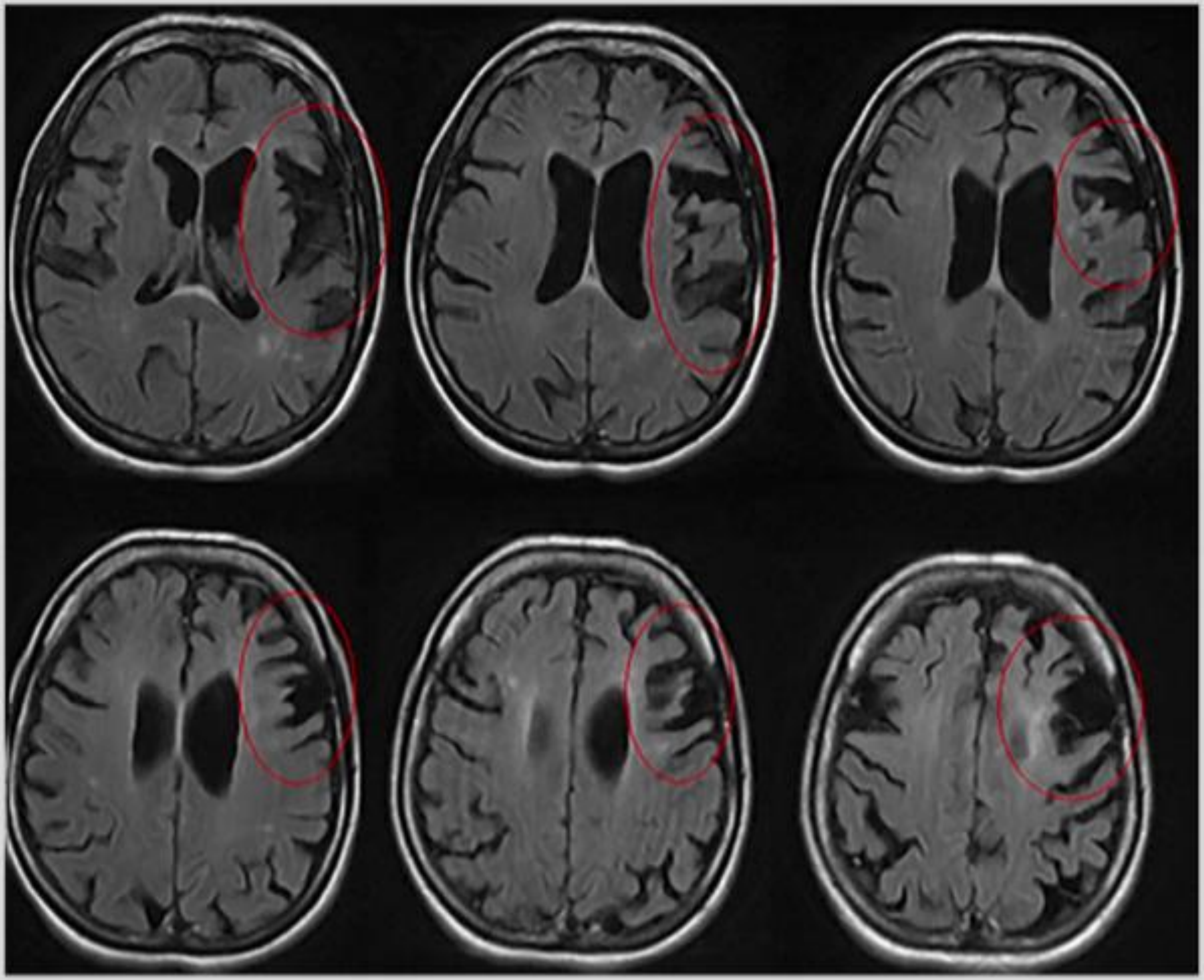
Cerebral Amyloid Angiopathy

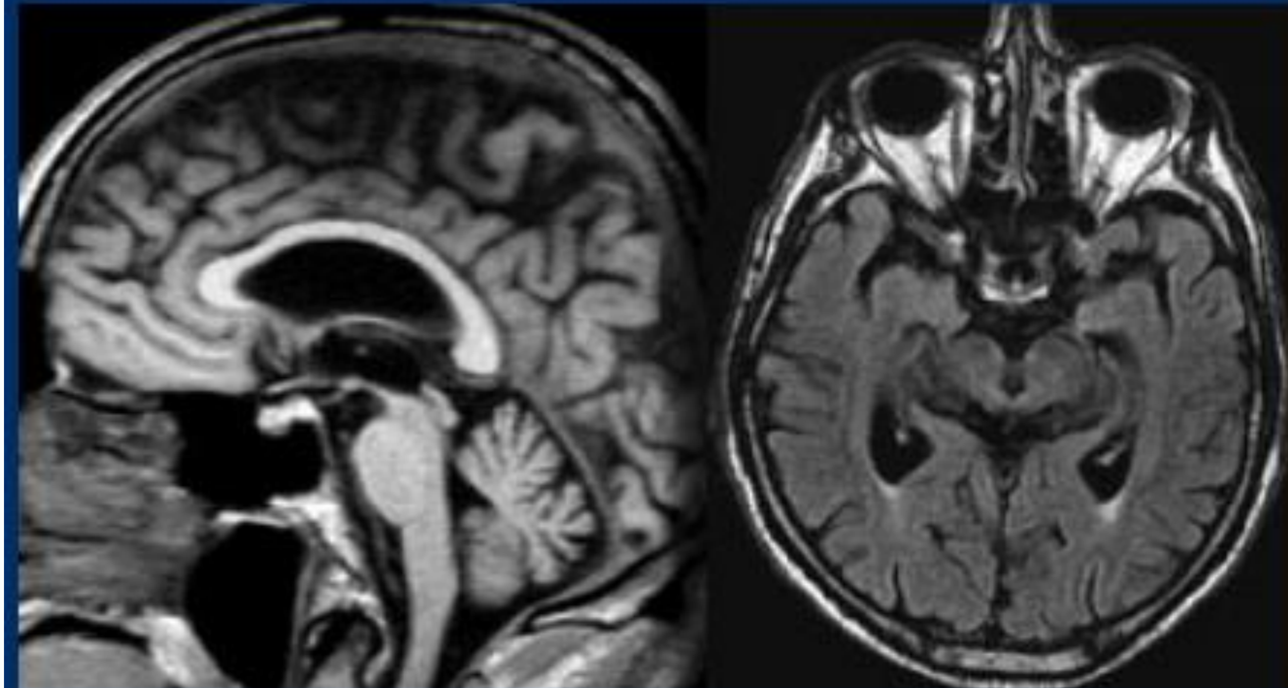



A
B



