Dementia

David Weidman, MD

Dec. 4, 2018

Goals of Presentation

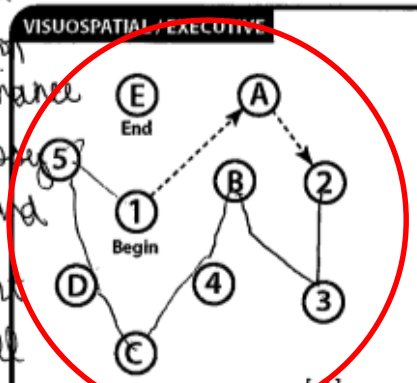
1. Define MCI, 4 criteria
2. Define dementia, diagnostic criteria
3. Review appropriate evaluation of MCI and dementia, with cognitive screening tests, laboratory and imaging tests
4. Compare and contrast AD, LBD, FTD, Vascular dementia and NPH

Case 1

- 77 year old male, retired physician (practiced for 35 years), presents to your office with his wife. They both report cognitive difficulties over about 10 months:
  - Very nervous to update his own will
  - Can't recall/retain as much; spouse: "a lot slips by"
  - Close acquaintances and friends now often called "that person"
  - Word finding difficulty more generally
  - Has insight: knows he's repeating to/for himself, such as looking in his travel bag before a trip, over and over, insecure he's packed a cell phone charger
  - Drove to a golf course for a game, halfway there forgot that event, forgot where he was headed, went home, wife had to notify the other players
  - May make a wrong turn driving but not correct quickly, limiting driving alone
  - Fears he will lose ability to help manage finances
- He does not drink or smoke
- Physical, Neurological exam (non-cognitive; elemental) both normal/unremarkable
- Lab work (CMP, CBC, TSH, B12 level normal)

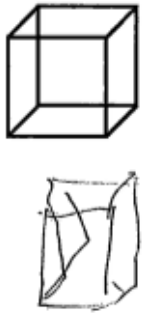
DOB/A
Evaluation D
Clinician Name: Weidman

VISUOSPATIAL / EXECUTIVE



[0]

Copy cube



[0]

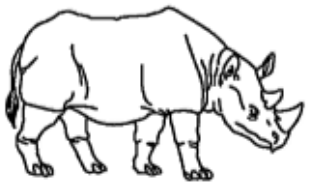
Draw CLOCK (Ten past eleven) (3 points)

[1] Contour [1] Numbers [0] Hands

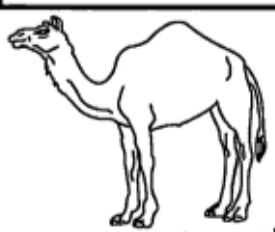
POINTS: 2/5

NAMING

lion [1]



Rhino [1]



camal [1]

3/3

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
1st trial	√	√	√	√	√
2nd trial	√	√	√	√	√

No points

ATTENTION

Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [1] 2 1 8 5 4

Subject has to repeat them in the backward order [0] 7 4 2 2 4

1/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[1] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

1/1

Serial 7 subtraction starting at 100 [1] 93 93 [0] 86 87 [1] 79 80 [0] 72 70 7 [1] 65 67

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

2/3

LANGUAGE

Repeat : I only know that John is the one to help today. [1]

The cat always hid under the couch when dogs were in the room. [1]

2/2

Fluency / Name maximum number of words in one minute that begin with the letter F [1] 20 (N ≥ 11 words)

1/1

ABSTRACTION

Similarity between e.g. banana - orange = fruit [1] train – bicycle [0] watch – ruler

1/2

DELAYED RECALL

Optional

Has to recall words	FACE	VELVET	CHURCH	DAISY	RED
WITH NO CUE	[0]	[0]	[0]	[0]	[0]
Category cue	X	X	X	X	X
Multiple choice cue	X	X	X	X	X

Points for UNCUED recall only

0/5

ORIENTATION

[1] Date [1] Month [1] Year [0] Day [0] Place [1] City

4/6

 Version 7.1 www.mocatest.org Normal ≥ 26 / 30

TOTAL 17/30

Mini Mental State Exam

Right Wrong Please ask the following questions, record verbatim response and check gray box for correct responses.

ORIENTATION

Total Score 22

1. *"What is today's date?"* (+/- 1) 14
2. *"What is the month?"* Jan
3. *"What is the year?"* 2015
4. *"What day of the week is it?"* MONDAY
5. *"What season is it?"* Spring
6. *"What is the name of this building?"* GOT ME OUT THAT ONE
7. *"What floor are we on?"* 3
8. *"What city are we in?"* PHX
9. *"What county are we in?"* PASS.
10. *"What state are we in?"* ARIZONA

Winter, Wednesday

Section Total 9 /10

REGISTRATION

"Listen carefully. I'm going to say three words. You say them back after I stop. Ready? Here they are..."

11. *"Pony"*
12. *"Quarter"*
13. *"Orange"*

Section Total 3 /3

"Please keep these words in mind. I'm going to ask you to say them again in a few minutes."

ATTENTION

"Please spell the word 'WORLD'." Correct any errors in spelling. *"Now spell 'WORLD' backwards."*

14. DD
15. L U
16. R R
17. O O
18. W W

Section Total 5 /5

COMPREHENSION

"Listen carefully because I'm going to ask you to do something. Take this piece of paper in your right hand, fold it in half and place it on your lap."

19. Takes in right hand Both hands
20. Folds in half
21. Places in lap

Section Total 2 /3

DRAWING

"Please copy this design." Use upper half of the back of this form.

22. Draws pentagons with all angles and lines present.

Section Total 1 /1

RECALL

"What were those three words I asked you to remember?"

23. Pony
24. Quarter
25. Orange

Section Total 0 /3

LANGUAGE

26. *"Can you tell me what this is?"* (watch)
27. *"Can you tell me what this is?"* (pen)
28. *"Repeat after me: 'No ifs, ands, or buts'."*
29. *"Read this and do what it says."* (Closes eyes)
30. *"Please write a sentence."* Use lower half of the back of this form.

Section Total 5 /5

Question 1A

- What is the present diagnosis (assume the patient is still overall independent, knows how to compensate)?
  - Amnestic MCI, single domain
  - Amnestic MCI, multiple domains
    - Memory, spatial, executive function
  - Non-amnestic MCI, meaning not memory predominant impairment
  - Vascular dementia

Question 1A
Answer

- **Amnestic MCI, multi-domain**

Mild Cognitive Impairment (MCI)

Cognitive decline more than expected for normal aging

- Cognitive decline *from a previous level of performance*
- Cognitive impairment **does not** impair everyday activities (work, IADLs, ADLs)
- Does not occur exclusively during the course of delirium
- Not accounted for by another mental disorder (depression, schizophrenia, etc.)

DSM V – Minor Neurocognitive Disorder

Cognitive Changes with Aging

- Mild changes in memory
  - decline in rate of learning new information but not in memory retention (rate of information processing slows, occasional "information overload")
- More difficulty with multi-tasking (divided attention)
- Mild word finding difficulty (especially names)
- "Sometimer's"
- Age "catching up with" longstanding ADD, depression, (longstanding compensatory strategies harder to implement)

Significant declines in cognitive function do not represent normal aging!

