Making a Differential Dementia Diagnosis

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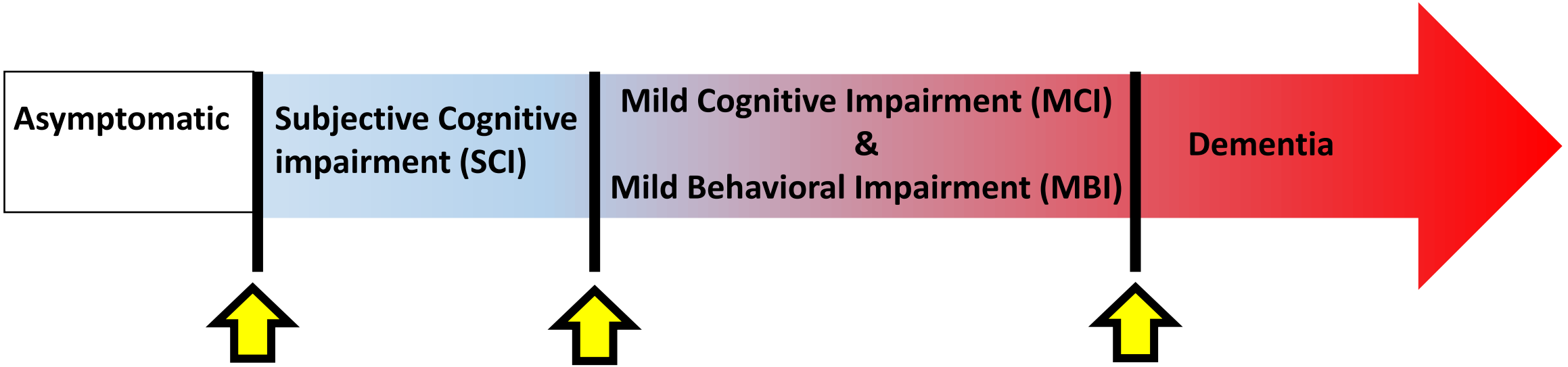
Disclosures

- Dr. Ljubenkov has no relevant financial disclosures to report
- All patients pictured have consented to allow their images to be used for education purposes.
  - **Please do not make any recordings of individual patient information**

Outline

- Dementia vs MCI
- Basic work up
- Common Causes of Dementia over age 65
  - Alzheimer's Disease
  - Lewy Body Disease
  - Vascular Disease
- Common Causes of Dementia under age 65
  - Frontotemporal Dementia Variants

Diagnoses is Broad Strokes



- **<u>New subjective cognitive symptoms</u>**
  - **Memory**
  - **Language**
  - **Personality**
- **Relative to peers**

- **<u>Objective evidence of change</u>**
  - Deficits on formal neuropsychological testing*
  - MoCA <26
  - Mini Mental Exam <24
- **Corroboration from collateral**

- **<u>Loss of Functional Independence in one of the following:</u>**
  - **In a professional sphere**
  - **In the community**
  - **At home**

Functional Independence

- **Trouble at work**
  - Coworkers worried about their performance
- **Financial management**
  - Missing bills? Falling for scams?
- **Driving**
  - Fender benders? Getting lost?
- **Managing medications**
  - Missing or doubling doses?
- **Home tasks**
  - Cooking, cleaning, shopping, using phone, using a computer, etc.
- **Self care**
  - Hygiene, missing meals, dressing

Work up for Dementia and MCI

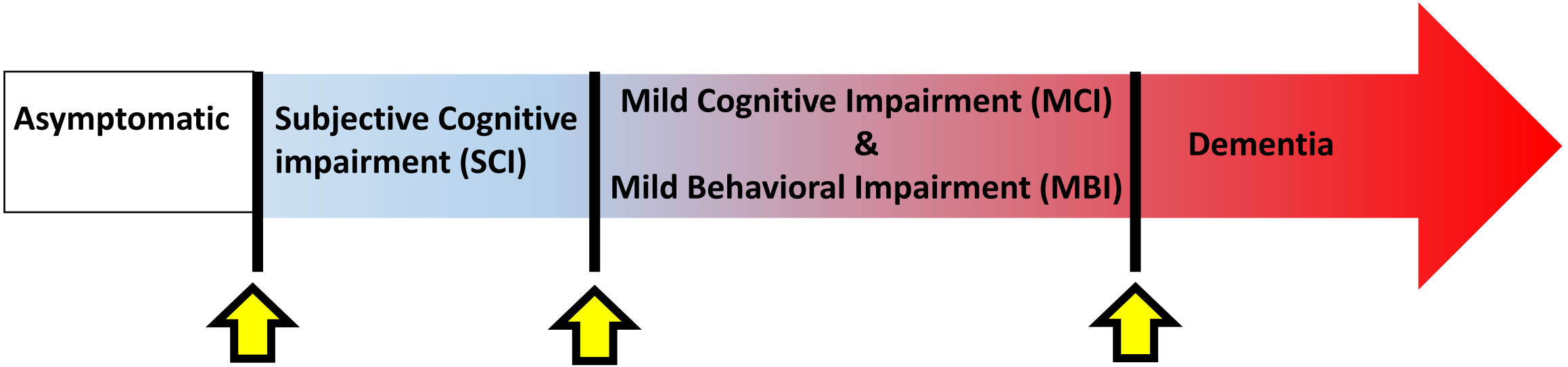
- **General medical work up**
  - **Update hearing and vision testing**
  - **Low threshold for a sleep study for OSA**
  - **Rule out delirium**
    - CBC, LFTs, BMP, UA
    - Review med list for anticholinergic and sedative medications
- **Reversible dementia labs**
  - TSH (+ Free T4)
  - B12 (+ MMA)
  - HIV and Syphilis Serology
- **Head imaging**
  - Non-contrast MRI >>> CT Head

Pharmacotherapy: What to Avoid in Elders

- **Anticholinergic medications**
  - Antihistamines
  - Central acting anti-muscarinics: (oxybutynin, etc.)
  - Tricyclic anti-depressants
  - Scopolamine
- **Over sedation**
  - Opioid abuse
  - Benzodiazepines
- **Antipsychotics in Lewy body disease**
- **Polypharmacy in general**

K Alagiakrishnan: *An approach to drug induced delirium in the elderly. BMJ 2004*

Diagnoses is Broad Strokes



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Pathology vs Clinical Syndrome (Phenotype)

“Selective vulnerability”

Functional Brain Anatomy

Pathological Entities

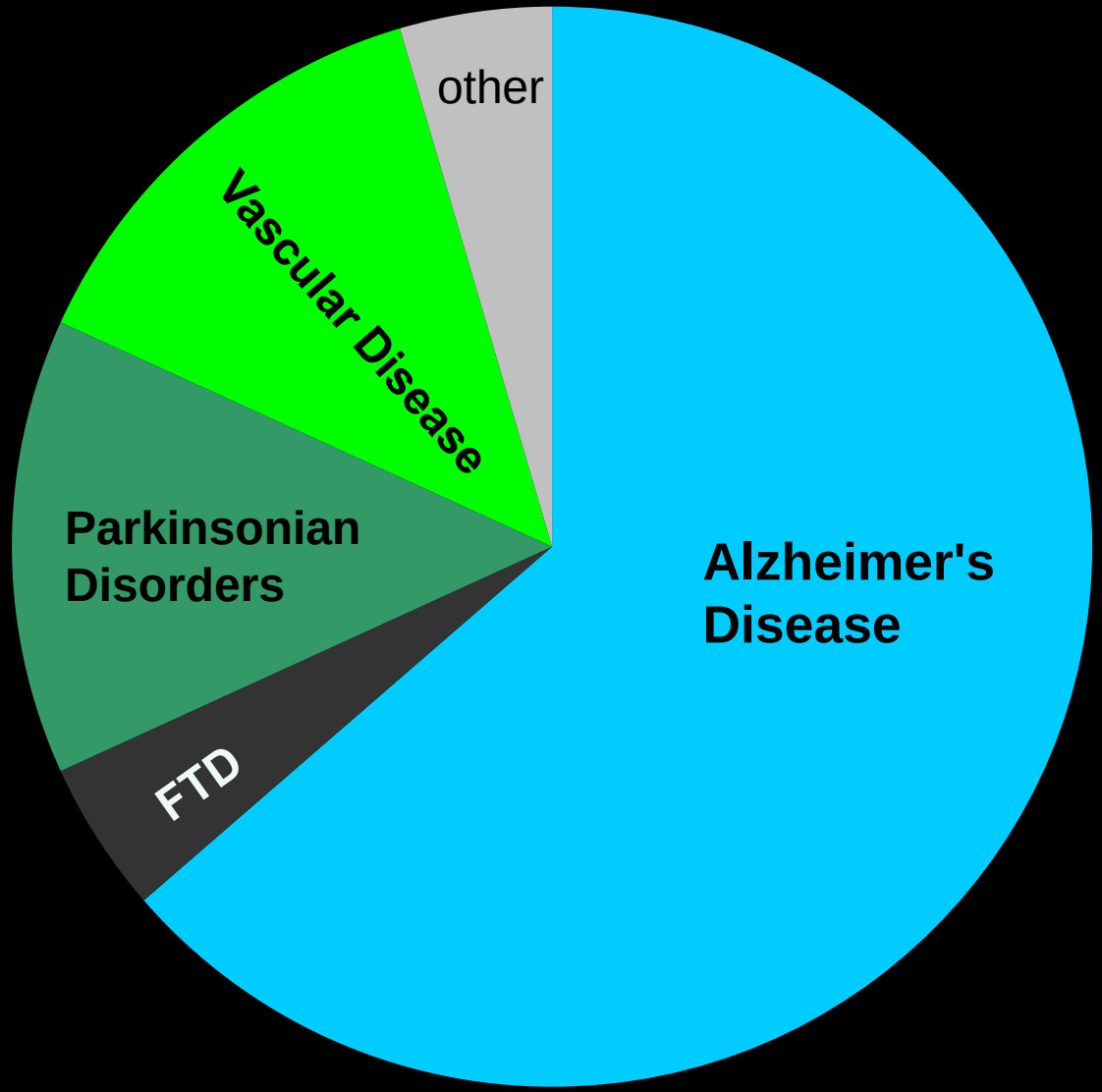
- Alzheimer's disease (tau and amyloid beta)
- Lewy Body Disease (alpha-synuclein)
- Frontotemporal Lobar Degeneration (tau, TDP-43, FUS, etc.)
- Vascular disease