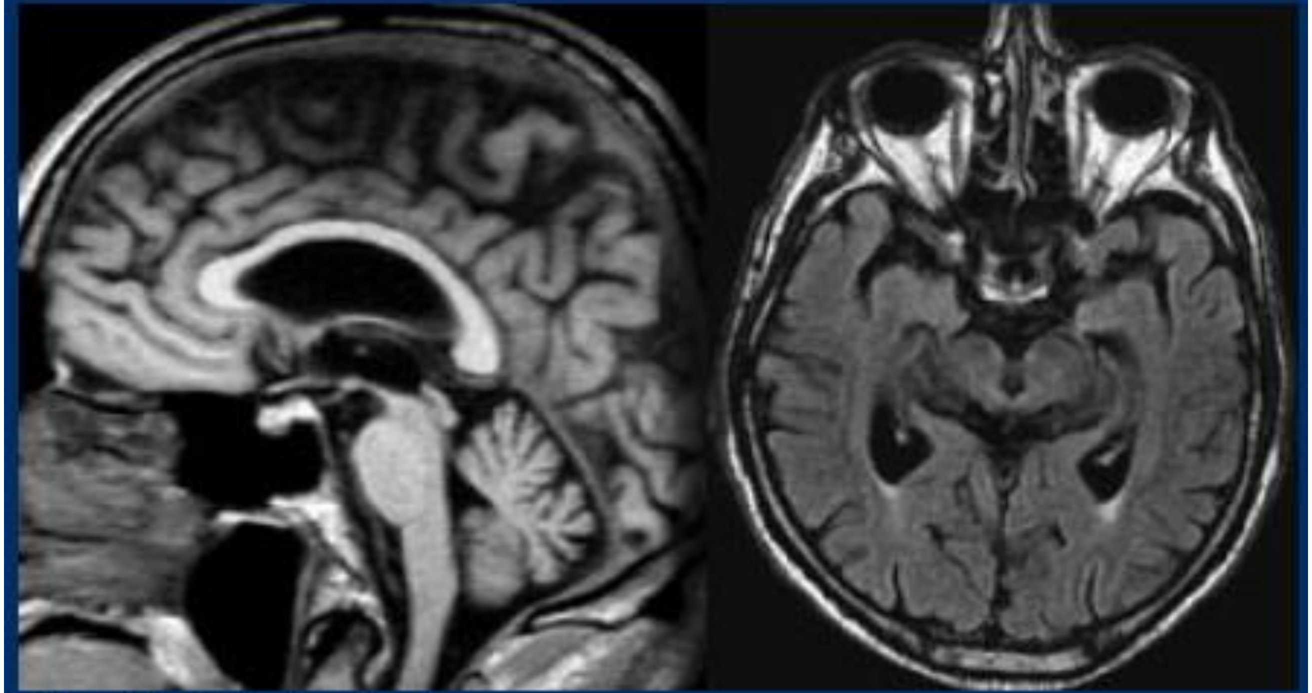
FTLD: T2WI and FLAIR with 'knife blade' atrophy of left temporal lobe with normal right temporal lobe