Evaluation of Cognitive Impairment

- Detailed history
  - Should have informant
  - Social and Family histories are important
- Examination
  - Mental status: alert, attentive, engaged, cooperative, etc
  - Non-cognitive neurological exam
  - Seeing, hearing, feeling, vital signs
- Laboratory testing
- Cognitive Testing (eg, MMSE, MoCA, “screening”)
- Imaging

Cognitive Impairment:

(Nasreddine et al, 2005)

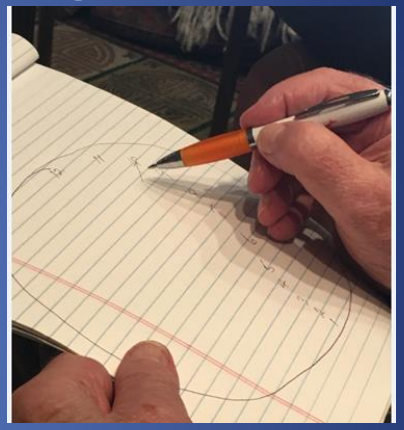
— A score of 26 or above is considered normal

— For individuals with 12 years or fewer of formal education, one point is added to the score as a correction

Sensitivity and Specificity (%) MoCA and MMSE			
Cut-off	>26	<26	<26
Group (n)	Normal Controls (90)	Mild Cognitive Impairment (94)	Alzheimer's Disease (93)
MoCA	87	90 %	100
MMSE	100	18 %	78

Appropriate Evaluation of a patient with MCI or dementia

- Screening metrics: MMSE, MoCA, Clock drawing



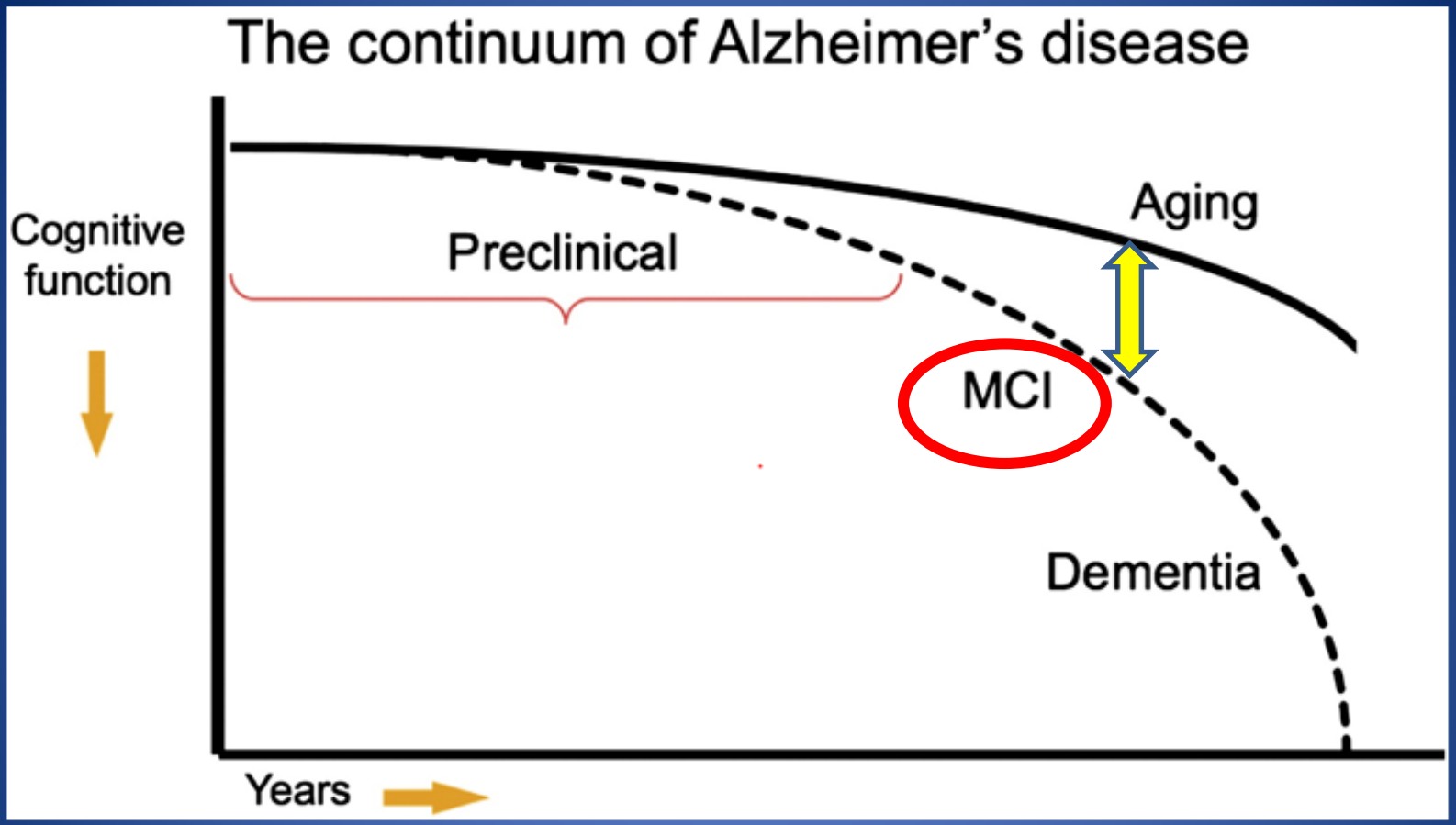
- Lab work to rule out reversible causes
  - **CBC, CMP**
  - **TSH level, reflex to TFT's**
  - **Vitamin B12 level**
  - ESR (sedimentation rate), in occasional cases
  - RPR (no longer routinely done, only if at increased risk)
  - Selectively: HIV, MMA if B12 level intermediate, FTA&CSF VDRL/cell count if suspected neurosyphilis
- Brain MRI (CT, if MRI not safe or feasible)

May Need:

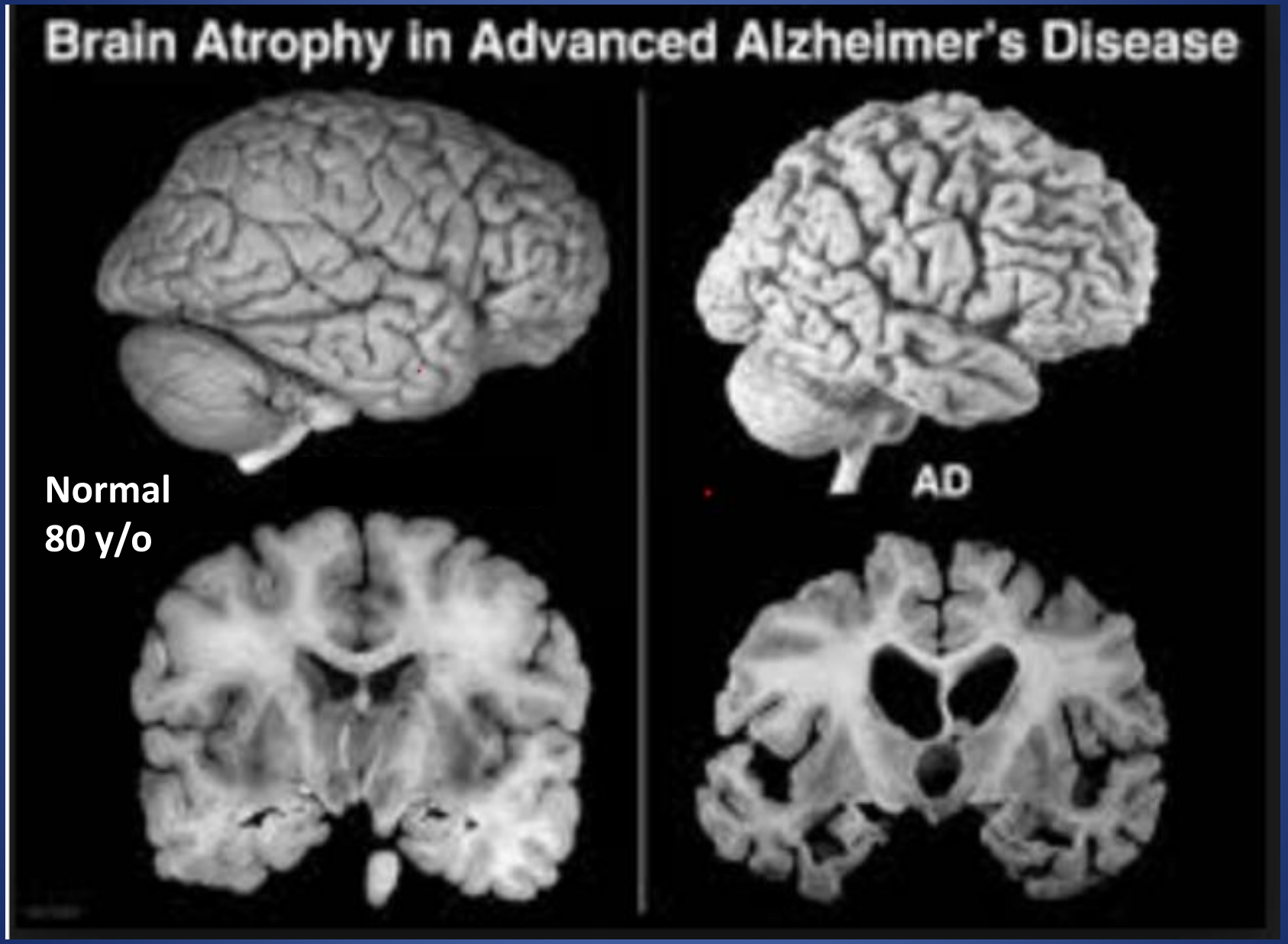
- Neuropsychiatric evaluation
  - 3-5 hours (simple vs. complex)
  - Provides a baseline (for potential future reference)
  - Assist with making a diagnosis
  - Relative strengths vs. weaknesses helps understand how to compensate, how to rehabilitate

MCI

- Emerging in late 1980's: A borderland or "grey zone" transition state, before functional decline, patients still accomplishing tasks independently, but problems forgetting noticed by patient, family and care partners, or his or her physician
- Termed Mild Cognitive Impairment: helpful to describe, detection needed to start treatment earlier, including drug trials
- Impairment in thinking skills ***which goes beyond normal age-related cognitive changes,*** but not dementia (and can't state "not yet" with certainty, doesn't always progress!)



Alzheimer's & Dementia: The Journal of the Alzheimer's Association 2011 7, 280-292DOI: (10.1016/j.jalz.2011.03.003)


Brain Atrophy in Advanced Alzheimer's Disease
Normal
80 y/o
AD

MCI

- No single cause of MCI
- Symptoms may remain stable for years, improve over time, or progress to dementia
- No FDA approved treatment at this time

  (my view: in contrast to early Alzheimer's, pre-dementia stage)

MCI Etiologies

Reversible, Readily treatable Conditions

- Depression
- Severe stress
  - anxiety
  - Occupational burnout
- Obstructive sleep apnea
- Metabolic disturbance
  - B12 lack; hypothyroid
- Alcohol
- Other toxins
- Infection
- Occ: lacunar infarct, heals

Neurodegenerative disorders

- Alzheimer's disease
- Vascular dementia
- Lewy Body dementia, PD
- Frontotemporal dementias
- Mixes of the above
- PSP/CBD, CJD, NPH, Amyloid angiopathy

Question 1B

- 77 year old male, retired physician (practiced for 35 years), presents to your office with his wife. They both report cognitive difficulties over about 10 months:
  - Very nervous to update his own will
  - Can't recall/retain as much; spouse: "a lot slips by"
  - Close acquaintances and friends now often called "that person"
  - Word finding difficulty more generally
  - Has insight: knows he's repeating to/for himself, such as looking in his travel bag before a trip, over and over, insecure he's packed a cell phone charger
  - Drove to a golf course for a game, halfway there forgot that event, forgot where he was headed, went home, wife had to notify the other players
  - May make a wrong turn driving but not correct quickly, limiting driving alone
  - Fears he will lose ability to help manage finances
- Physical, Neurological exam (non-cognitive; elemental) both normal/unremarkable
- Lab work (CMP, CBC, TSH, B12 level normal)

– **The most likely etiology for the MCI in this same patient is:**
  - **Vascular dementia**
  - **Alzheimer's disease**
  - **Lewy body dementia**
  - **Depression**

Question 1B

- 77 year old male, retired physician (practiced for 35 years), presents to your office with his wife. They both report cognitive difficulties over about 10 months:
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  - May make a wrong turn driving but not correct quickly, limiting driving alone
  - Fears he will lose ability to help manage finances
- Physical, Neurological exam (non-cognitive; elemental) both normal/unremarkable
- Lab work (CMP, CBC, TSH, B12 level normal)

  - **The most likely etiology for the MCI in this patient is:**

    - **Alzheimer's disease**

PROGNOSIS of MCI (2008)

- In a 2008 meta-analysis of 15 studies, for example, the total number of patients who had progressed to a dementia in studies lasting less than 5 years was 27.4%, while the total number of patients who had progressed to dementia by the end of studies lasting up to 10 years was 31.4%.
- Meaning … **if the loved one is going to develop dementia, it usually happens within the first 3 years after diagnosis, and the conversion rate drops dramatically in later years.**

2016

- MCI was diagnosed according to DSM-5 (DSM5-MCI; n=139; the criteria exclude psychotic or severely depressed patients) or Petersen's criteria (P-MCI; n=303; **no exclusions**). Patients were assessed comprehensively for conversion to dementia at 2.5 and 4.5 years after study entry
- Among patients aged ≥65, conversion rates at 4.5 years to all-cause dementias were 3.4% in non-MCI individuals, 8.7% in P-MCI diagnosed cases, and **15.1%** in DSM5-MCI diagnosed cases. **For AD specifically, conversion rates were, respectively, 2.2%, 5.6%, and 9.8%**
- **BUT: *Amnestic* MCI does have a much higher risk progressing to a full dementia, usually Alzheimer's disease**
  - **Single domain: 1/3 of patients develop a dementia over next 3 years (about 1 in 9 patients yearly convert; FOR YOUR PURPOSES: 10 TO 15% PER YEAR CHANGE OF PROGRESSING**
  - **Multi-domain ¾ patients develop a dementia over next 3 years (about 1 in 4 patients yearly convert)**
- **Non-amnestic MCI single domain "patients" do not carry an increased risk of dementia compared to those with normal cognitive functioning**

Mild Cognitive Impairment: What Are the Odds for Later Dementia?
Joel Yager, MD reviewing Marcos G et al. Acta Psychiatr Scand 2015 Dec 21