- **Specific Brain Regions**
- **Specific Brain Networks**

Clinical Syndromes

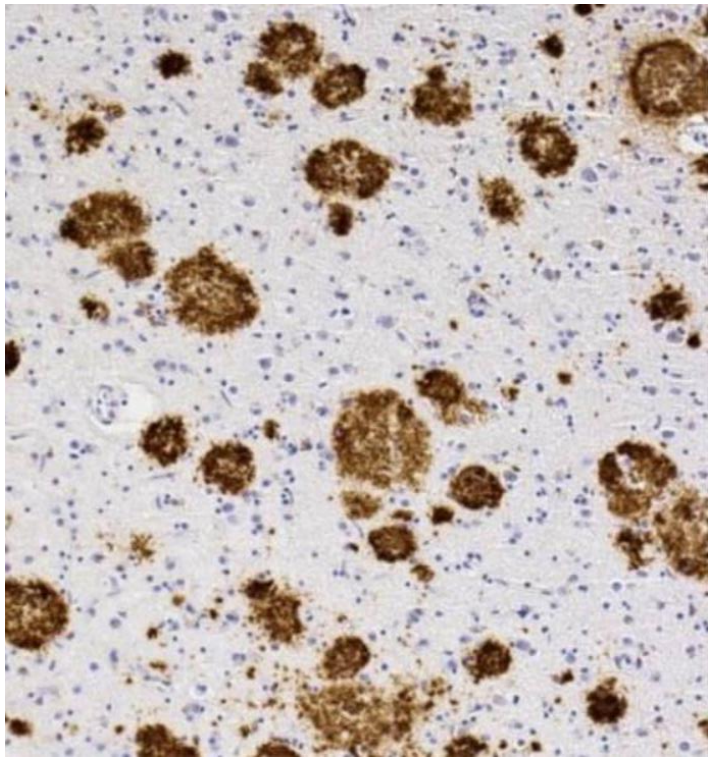
- Amnestic Syndrome
- bvFTD
- PPA (nfvPPA, svPPA, lvPPA)
- PCA
- Lewy Body Dementia Syndrome

Dementia over 65 years (95% of all dementia)

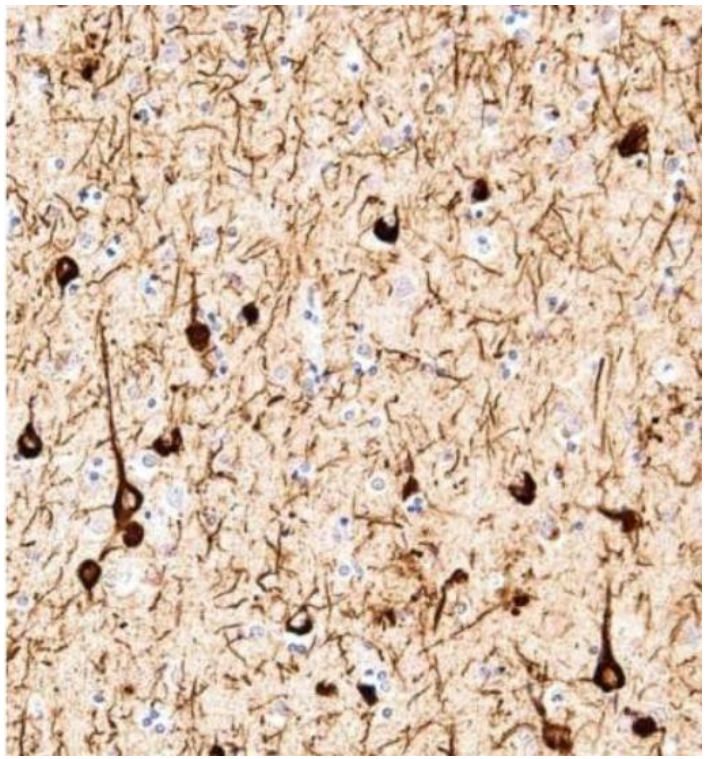


Slide courtesy of David Knopman, MD, at Mayo

A Review of Alzheimer's Disease Pathology



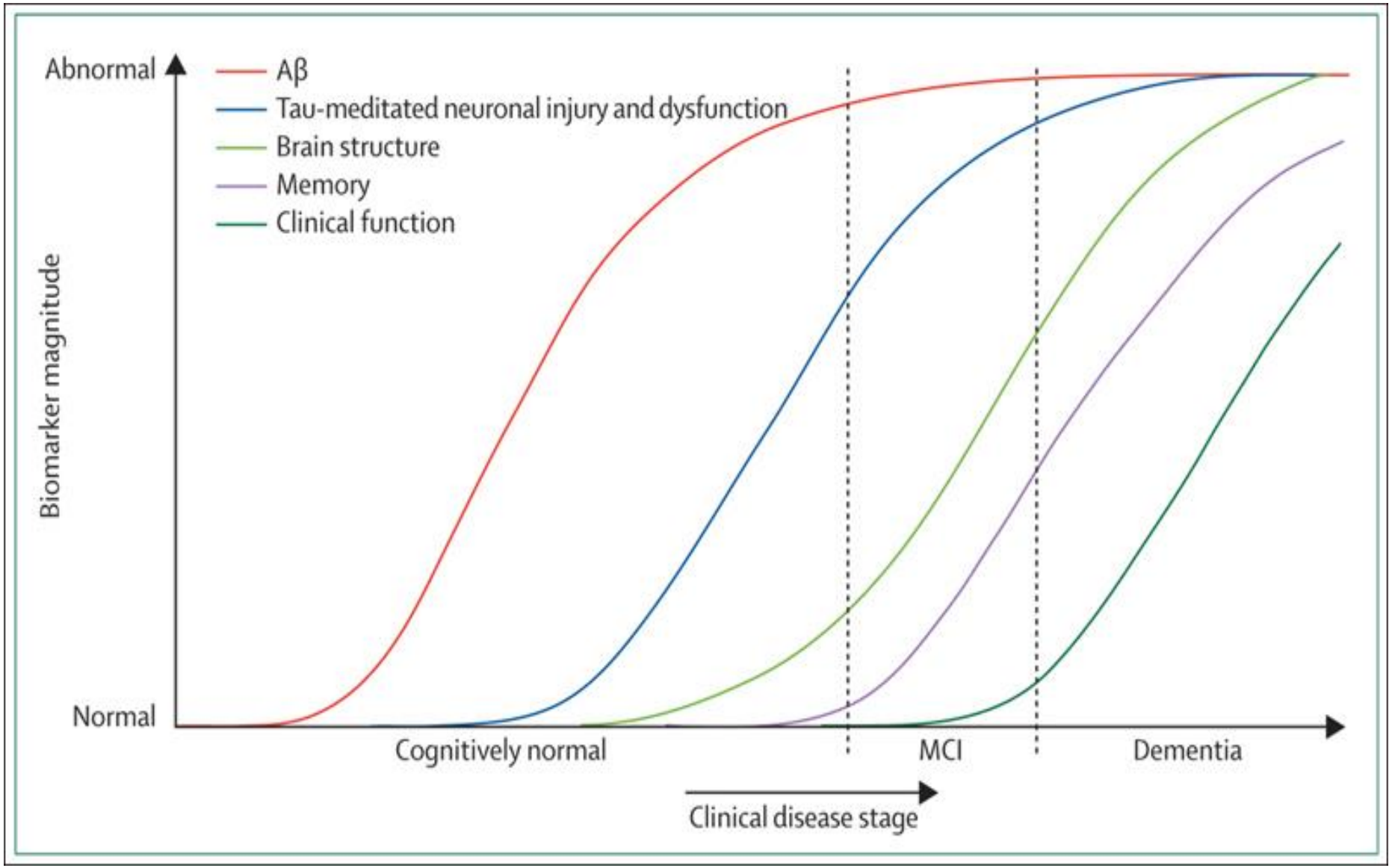
Amyloid-beta plaques



Hyperphosphorylated tau tangles

Jack et al, NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease, Alzheimers Dement. 2018

Alzheimer's Disease



Jack et al, Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurology, 2010

A (amyloid beta) T (tau) N (neurodegeneration)

A: Amyloid Beta Biomarkers

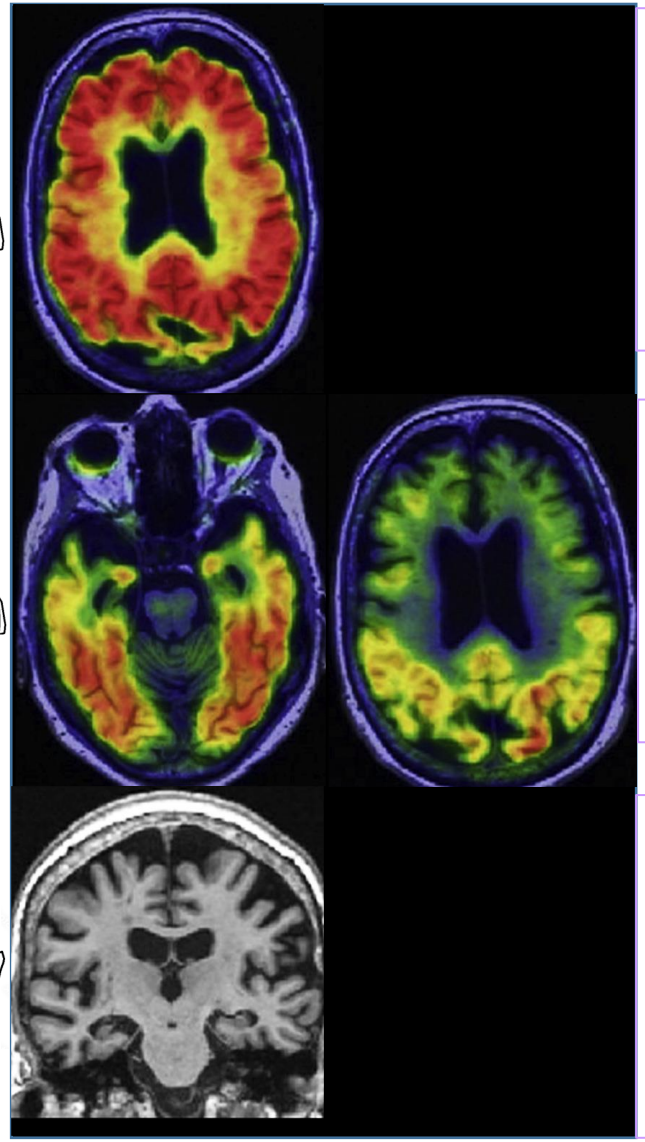
- Amyloid PET
- CSF Amyloid Beta***
  - Low Aβ42
  - (Low Aβ42/Aβ40 Ratio)
- Blood Aβ42/Aβ40 Ratio?