PSP with midbrain atrophy

PSP: 'humming bird sign' due to midbrain atrophy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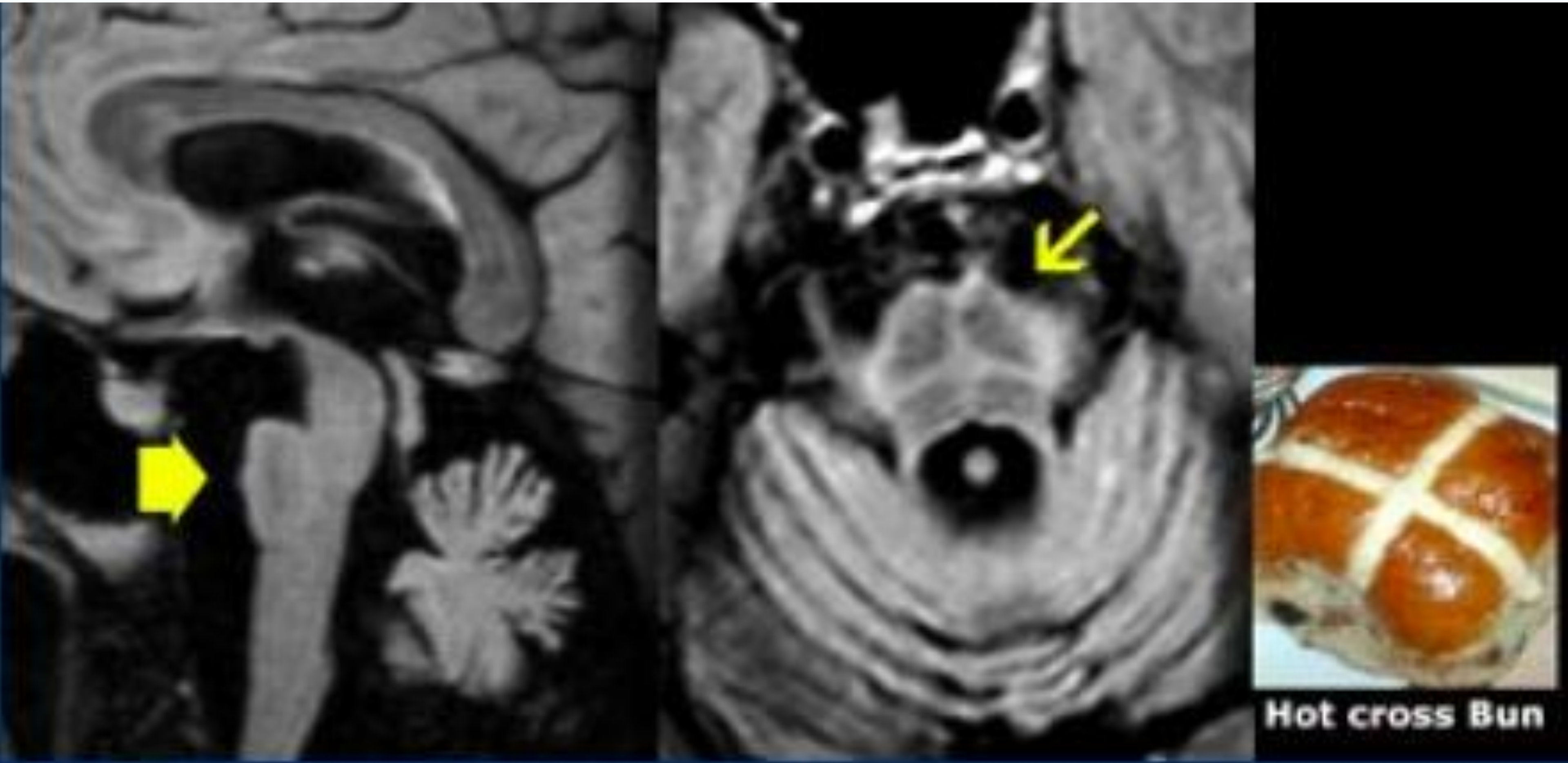