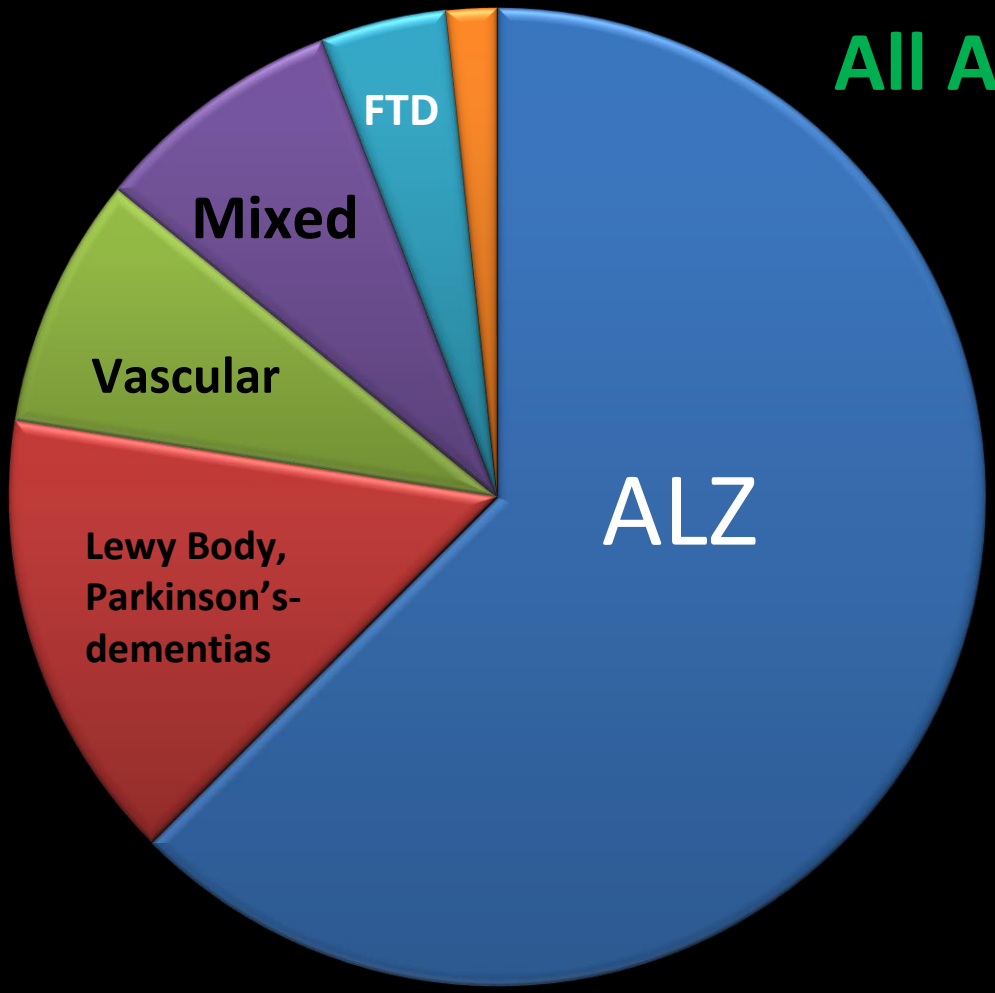
Perez, F. Practical Neurology, September 2015

Alzheimer's vs. Dementia

What is “dementia?”

- A syndrome, not a specific disease
  - Like saying “cancer”
  - Does not say what lies ahead or how to treat
- Characterized most often by progressive loss of thinking and/or memory
- Results in inability to function on a daily basis
- Not uncommonly results in changes in emotions and personality
- Eventually causes neurological dysfunction beyond cognitive problems:
  - Examples: incontinence, swallowing problems, balance and walking problems
- There are many causes of this syndrome, not just Alzheimer’s
  - But Alzheimer’s is the most common cause

DEMENTIA
All Age Groups



- Alzheimer's disease
- Dementia with Lewy Bodies / PDD
- Vascular Dementia
- Mixed Dementia
- Frontotemporal Dementias
- Others — NPH, CJD, PSP, CBD, HC-Sclerosis Amyloid-angiopathy, MS, CTE, HD, HIV, syphilis, MSA, ETOH

DEMENTIAS

- Alzheimer's disease
- Dementia with Lewy Bodies:
  - Lewy Body Dementia
  - Parkinson's disease- Dementia
- Vascular Dementia
- Mixed Dementia
- Frontotemporal Dementia
- Other (eg, Normal Pressure Hydrocephalus)

Dementia - Definition

- Cognitive decline from a previous level of performance
- Cognitive impairment **does** impair everyday activities (work, IADLs, ADLs)
- Does not occur exclusively during the course of delirium
- Not accounted for by another mental disorder (depression, schizophrenia, etc.)

DSM V – Major Neurocognitive Disorder

Case #2

- An 87-year-old woman and widow is evaluated for dementia. She is brought to the office by her son, who reports first noticing gradually progressive symptoms 2-3 years ago when his mother began showing difficulty recalling recent information/events, and a tendency to repeat herself is increasing in frequency.
- He also notes he is helping more with finances, and has set up a pill organizer for what are only 3 medications, but one needs to be taken before breakfast. She recently lost ability to play bridge as well as she used to, friends have told him. She stopped driving 1 year ago after getting lost several times.
- She has sick sinus syndrome and hypothyroidism treated with levothyroxine.
- On physical examination, blood pressure is 155/60 mm Hg and pulse rate is 55/min and intermittently irregular. She scores 20/30 (normal, ≥26) on the Montreal Cognitive Assessment (MoCA) but all other findings from the elemental neurologic examination are unremarkable.

QUESTION 2A

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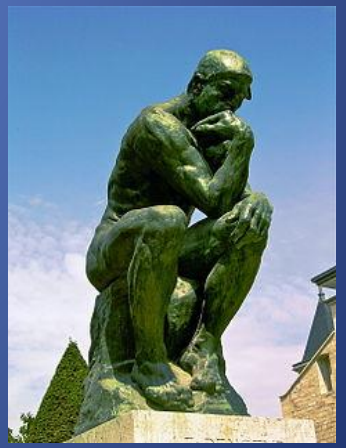
- **What is the most likely diagnosis?**
  - **Frontotemporal dementia**
  - **Alzheimer's disease**
  - **Lewy body dementia**
  - **Vascular dementia**



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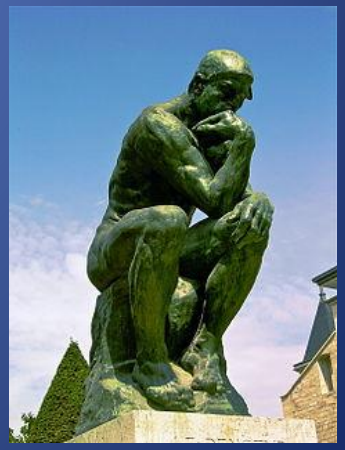
- **What is the most likely diagnosis?**
  - **Alzheimer's disease**



Alzheimer’ s Disease - Symptoms

Insidious onset and progressive decline

- Memory changes
  - Increasing forgetfulness (repeating, loss of recall of events, information, conversations)
- Mild confusion
- Repetitive questions or stories
- Misplacing items
- Difficulty planning, organizing
- Personality and behavior changes
  - Neuropsychiatric Symptoms
  - Depression, anxiety, withdrawal, irritability, aggression, etc.
- **EARLY ON: Should be no motor symptoms and**
  - **Non-cognitive or elemental neurologic examination expected to be unremarkable**

Alzheimer's Disease

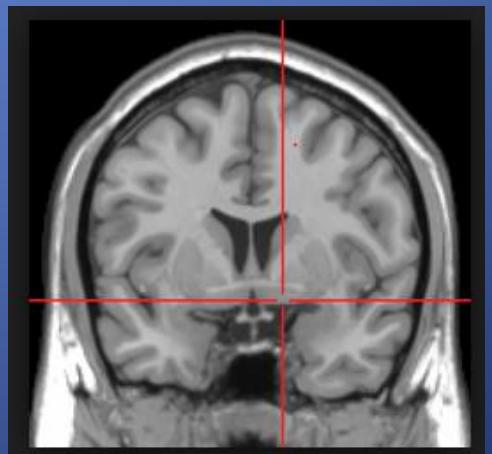
- Most common form of dementia
- Progressive neurodegenerative disorder that damages and eventually destroys brain cells
- Greatest known risk factor is age*
- 5% of people with the disease are < 65 years
- Microscopic changes in the brain begin long before the first signs of memory loss (preclinical phase)