T: Tau Biomarkers

- Tau PET
- High CSF p-tau
- High plasma p-tau (181 or 217)

N: Neurodegeneration

- MRI: Hippocampal Atrophy
- FDG PET: temporal-parietal hypometabolism
- CSF total tau
- (plasma and CSF NfL)



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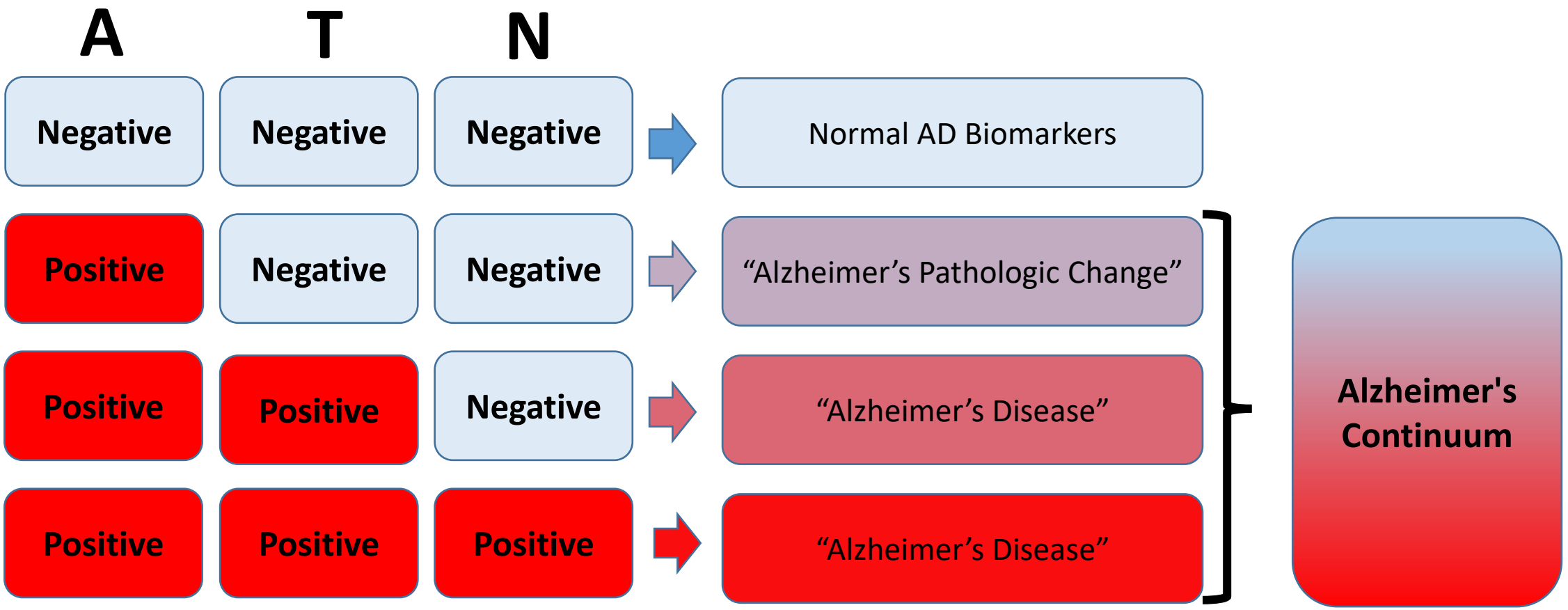

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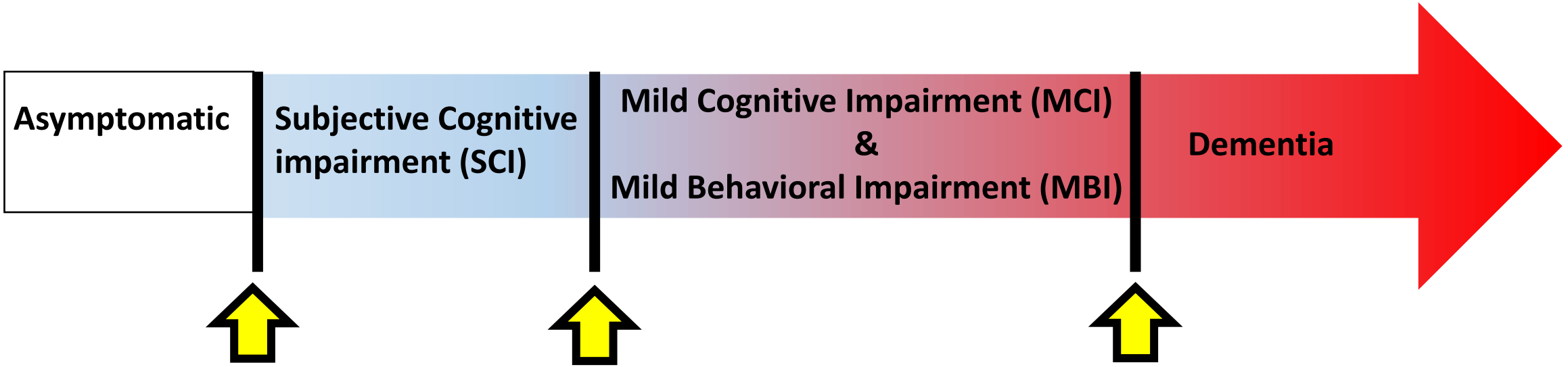

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When to suspect Alzheimer's Disease

- Insidious (not rapid) in onset
- Clear cut history of decline
- **Memory loss a core salient feature** (new worse than old)
  - Excessively repetitive questions or story telling
  - Trouble with appointments (date, time, etc.)
  - Relying heavily on notes, calendar, and other people to remember information
  - Misplacing items is a regular occurrence and disruptive to daily schedule

McKhann GM, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guideline for Alzheimer's disease. Alzheimer's & Dementia 2011; 7: 263-69.

Finalizing an Alzheimer's Disease Diagnsosis

<u>Probable AD dementia with evidence of the AD pathophysiological process</u>

- Core criteria for probable AD dementia (previous slide)
- Additionally ATN biomarker data
  - **Emphasis on presence of Amyloid Beta to determine “AD Continuum”**

McKhann GM, et al. The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guideline for Alzheimer’s disease. Alzheimer’s & Dementia 2011; 7: 263-69.

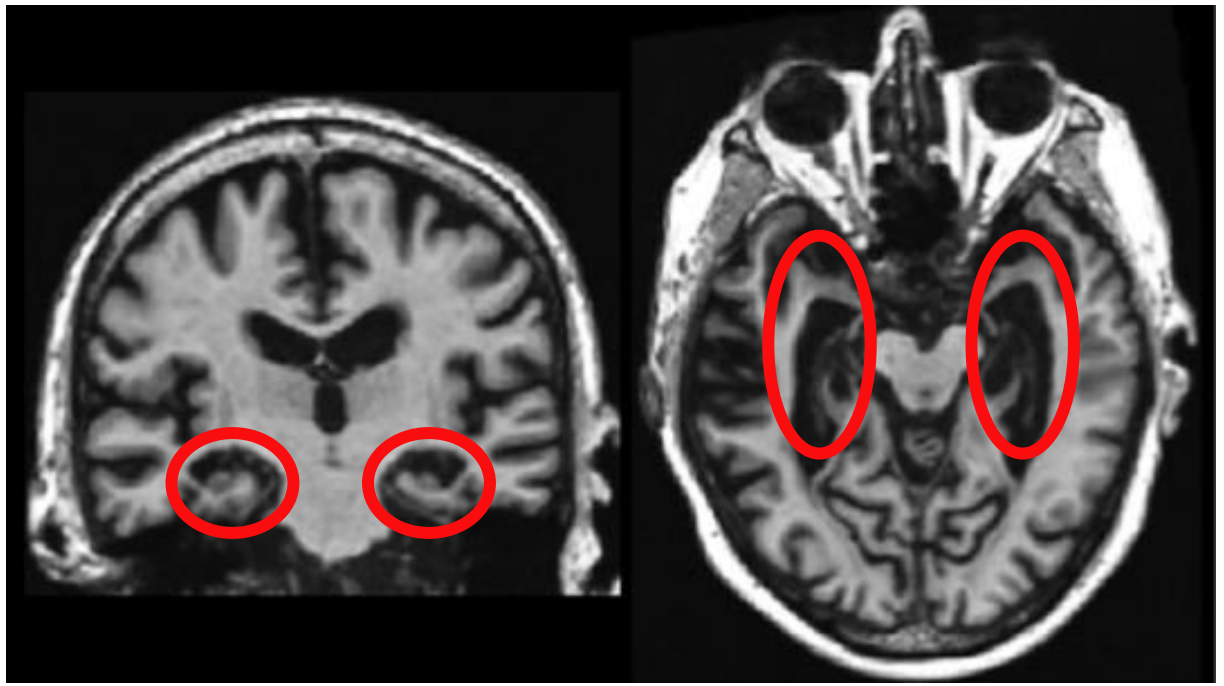
Amnestic Clinical Syndrome = Hippocampal Pathology
(not always Alzheimer's disease)

91 yo male with prominent memory loss and functional decline

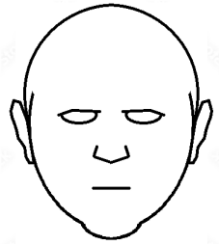
A	T	N
Amyloid PET+	Tau negative	Hippocampal atrophy

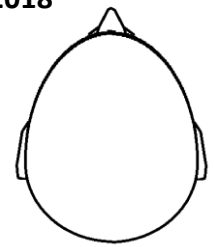
- "Alzheimer's continuum" but not confirmed evidence of "Alzheimer's disease"

- What is going on?
  - Limbic-predominant age-related TDP-43 encephalopathy (LATE)
  - Argyrophilic Grain Disease (AGD)
  - Forms of FTLD