'Hot cross bun sign' in MSA

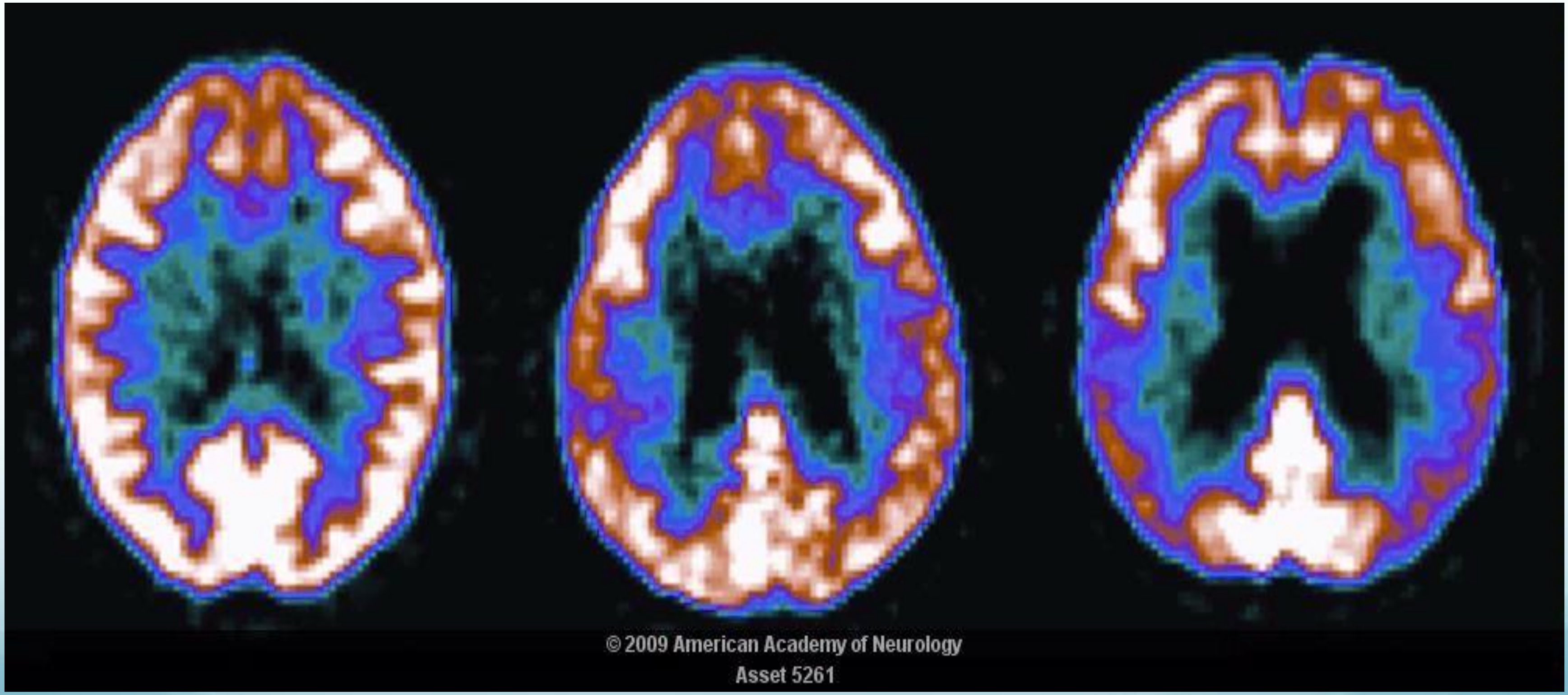
Neuroimaging Tests

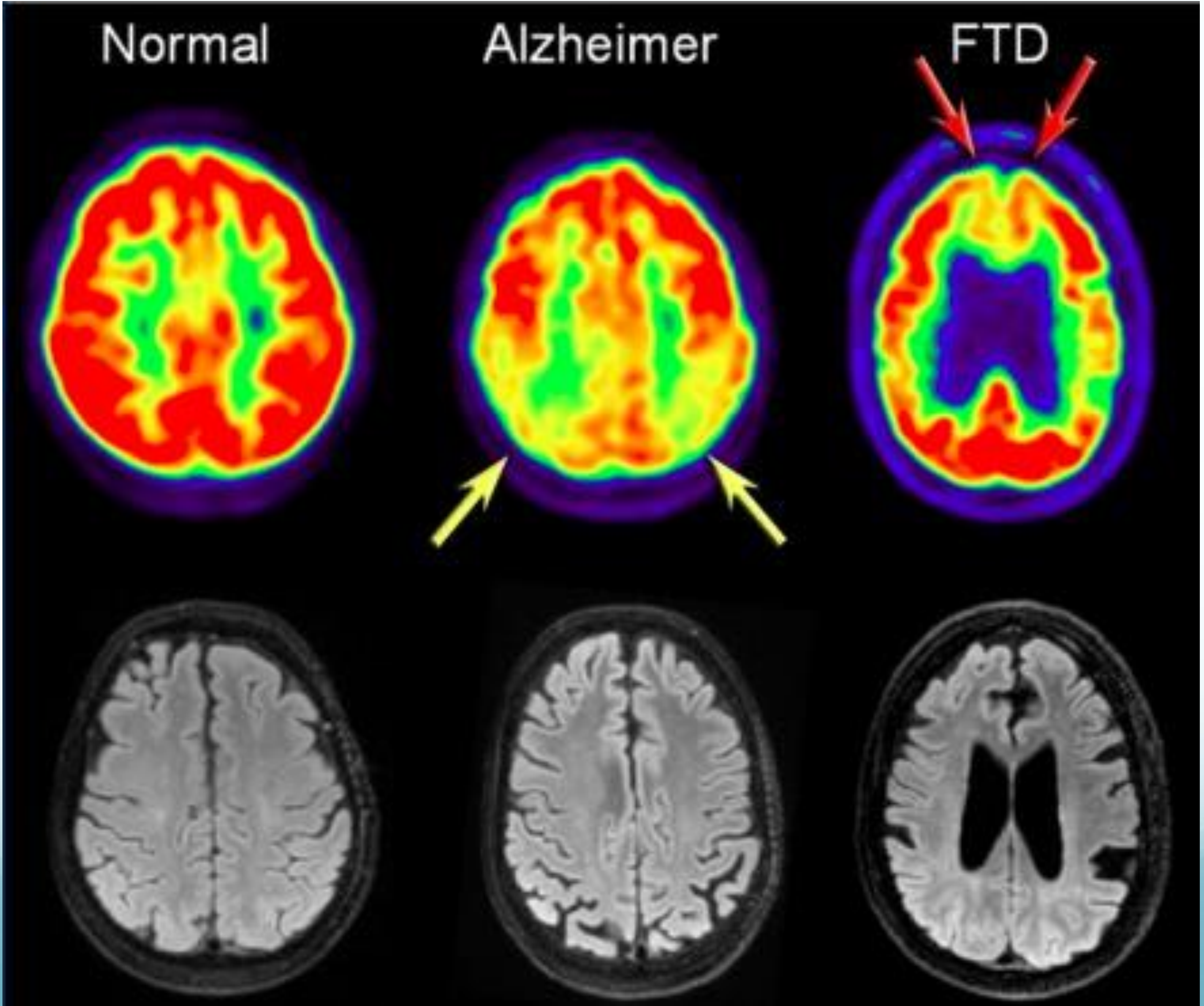
- Functional
  - Single Photon Emission Computed Tomography (SPECT)
  - **18F-Fleurodeoxyglucose (FDG) Positron Emission Tomography (PET)**

- **Positron Emission Tomography (PET) amyloid imaging**
  - Pittsburgh Compound B
  - Florbetapir F18 (Amyvid)
  - Flutemetamol F18 (Vizamyl)
  - Florbetaben F18 (Neuraceq)

Positron Emission Tomography (PET)

- [18F]Fluorodeoxyglucose (FDG) PET images from a healthy control (left), a patient with mild cognitive impairment (middle), and a patient with Alzheimer's disease (right).