*85-90+ group

Alzheimer's

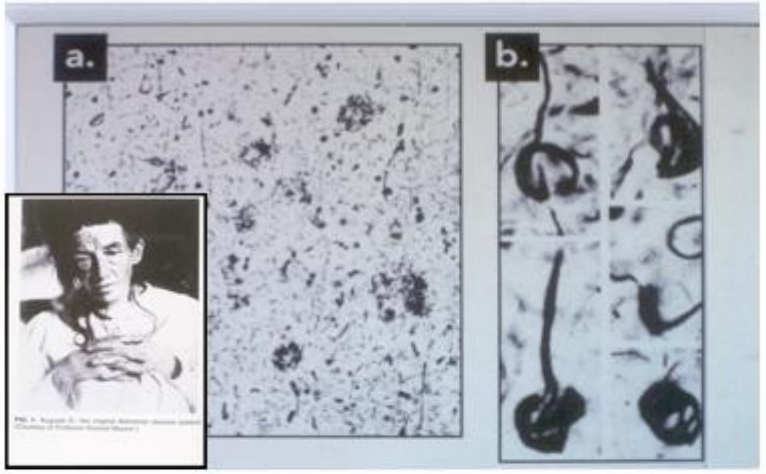
- Age is the single greatest risk factor
- Acetylcholine is the main transmitter affected*
  - Glutamate, NE, 5-HT, & others are affected
- Apo-E status increases risk: 2,3, vs. 4
- Role of insulin-like growth factors unclear
- Aβ-42 is increased in brain but *low* in CSF
- Tau is increases in CSF and cerebral cortex
- Amyloid-PET is approved, but insurance coverage…

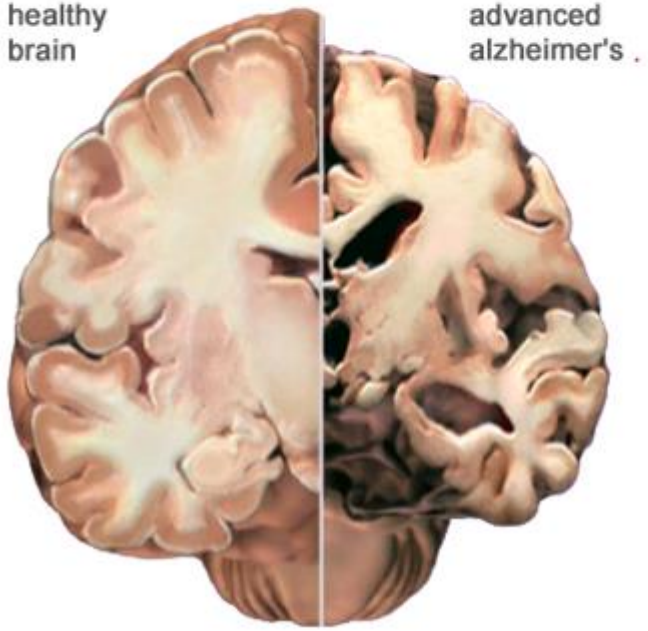
- *What nucleus synthesizes?

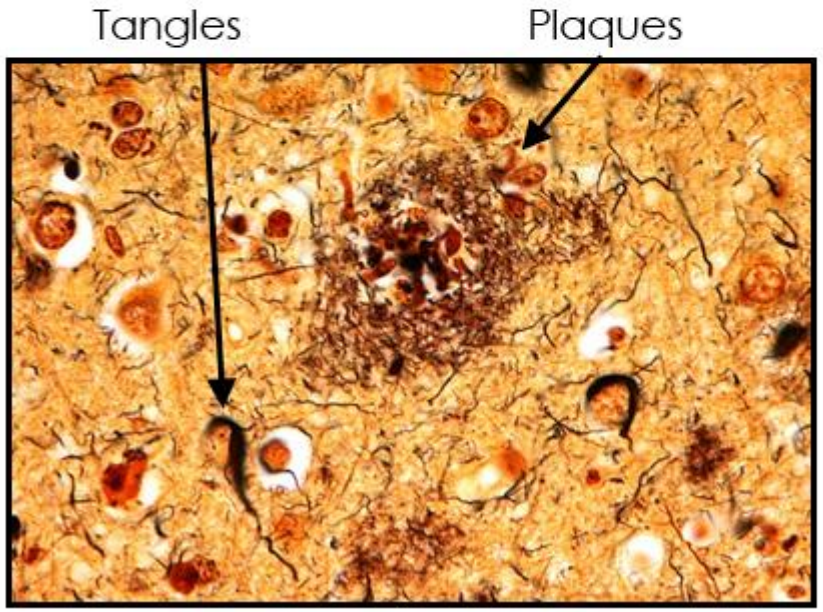


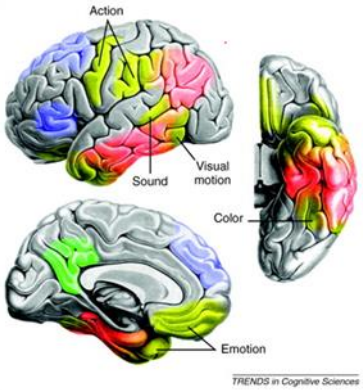
The Main Changes in the Brain

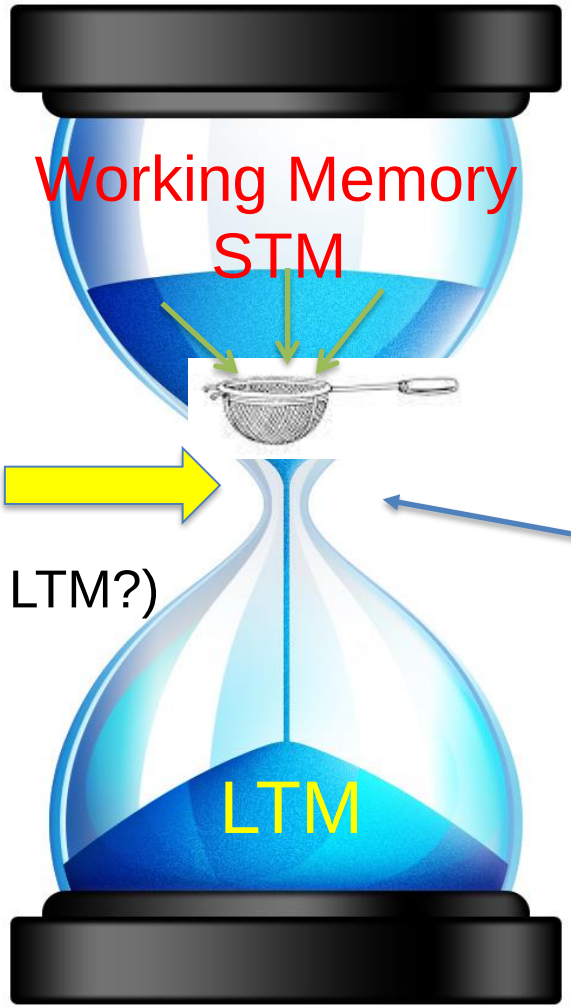
- Amyloid plaques
- Neurofibrillary tangles
- Death of brain cells (neurons)
- Shrinkage of the brain
- Inflammation