Picture from Jack et al, Alzheimers Dement. 2018





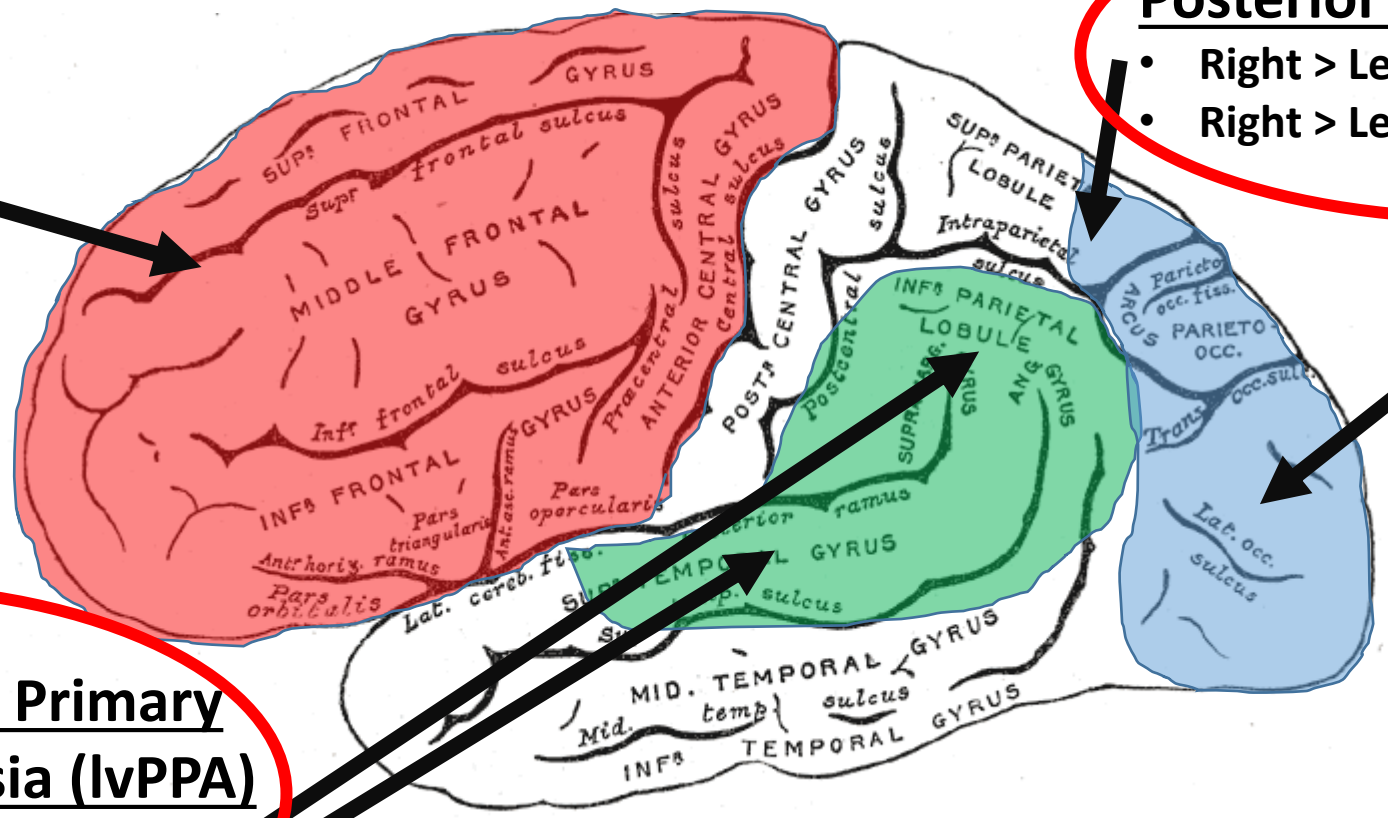
Atypical Alzheimer's Disease = Atypical Tau patterns

Frontal AD

- Frontal Lobes
- Resembles bvFTD

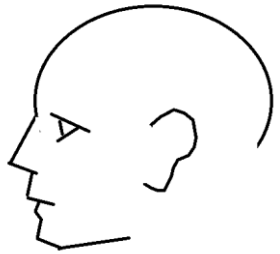
Posterior Cortical Atrophy

- Right > Left Parietal Lobes
- Right > Left Occipital Lobes



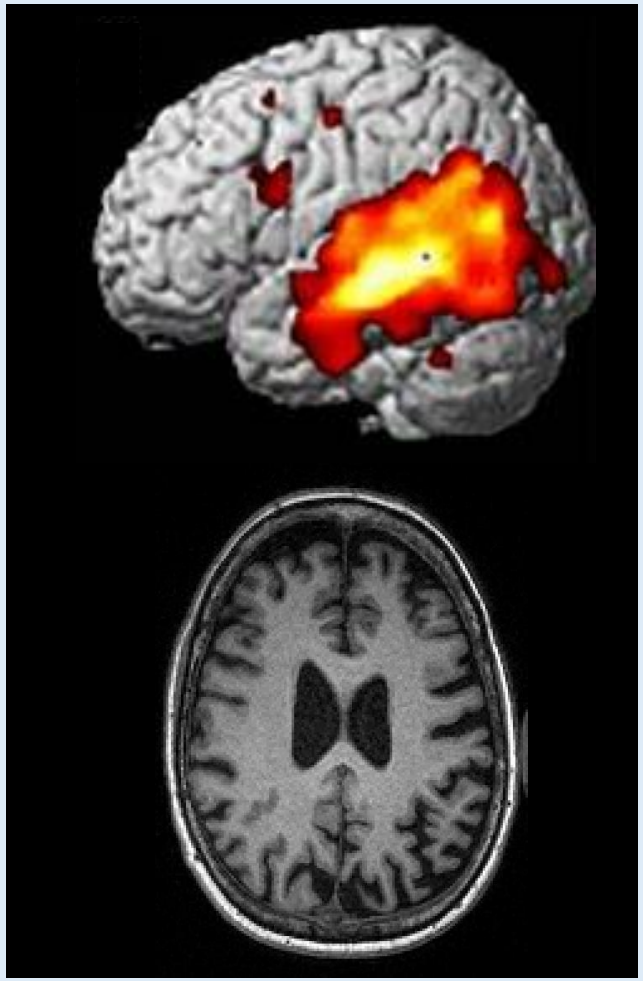
Logopenic Variant Primary Progressive Aphasia (lvPPA)

- Superior Parietal Lobule
- Left Superior Temporal Lobe



Language Variant of Alzheimer's Disease
"Logopenic Variant Primary Progressive Aphasia (lvPPA)"

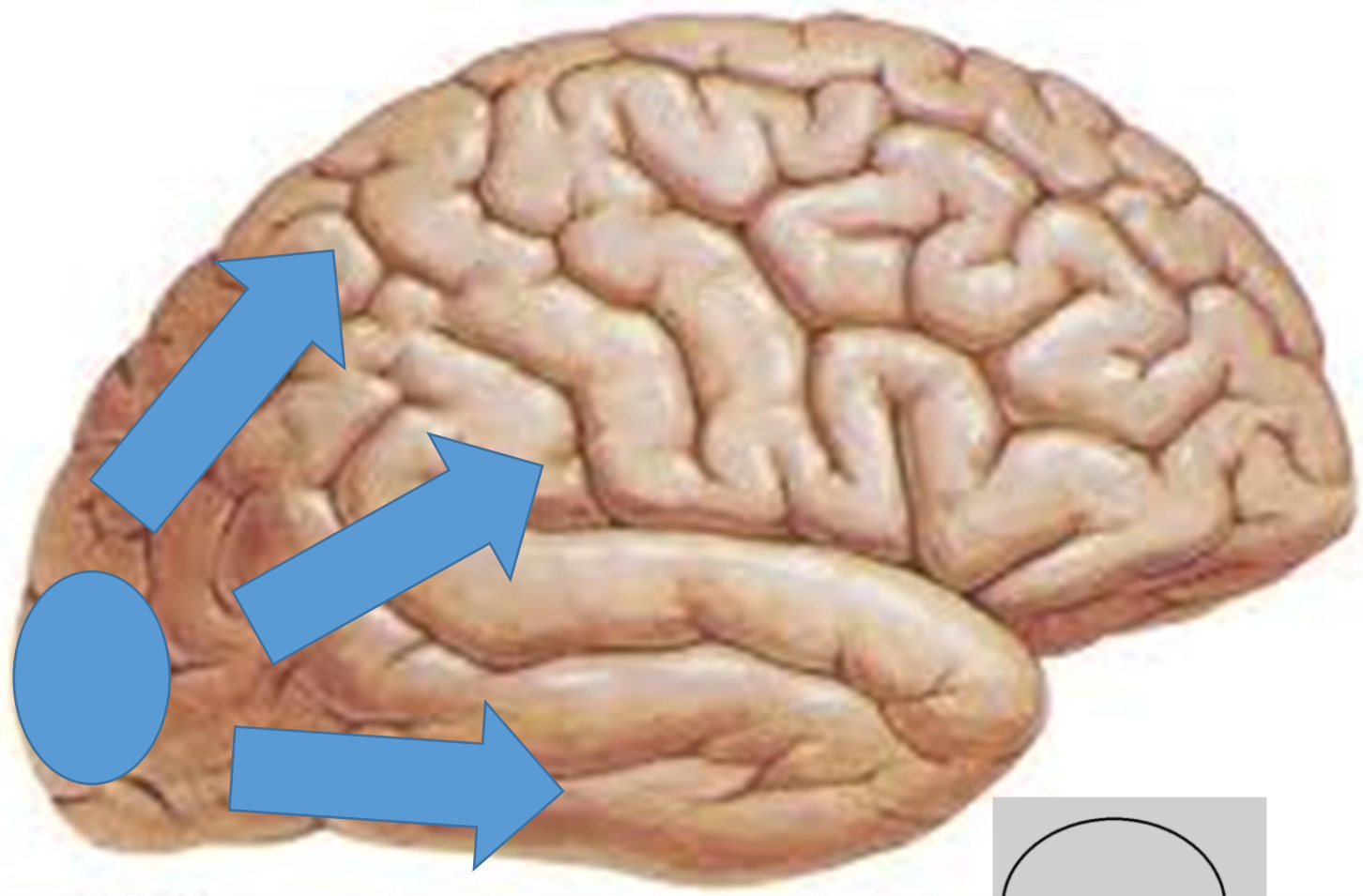
- **Language is the first and most disabling issue**
- **Impaired single word retrieve issue**
  - It is very hard to come up with a word
  - Conceptually know what they want to say
  - Vague speech
    - Pausing for words
    - Circumlocution
- **Spared comprehension/knowledge of single words**
- **Paraphasic errors "staying the wrong words and syllables"**
  - Semantic paraphasias (ear → eye)
  - Phonemic paraphasias (pineapple → dinetapple)
  - "Clean" sounds that sound like real words
    - Intact "motor speech"
- **Impaired repetition of sentences and phrases**
- **Lots of short "islands of fluency" with intact grammar and many pauses to find words**