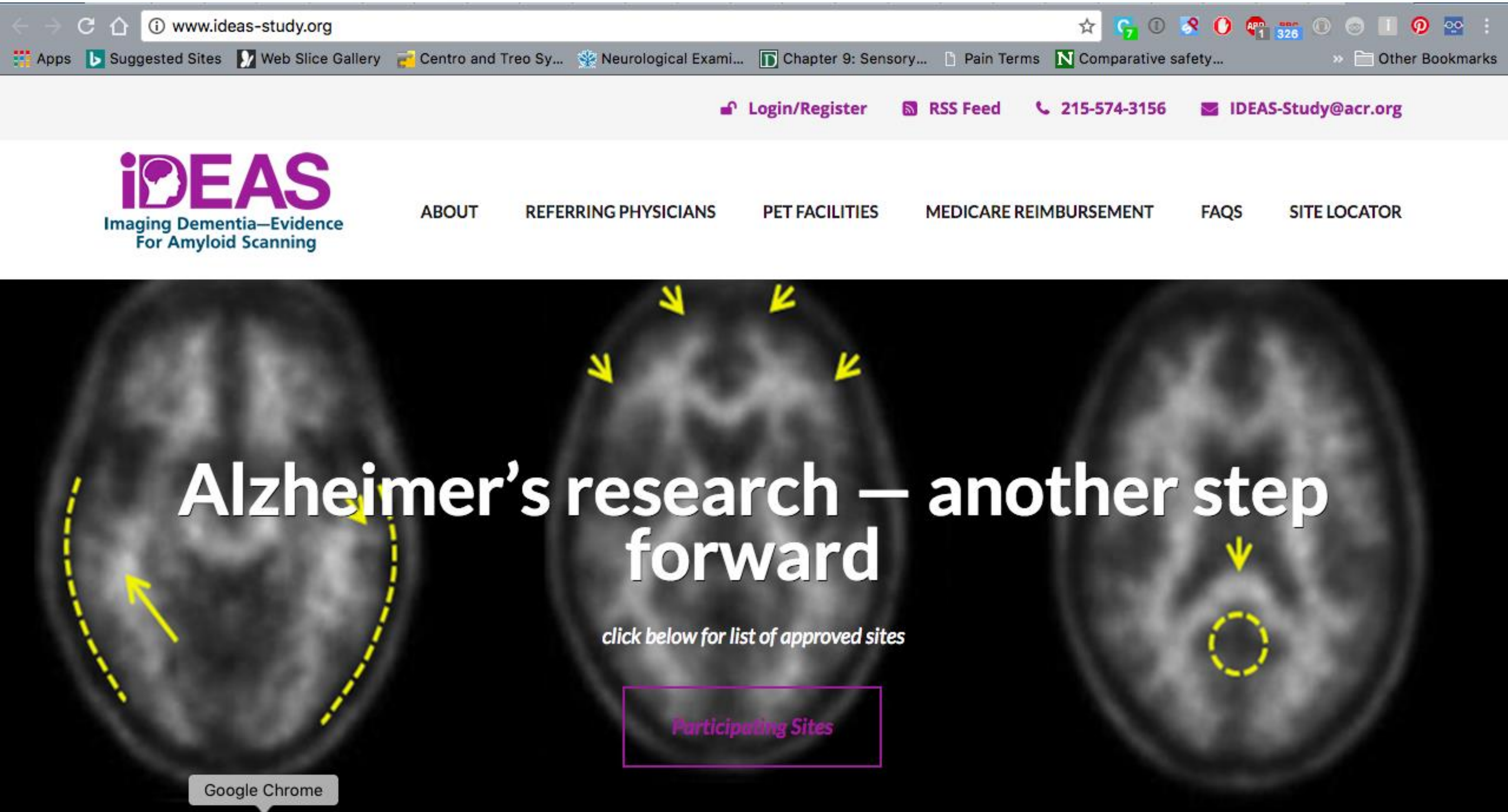

Normal
Alzheimer
FTD

Amyloid Imaging with PET

- Major recent advance
- Ability to identify amyloid plaques ante-mortem
- Radioactive tracers bind to aggregated fibrillar Aβ deposits
- Highly sensitive and specific (as is CSF Aβ)
- vs MRI hippocampal atrophy and FDG-PET (↑ sens; ↓ spec)
- Very useful in ddx of dementia: AD/DLB vs FTD
- Potential to revolutionize patient dx & mx, conduct of clinical trials