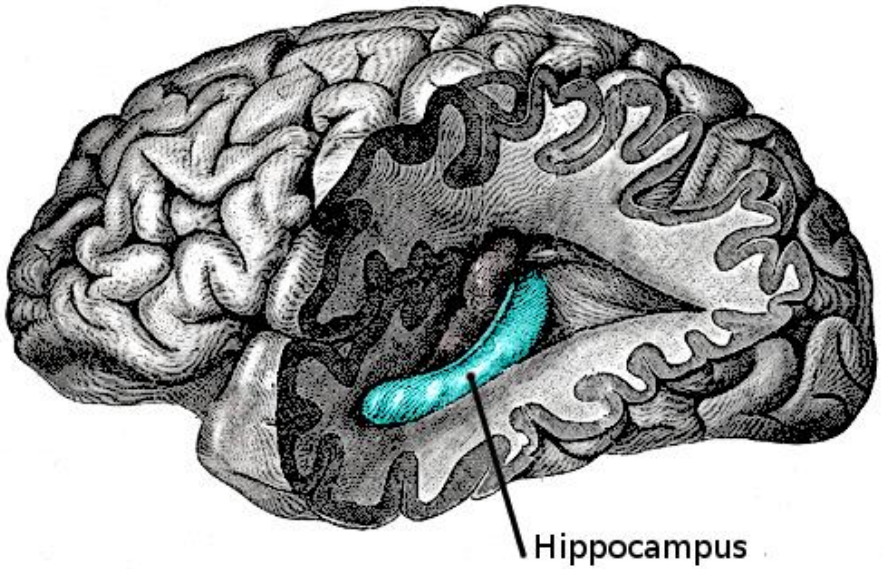


So what brain area filters all new info?

(if a STM is to become a LTM?)

Encoding

Banner Alzheimer's Institute



Hippocampal volume
Total brain volume

Duration of Illness from Diagnosis to Death

Studies indicate that people age 65 and older survive an average of 4 to 8 years after a diagnosis of Alzheimer's dementia, yet some live as long as 20 years with Alzheimer's dementia

Alzheimer's Association. 2019 Alzheimer's Disease Facts and Figures. Alzheimers Dement 2019;15(3):321-87.

Functional Decline – Symptoms

1. Occupational
2. Social
3. Instrumental ADLs (IADLs)

usually affected earlier in the disease process

- Housework
- Shopping
- Using the telephone
- Medications
- Managing money
- Transportation

4. Basic ADLs –

affected later in disease process

- Functional mobility
- Bathing/showering
- Dressing
- Grooming and hygiene
- Toileting

QUESTION 2B

- An 87-year-old woman and widow is evaluated for dementia. She is brought to the office by her son, who reports first noticing gradually progressive symptoms 2-3 years ago when his mother began showing difficulty recalling recent information/events, and a tendency to repeat herself is increasing in frequency. He also notes he is helping more with finances, and has set up a pill organizer for what are only 3 medications, but one needs to be taken before breakfast. She recently lost ability to play bridge as well as she used to, friends have told him. She stopped driving 1 year ago after getting lost several times. She has sick sinus syndrome and hypothyroidism treated with levothyroxine.
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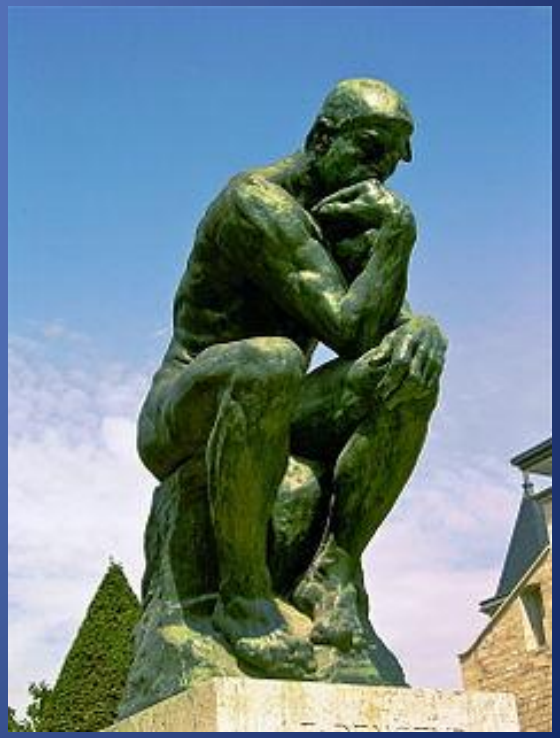
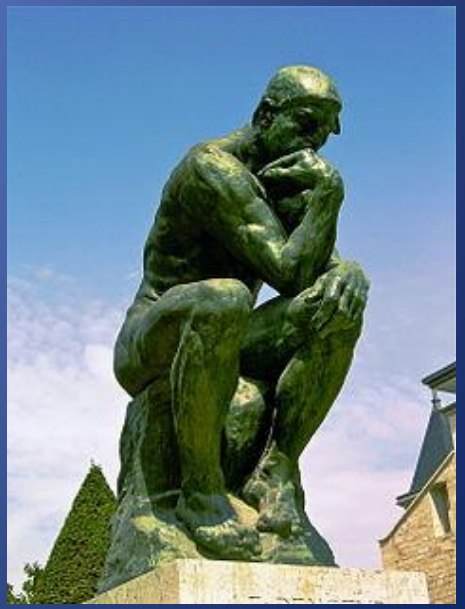
- **Would you order an MRI?**
  - **Yes**
  - **No**
  - **Optional**
  - **Need more information**



QUESTION 2B

- An 87-year-old woman and widow is evaluated for dementia. She is brought to the office by her son, who reports first noticing gradually progressive symptoms 2-3 years ago when his mother began showing difficulty recalling recent information/events, and a tendency to repeat herself is increasing in frequency. He also notes he is helping more with finances, and has set up a pill organizer for what are only 3 medications, but one needs to be taken before breakfast. She recently lost ability to play bridge as well as she used to, friends have told him. She stopped driving 1 year ago after getting lost several times. She has sick sinus syndrome and hypothyroidism treated with levothyroxine.
- On physical examination, blood pressure is 155/60 mm Hg and pulse rate is 55/min and intermittently irregular. She scores 20/30 (normal, ≥26) on the Montreal Cognitive Assessment (MoCA) but all other findings from the elemental neurologic examination are unremarkable.