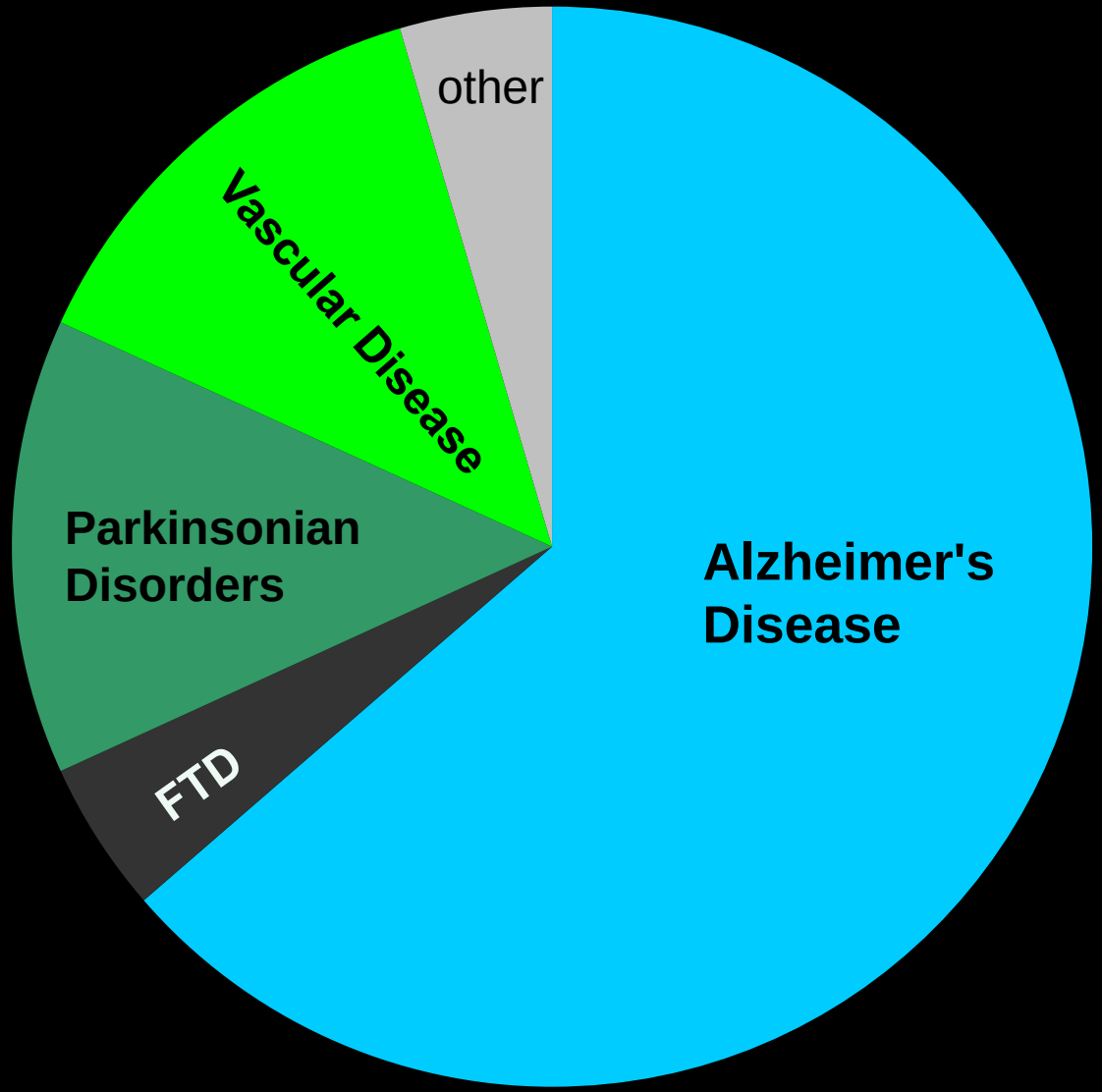
Gorno-Tempini ML, et al. Classification of primary progressive aphasia and its variants. Neurology. 2011

Posterior Cortical Atrophy (PCA)

- **Primary vision intact but visual processing is impaired**
- **Visual Neglect**
- **Apraxia**
- **"Where" Path**
  - Hard to guide eyes and limbs using vison
  - Understanding spacial relationships
- **"What" Path**
  - Visual agnosias
  - Prosopagnosia
- **Gerstmann syndrome**
  - Acalculia, Agraphia
  - Left-Right issues
  - Finger agnosia

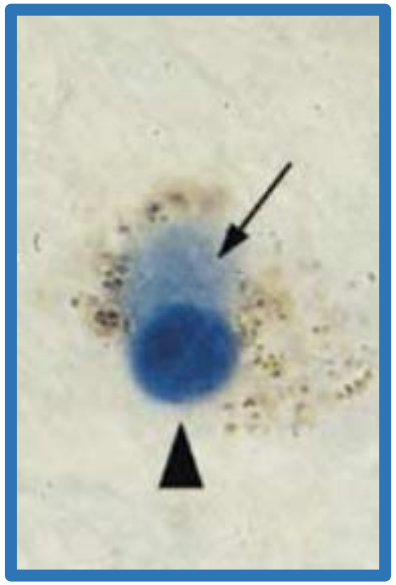


Dementia over 65 years (95% of all dementia)

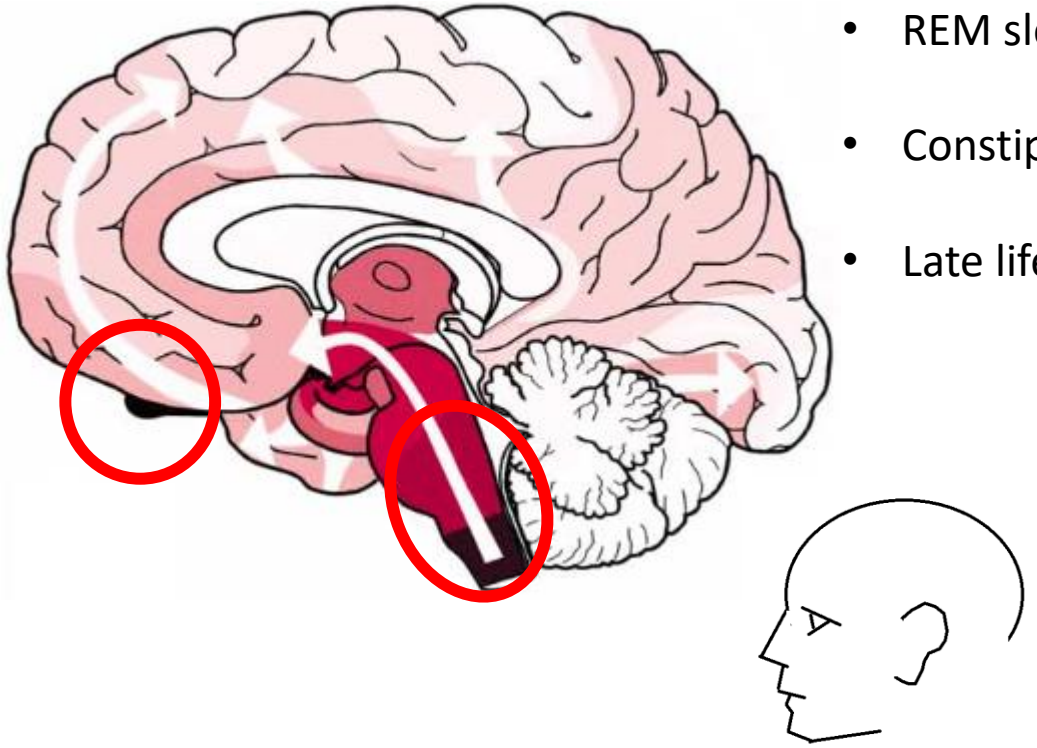


Slide courtesy of David Knopman, MD, at Mayo

Lewy Body Disease



A Lewy Body

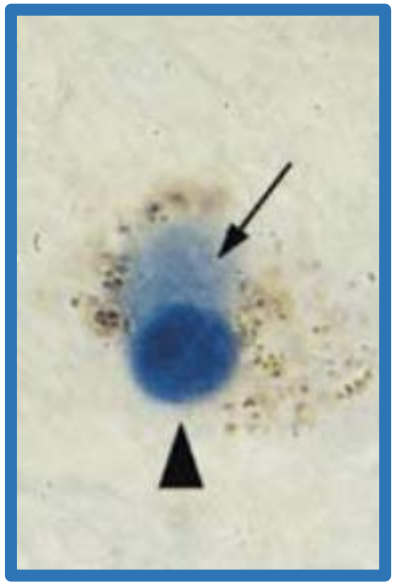


Clinical Prodrome

- Loss/decline of sense of smell
- REM sleep behavior disorder
- Constipation
- Late life depression/anxiety

Braak et al, Neurobiology of Aging, 2003

Lewy Body Disease



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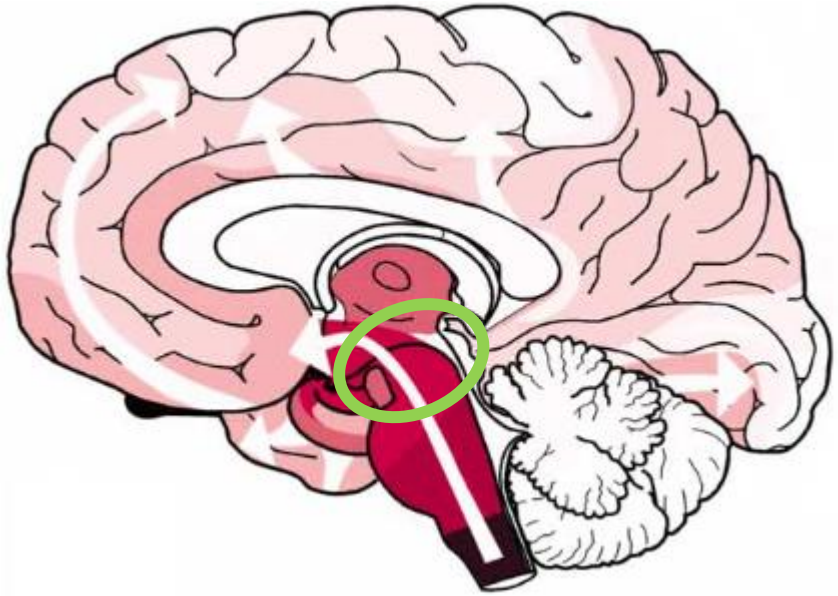