Amyloid PET

- Appropriate Use Criteria (Amyloid Imaging Task Force 2013):
  - Patients with mild NCD (aMCI)
  - Patients with atypical AD (to distinguish from FTD)
  - Patients with early onset dementia (<65 yrs)
- Drawbacks
  - Unproven economic benefit while effective disease modifying medications are unavailable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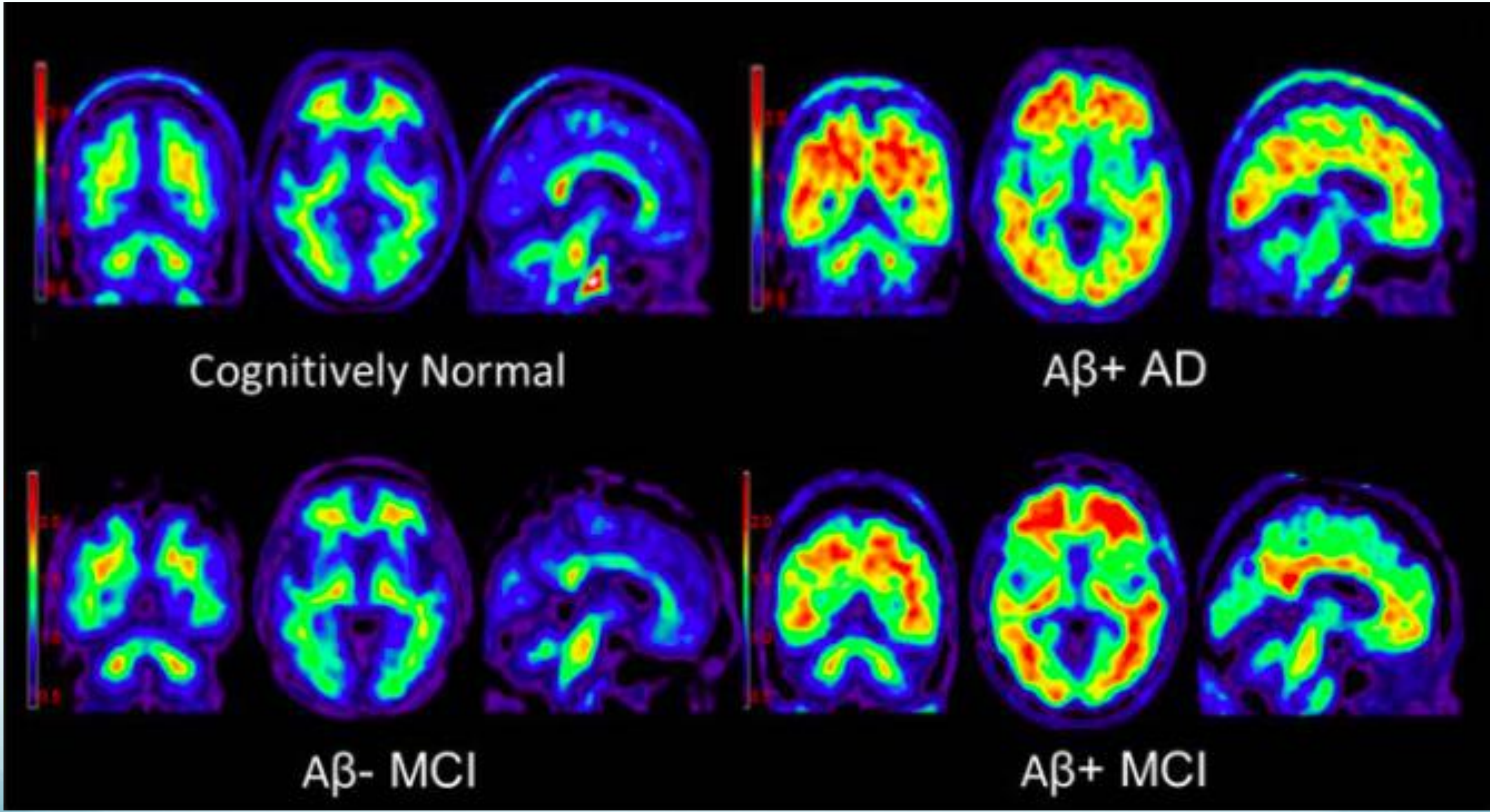
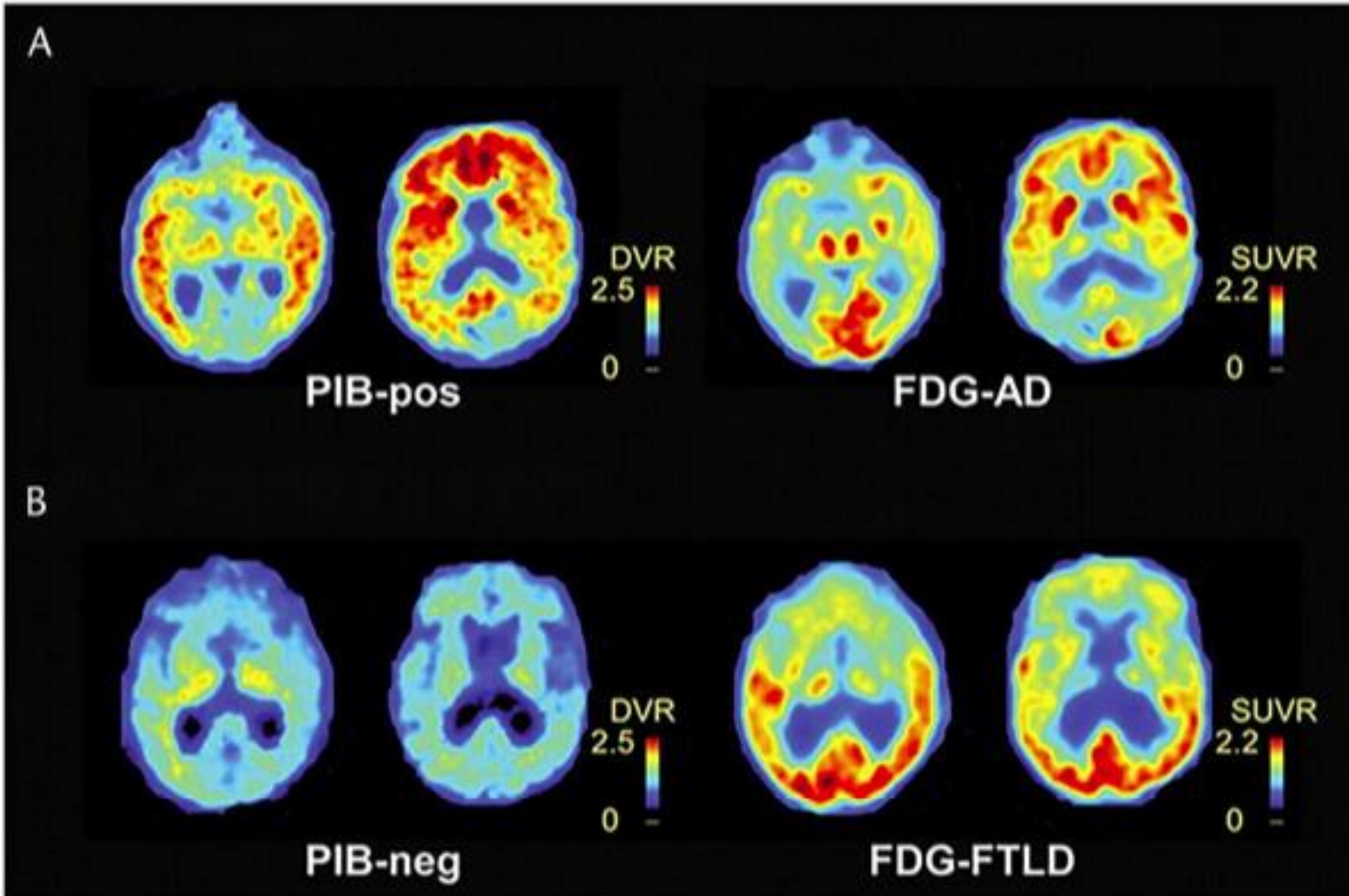
MEDICARE REIMBURSEMENT
FAQS
SITE LOCATOR
Alzheimer's research — another step forward
click below for list of approved sites
Participating Sites
Google Chrome