- **Should you order an MRI?**
  - **–Yes**



American Academy of Neurology Guidelines on Dementia

- 1994:
  - Did NOT require structural imaging for such a patient

- 2001:
  - Structural imaging became "appropriate"
  - Rationale: Structural lesions are **among** the possible **reversible** cause of dementia

Figure 3. Brain Magnetic Resonance Imaging Showing a Right Frontal Extra-Axial Mass (asterisks) With Extensive Intraparenchymal Inflammatory Reaction (arrows)

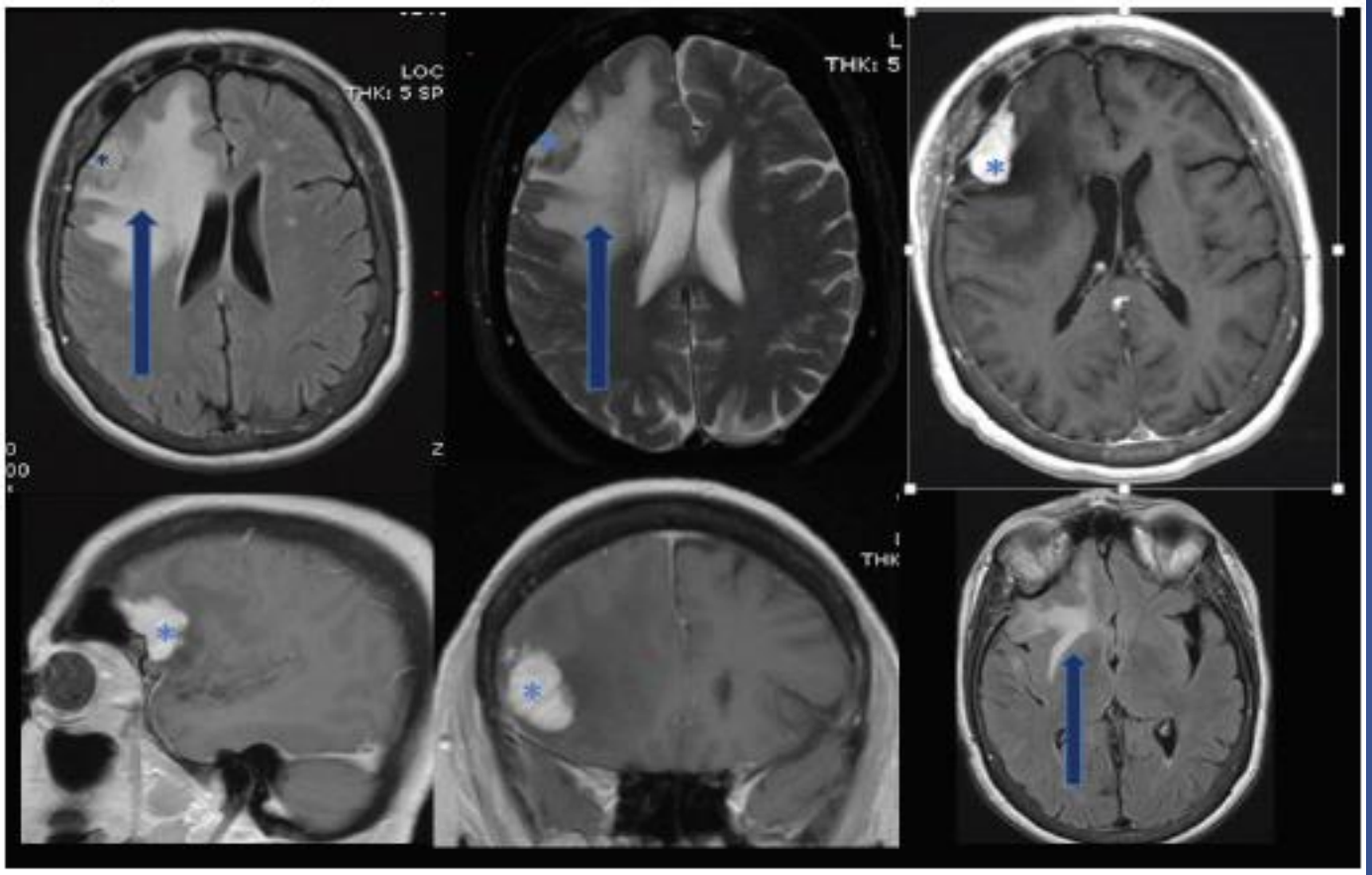
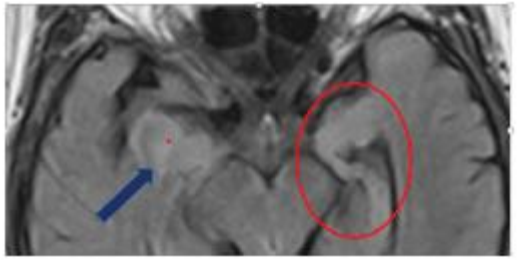
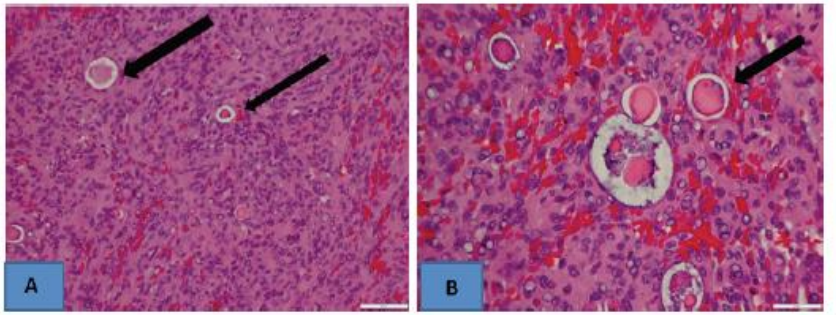


Figure 4. Axial Fluid-Attenuated Inversion Recovery Image at the Midbrain and Medial Temporal Lobes[a]



[a]Edema or inflammation extends down to the right hippocampus (arrow), with effacement of the temporal horn, right lateral ventricle. Compare to the normal left hippocampus (red oval).

Figure 5. Brain Biopsy Histology, Right Frontal Head Region[a]



Low power view (A) and high power view (B) show a secretory meningioma with scattered intracellular lumina containing eosinophilic secretory material (arrows).

Case 3

- 62 y/o male battling several years of anxiety and depression, starting around age 53. More recently, about 4-5 years ago started having episodes of violent dream enactment, usually that escaping from jail, wife would witness, he wouldn't always sleep though this. About 2-3 years ago, he began losing balance, when walking, without vertigo, and falls have increased in frequency this year. Has a history of sleep apnea, unable to tolerate CPAP, but besides more daytime sleepiness, he shows worse days and better days of focus/concentration. He has intact behavior, acts appropriately
- At home, a very occasional tremor at rest seen in the left hand, like "I'm flipping the bird"
- Cognitively: misplacing items more often, mild difficulty recalling comes back later, overall not worse this year
- FUNCTION: stopped driving months prior to presentation, could no longer navigate well enough, lost depth perception for cars in front him, at intersections; still set up own medications (retired pharmacy manager)
- Lab work and brain MRI are normal

Case 3

- **EXAMINATION:**
- **Alert, engaged, normal grooming and comportment; good eye contact; awareness/insight/judgment about why here today: good Thought process is: goal-directed; some psychomotor slowing in responses, no fluctuation in arousal, today**
- **Cognitive: MMSE score is 20, MoCA score is 13/30, with relatively spared language and orientation compared to other domains, suspect memory problems relate more to retrieval, than storage**
- **Cranial Nerves:Function of CN2-12: mildly reduce upgaze, Extraocular movements full in other planes, but with saccadic substitution, mildly, all planes, on smooth pursuits. The face was symmetric with normal sensation. Hearing was adequate for interview and examination. The tongue and palate were midline. There is some loss of prosody in speech**
- **Motor: 5/5 power throughout, normal tone in lower limbs, mild cogwheeling in upper limbs; no involuntary movements are seen; mild motor perseveration after switching from one motor exam test to another, mainly in left hand (side of his rest tremor at home); minimal to mild bradykinesia in some natural movements**
- **Sensory: No distal sensory loss to any modality**
- **Coordination: No dysmetria on finger to nose or heel to shin; there is arrhythmia at times, with slight arrests in testing RAM's, feet and hands dysdiadochokinesis**
- **Reflexes: trace to absent throughout, symmetric; plantar responses are downgoin**
- **Gait: Minimally reduced speed, with cadence compensating for slightly reduced stride length, normal arm swing, turning involves a few extra steps, feet mildly wider apart; Romberg sign is equivocal**
- **Frontal release signs: None present**