Midbrain Lewy Bodies Cause
"Parkinson's Disease" (TRAP clinical features)

T = Tremor (pill rolling, prominent at rest)

R = Rigidity

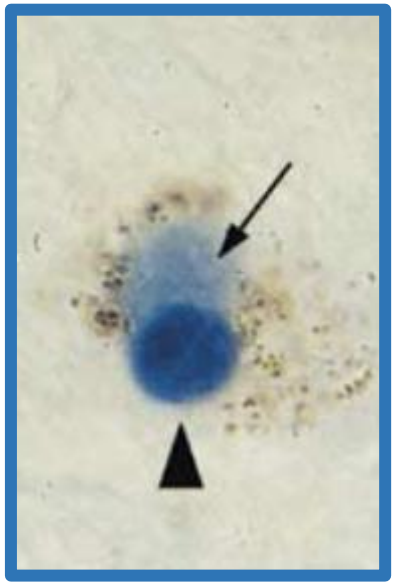
A= Akinesia (really Bradykinesia)

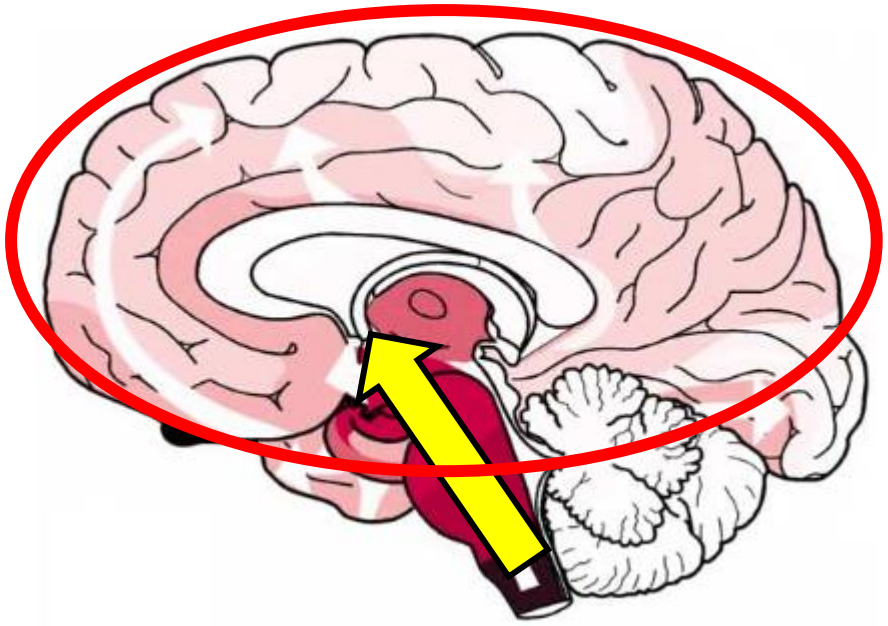
- Slow movements
- Masked face
- Shuffling steps
- Decreased arm swing

P= Postural Instability (late in disease)

Braak et al, Neurobiology of Aging, 2003

Lewy Body Disease





“Lewy Body Dementia”

- Cognitive changes first or within 1 year of parkinsonism
- Early cortical involvement

“Parkinson’s Disease Dementia”

- Parkinsonism over 1 year before cognitive changes

Braak et al, Neurobiology of Aging, 2003

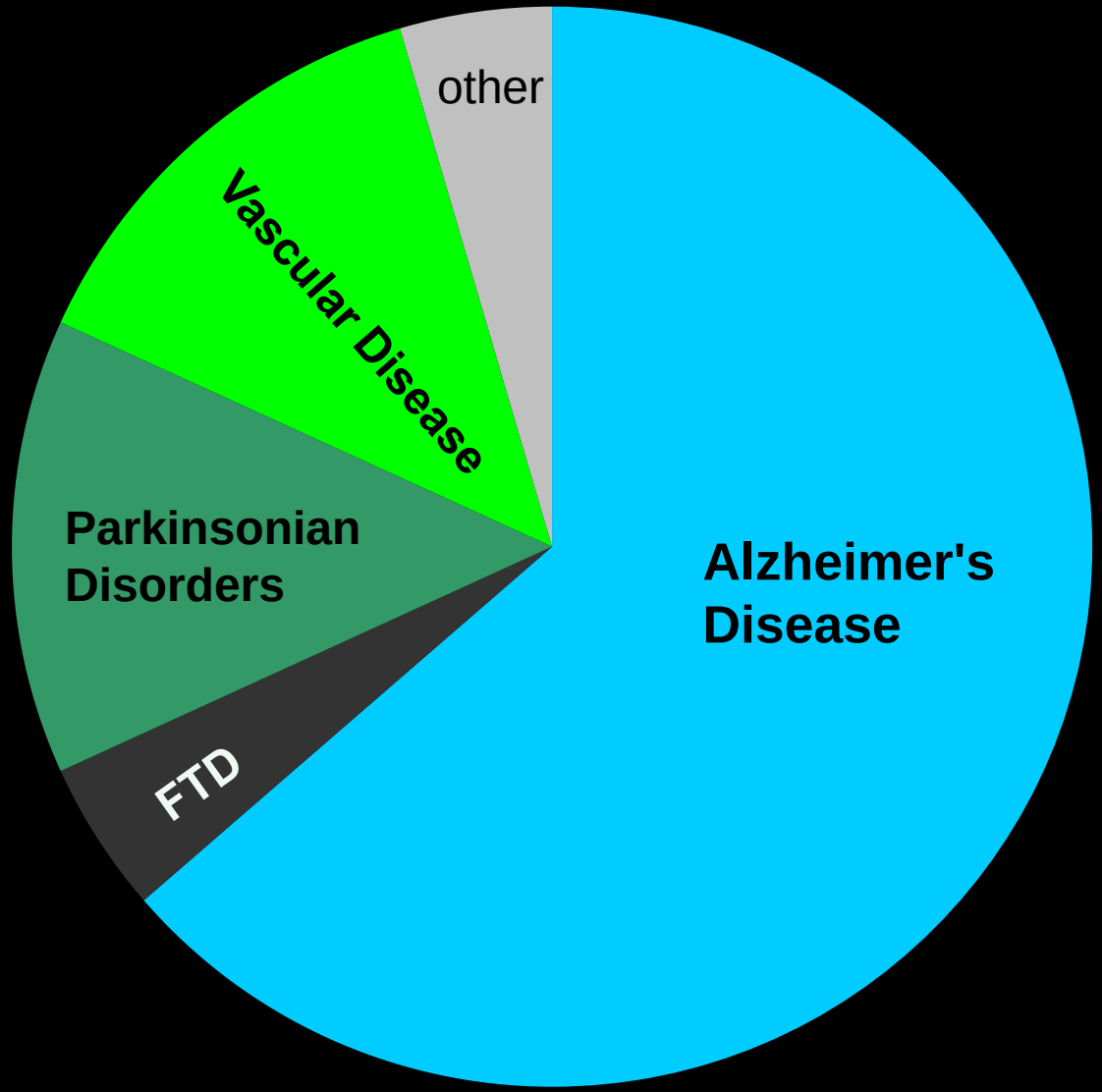
Clinical Feature of Lewy Body Dementia

- **Parkinsonism**
- **Fluctuations**
  - Pronounced waxing/waning over minutes, hours, days, or weeks
- **Hallucinations**
  - Commonly formed hallucinations of animals or people
  - May start as extra-campine (a feeling of a person over their shoulder)
- **Deficits attention, executive function, visuospatial ability on testing**
- **Other Supportive Features**
  - Severe sensitivity to antipsychotics
  - Delusions (people living upstairs)
  - Visual misperceptions/ illusions
  - Dysautonomia (orthostatic hypotension)

Visual illusions in DLB (80%)

Ebersbach, Movement Disorders, 2003

Dementia over 65 years (95% of all dementia)



Slide courtesy of David Knopman, MD, at Mayo

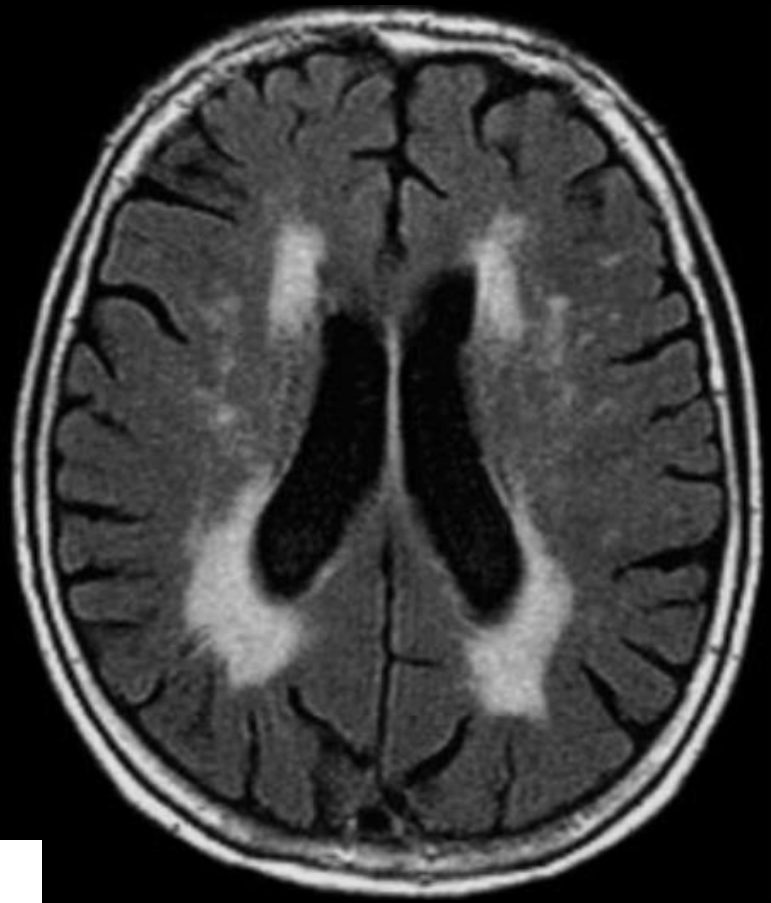
Vascular Cognitive Impairment (VCI)