Cognitively Normal
Aβ+ AD
Aβ- MCI
Aβ+ MCI

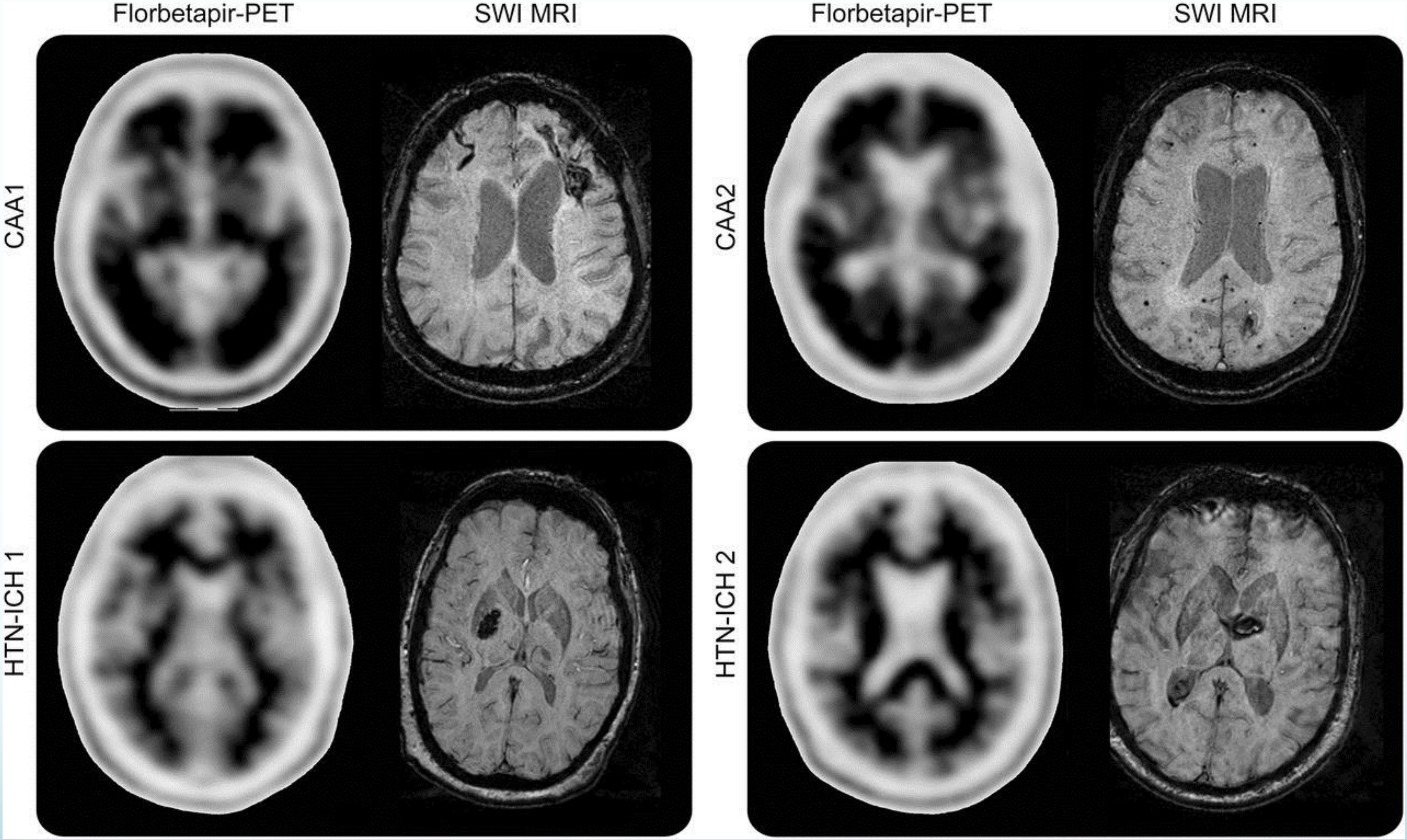

A
DVR
2.5
0
PIB-pos
SUVR
2.2
0
FDG-AD
B
DVR
2.5
0
PIB-neg
SUVR
2.2
0
FDG-FTLD

Florbetapir-PET to diagnose cerebral amyloid angiopathy

by M. Edip Gurol, J. Alex Becker, Panagiotis Fotiadis, Grace Riley, Kristin Schwab, Keith A. Johnson, and Steven M. Greenberg

Neurology
Volume 87(19):2043-2049
November 8, 2016

Figure 4. Examples of florbetapir-positive and -negative scans from patients with cerebral amyloid angiopathy (CAA) and hypertensive intracerebral hemorrhage (HTN-ICH)



M. Edip Gurol et al. Neurology 2016;87:2043-2049

Annals of NEUROLOGY
An Official Journal of the American Neurological Association and the Child Neurology Society

RESEARCH ARTICLE

Tau Positron Emission Tomographic Imaging in Aging and Early Alzheimer Disease

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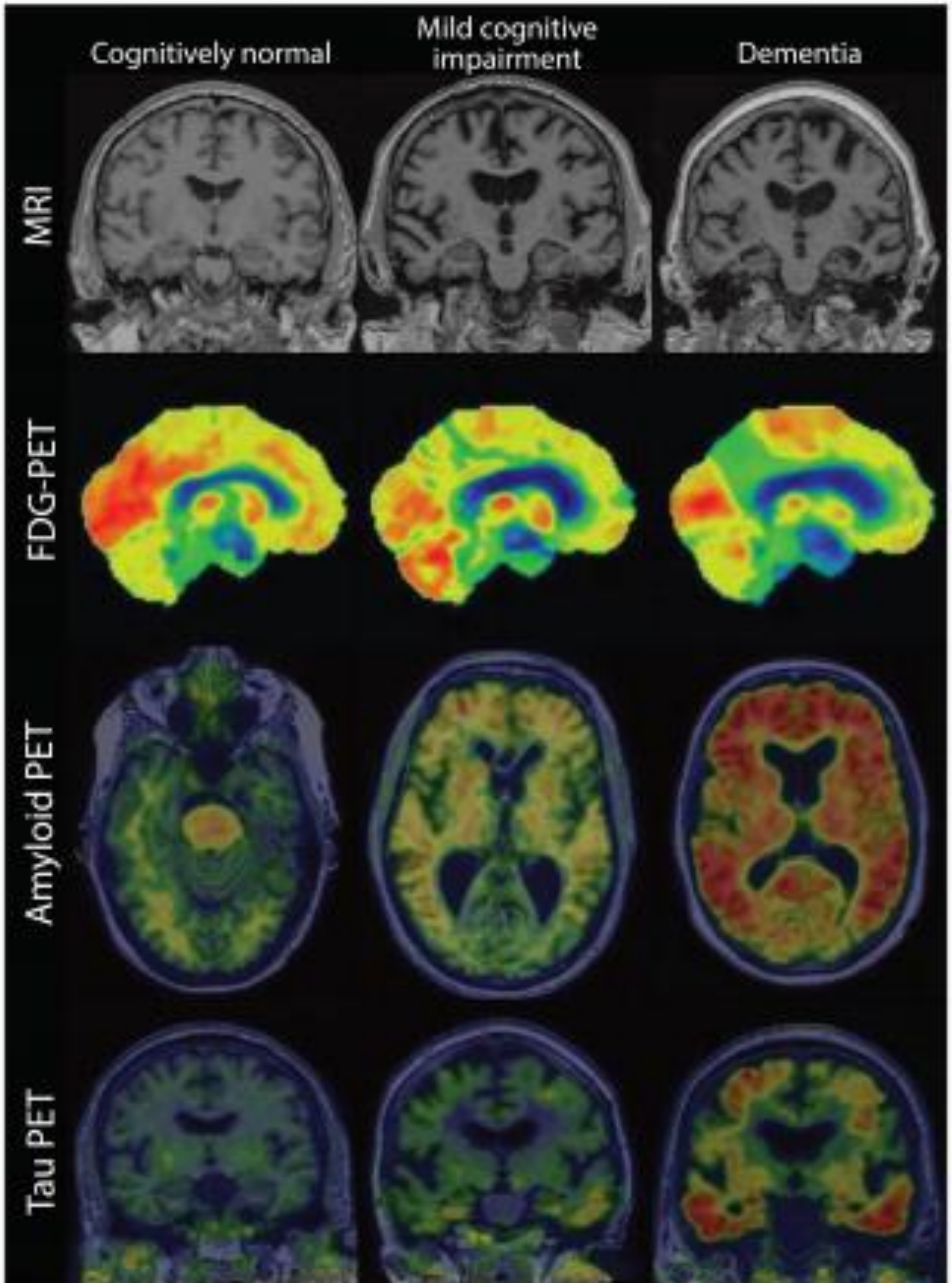
Objective: Detection of focal brain tau deposition during life could greatly facilitate accurate diagnosis of Alzheimer disease (AD), staging and monitoring of disease progression, and development of disease-modifying therapies.
Methods: We acquired tau positron emission tomography (PET) using ^{18}F T807 (AV1451), and amyloid-β PET using ^{11}C Pittsburgh compound B (PiB) in older clinically normal individuals, and symptomatic patients with mild cognitive impairment or mild AD dementia.
Results: We found abnormally high cortical ^{18}F T807 binding in patients with mild cognitive impairment and AD dementia compared to clinically normal controls. Consistent with the neuropathology literature, the presence of elevated neocortical ^{18}F T807 binding particularly in the inferior temporal gyrus was associated with clinical impairment. The association of cognitive impairment was stronger with inferior temporal ^{18}F T807 than with mean cortical ^{11}C PIB. Regional ^{18}F T807 was correlated with mean cortical ^{11}C PiB among both impaired and control subjects.
Interpretation: These findings suggest that ^{18}F T807 PET could have value as a biomarker that reflects both the progression of AD tauopathy and the emergence of clinical impairment.


Cognitively normal
Mild cognitive impairment
Dementia
MRI
FDG-PET
Amyloid PET
Tau PET