Diagnoses under 2 scenarios:

1) **A patient has a stroke → Cognitive symptoms immediately follow**
   - Symptoms may be unique to the brain area: aphasia, blindness, weakness, etc.
2) **Cognitive symptoms noted first → vascular disease on MRI**
   - May be small vessel changes (not a large stroke)
   - Often executive symptoms
     - Attention, planning, multitasking, organization

Smith EE. Clinical presentations and epidemiology of vascular dementia. Clin Sci 2017

Ischemic Small Vessel Disease on T2 FLAIR



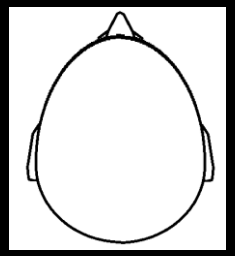


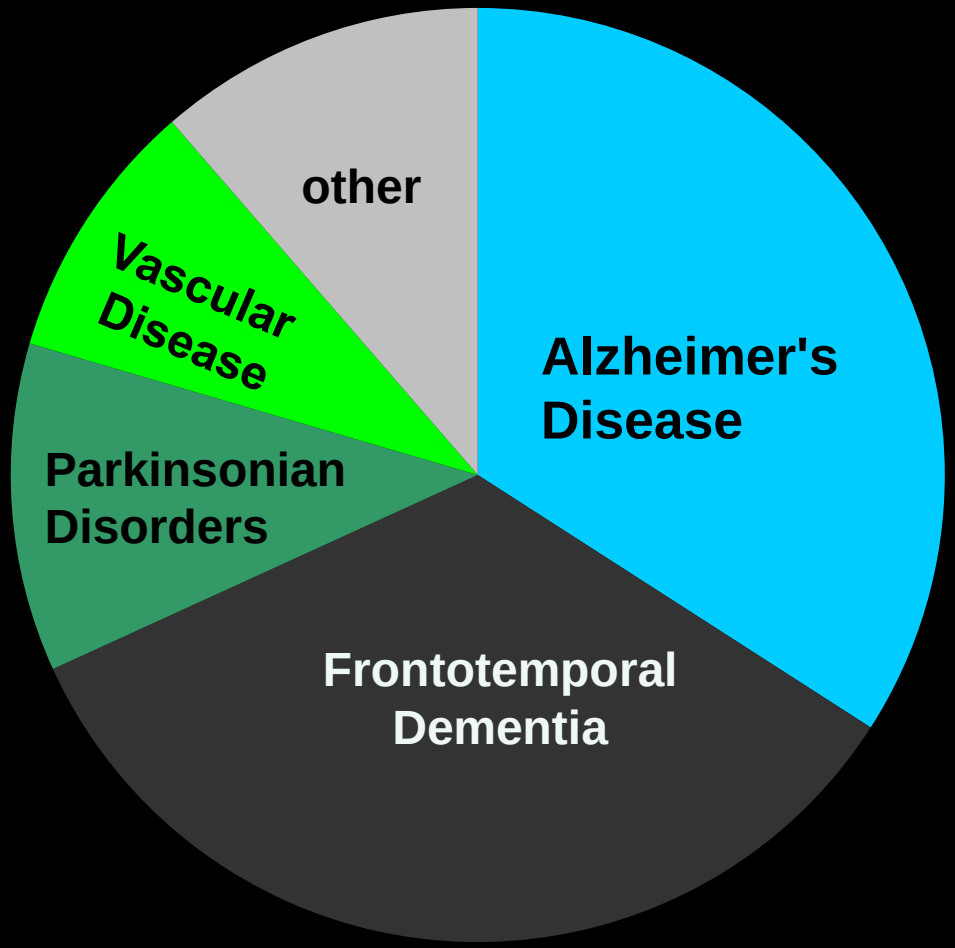
Image from Fazekas et al. Cerebrovasc Dis 2002

VCI Continued..

- **<u>Vascular risk factors</u>**
  - **Advanced age, hypertension, high cholesterol, diabetes, smoking, CAD, A.fib**
- **<u>Common Features</u>**
  - Executive dysfunction: Attention, organization, multitasking…
  - Focal feature attributable to the stroke
    - Aphasia, vision loss, weakness, etc.
  - Psychiatric features:
    - depression very common
    - irritability very common
  - Parkinsonian gait features are common

Smith EE. Clinical presentations and epidemiology of vascular dementia. Clin Sci 2017

Dementia under 65 years (~5% of all dementia)

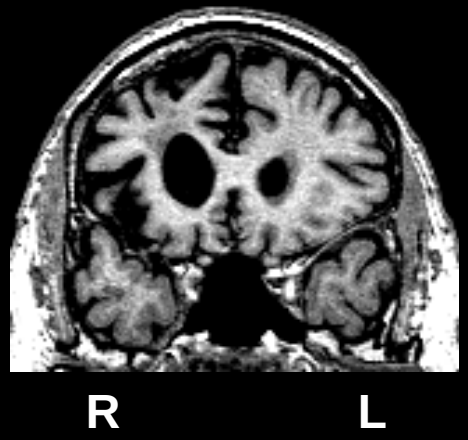


Slide courtesy of David Knopman, MD, at Mayo

3 traditional variants of frontotemporal dementia

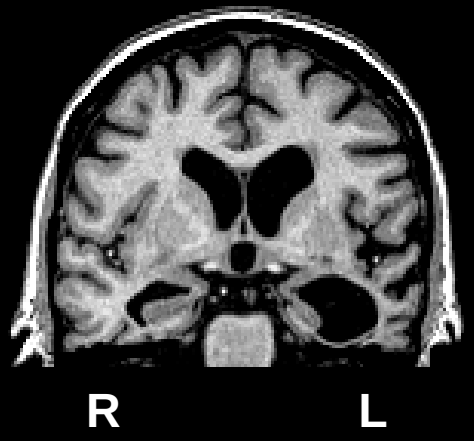
Atypical Alzheimer's

Behavioral Variant FTD (bvFTD)

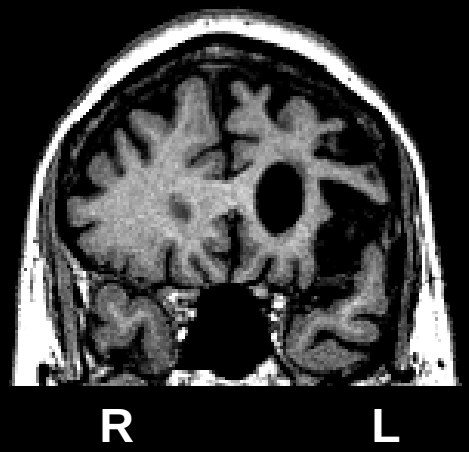


Primary Progressive Aphasias (PPA)

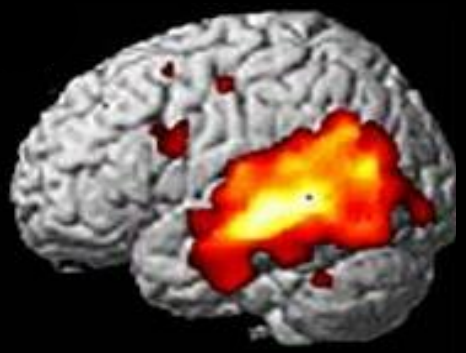
Semantic variant (svPPA)



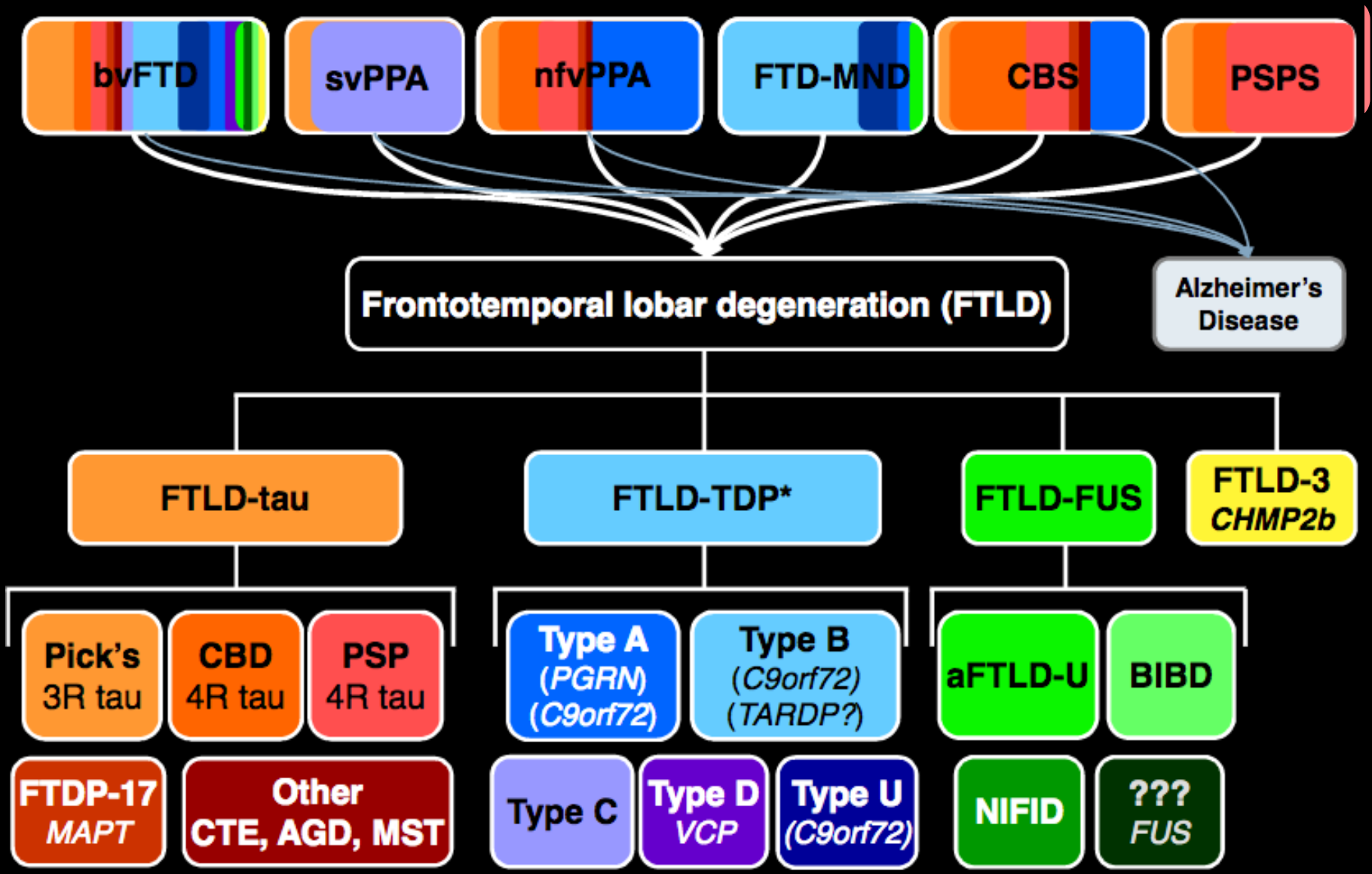
Nonfluent variant (nfvPPA)



Logopenic variant (lvPPA)



Clinical syndromes & FTLD Pathology



Courtesy of Bill Seeley

Behavioral Variant Frontotemporal Dementia (bvFTD)

<u>At least 3 of the following core features</u>:

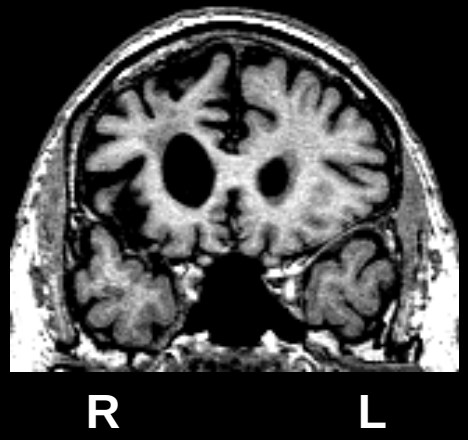
- **Apathy**
- **Disinhibition**
  - Loss of social decorum
  - Rash or impulsive
  - Loss of disgust
- **Loss of sympathy or empathy**
- **Compulsive/ritualistic behaviors**
- **Hyperorality/altered food preferences**
- **Predominately executive dysfunction on formal testing**

Rascovsky et al. Sensitivity of revised diagnostic criteria for the behavioral variant of frontotemporal dementia. Brain 2011

3 traditional variants of frontotemporal dementia

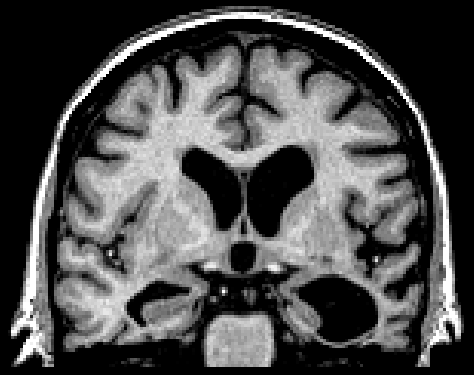
Atypical Alzheimer's

Behavioral Variant FTD (bvFTD)



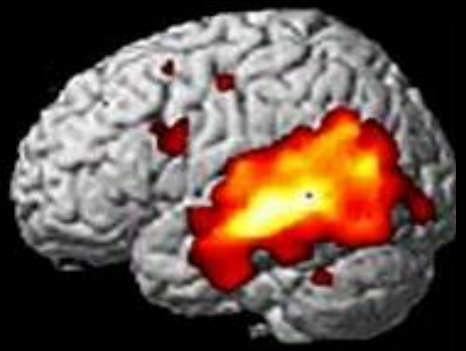
Primary Progressive Aphasias (PPA)

Semantic variant (svPPA)



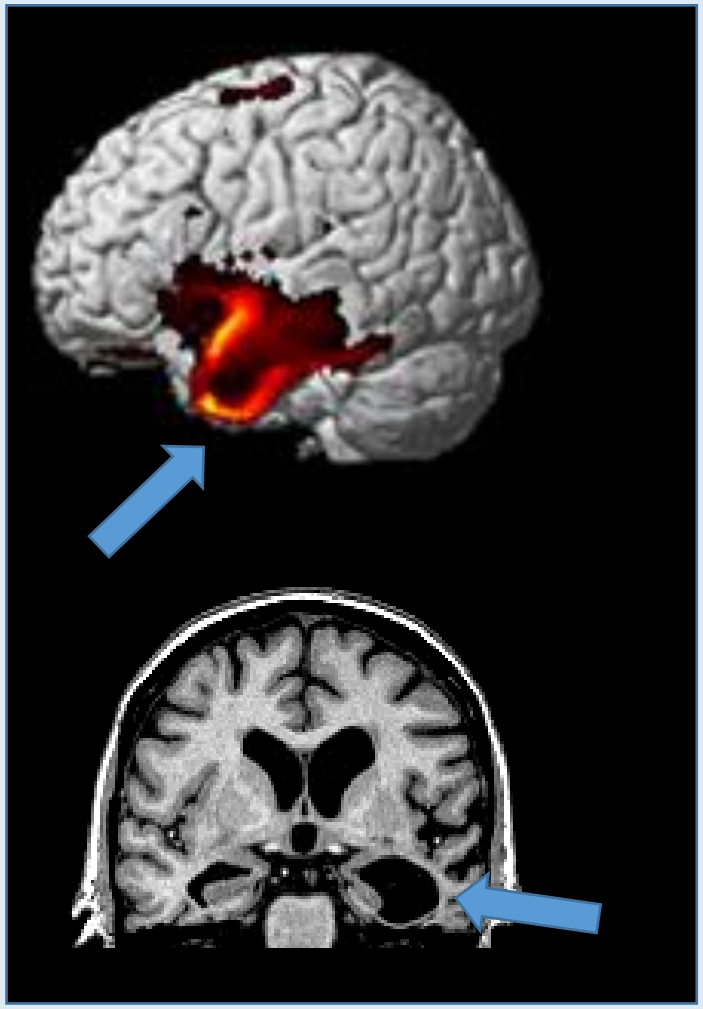
Nonfluent variant (nfvPPA)

Logopenic variant (lvPPA)



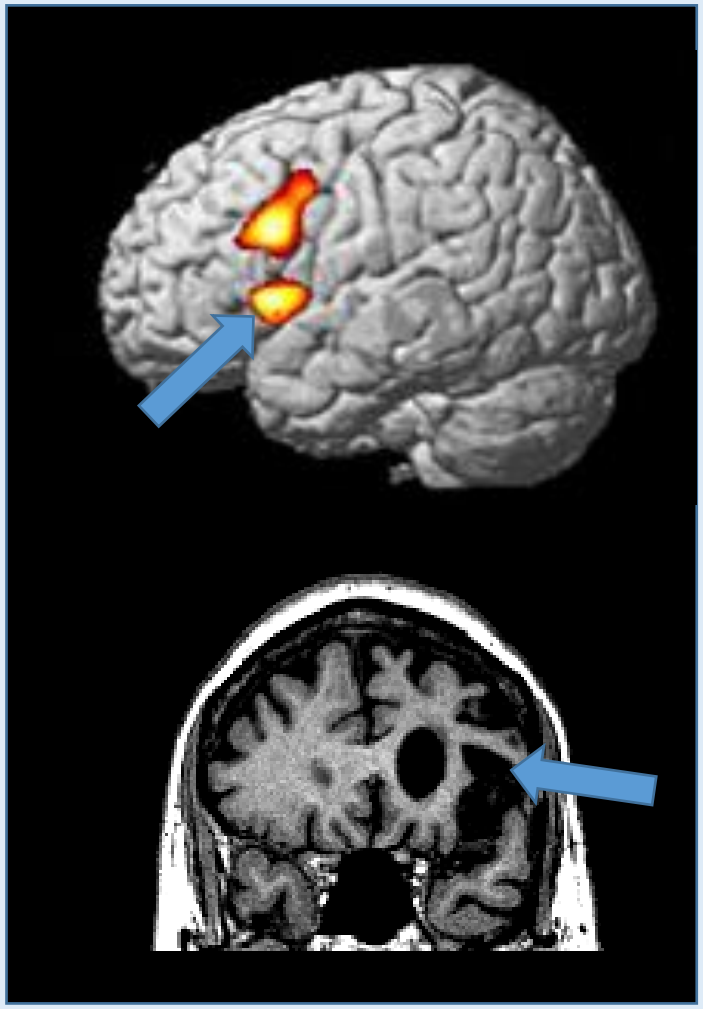
Semantic Variant Primary Progressive Aphasia (svPPA)

- Poor naming
  - Poor knowledge of the words themselves!
  - Lose knowledge of the object, people, etc.
- Very fluent vague speech
- Intact repetition



Nonfluent/Agrammatic Variant Primary Progressive Aphasia (nfvPPA)

- **Effortful/halting speech**
  - Apraxia of speech (inconsistent speech sounds)
  - Their errors are hard to spell
- **Impaired grammar**
  - Telegraphic speech
  - Hard to interpret grammatically complex sentence ("The little boy was kicked by the girl")
- **Intact knowledge of words and objects**



Take home points

- The term “Alzheimer's disease” is shifting and now based on amyloid and tau protein biomarkers
- Symptomatic Alzheimer's disease usually cases memory symptoms first, but can present with behavioral, language, and visuospatial symptoms
- Lewy body disease commonly starts with prodromal features (dream enactment, depression, constipation, loss of smell)
- Parkinson’s disease and Lewy body dementia exist on a spectrum, depending on the regions of brain involvement (and timing of parkinsonism).
- Lewy Body Dementia involves prominent fluctuations and formed visual hallucinations
- Frontotemporal dementia is a major cause of dementia under 65 and typically presents with behavioral or language changes (with PPA variants distinct from the PPA variant of Alzheimer's disease)

Thank You!

- Any questions?