QUESTION 3A

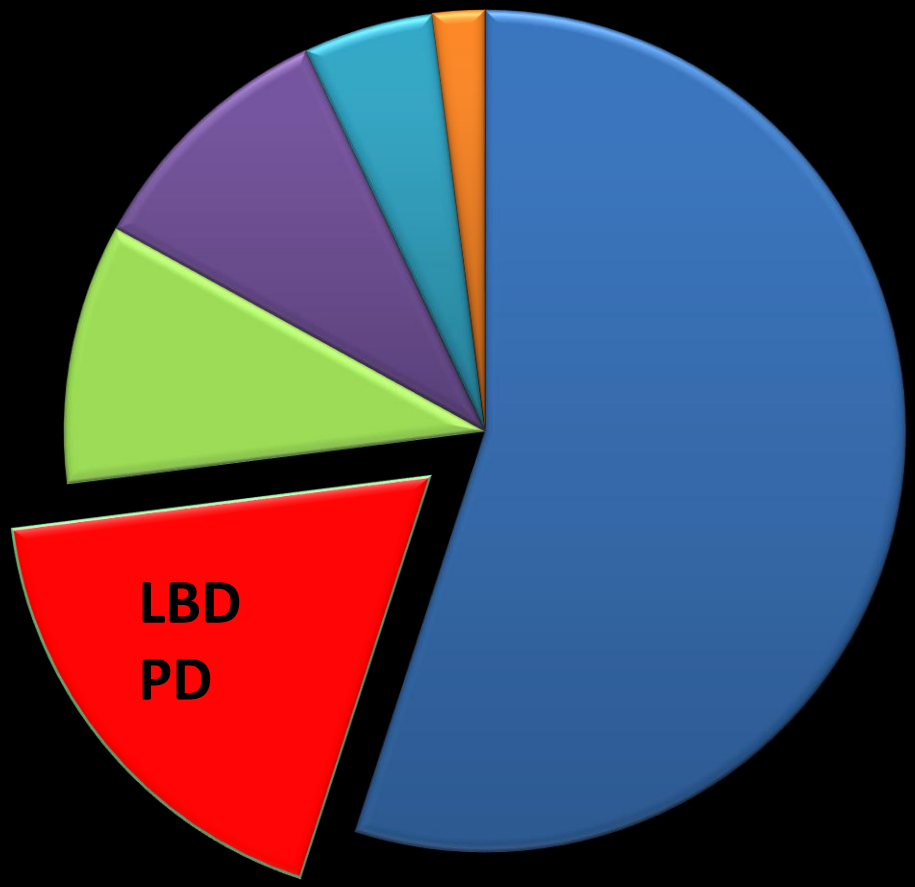
- Assuming a degenerative dementia is present, the most likely etiology of this presentation is:
  - Alzheimer's disease, atypical
  - PD-dementia
  - Dementia with Lewy bodies (Lewy body dementia)
  - Frontotemporal dementia

QUESTION 3A

- Assuming a degenerative dementia is present, the most likely etiology of this presentation is:

  - Dementia with Lewy bodies (Lewy body dementia)

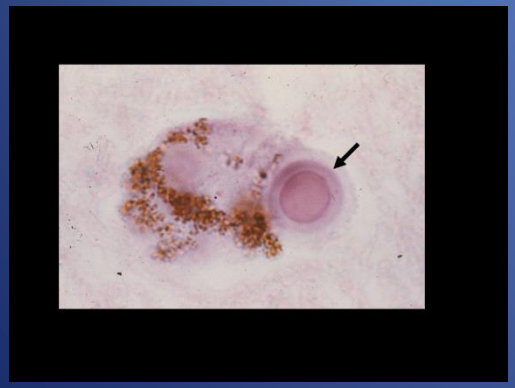
All Age Groups

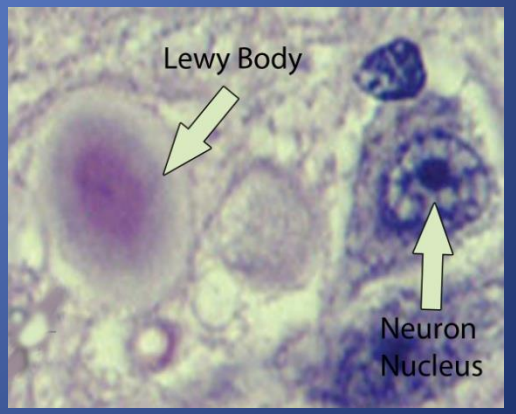


- Alzheimer's disease
- Dementia with Lewy Bodies / PDD
- Vascular Dementia
- Mixed Dementia
- Frontotemporal Dementia
- Others

Dementia with Lewy Bodies

- Progressive neurodegenerative disease
- Proteins called Lewy Bodies (alpha synuclein) are deposited in nerve cells
- Prominent memory impairment may not be evident in early stages





Dementia with Lewy bodies

Early impairment of visual-spatial skills and attention

4 Core Clinical Features

- Fluctuations in
  - Cognition and levels of alertness
  - Subtle or dramatic
- Visual Hallucinations
  - Occur early in the disease (occurs later in other forms of dementia)
- Parkinsonism
  - Bradykinesia, gait disorder, limb rigidity
  - Usually more symmetric than PD and often without tremor
- RBD (REM-sleep Behavioral Disorder)
  - Dream enactment and vocalizations
  - Usually occurs early in the course of the disease

Table 1 Revised[1,2] criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies (DLB)

Essential for a diagnosis of DLB is dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuoperceptual ability may be especially prominent and occur early.

Core clinical features (*The first 3 typically occur early and may persist throughout the course.*)

Fluctuating cognition with pronounced variations in attention and alertness.
Recurrent visual hallucinations that are typically well formed and detailed.
REM sleep behavior disorder, which may precede cognitive decline.
One or more spontaneous cardinal features of parkinsonism: these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity.

Supportive clinical features

Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction, e.g., constipation, orthostatic hypotension, urinary incontinence; hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; apathy, anxiety, and depression.

Indicative biomarkers

Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET.
Abnormal (low uptake) ^{123}iodine-MIBG myocardial scintigraphy.
Polysomnographic confirmation of REM sleep without atonia.

Supportive biomarkers

Relative preservation of medial temporal lobe structures on CT/MRI scan.
Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity ± the cingulate island sign on FDG-PET imaging.
Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range.

Probable DLB can be diagnosed if:

a. Two or more core clinical features of DLB are present, with or without the presence of indicative biomarkers, or

b. Only one core clinical feature is present, but with one or more indicative biomarkers.

Probable DLB should not be diagnosed on the basis of biomarkers alone.

Possible DLB can be diagnosed if:

a. Only one core clinical feature of DLB is present, with no indicative biomarker evidence, or

b. One or more indicative biomarkers is present but there are no core clinical features.

DLB is less likely:

a. In the presence of any other physical illness or brain disorder including cerebrovascular disease, sufficient to account in part or in total for the clinical picture, although these do not exclude a DLB diagnosis and may serve to indicate mixed or multiple pathologies contributing to the clinical presentation, or

b. If parkinsonian features are the only core clinical feature and appear for the first time at a stage of severe dementia.

DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism. The term Parkinson disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson disease. In a practice setting the term that is most appropriate to the clinical situation should be used and generic terms such as Lewy body disease are often helpful. In research studies in which distinction needs to be made between DLB and PDD, the existing 1-year rule between the onset of dementia and parkinsonism continues to be recommended.

QUESTION 3B

- The same 62 yr. old man with DLB develops urosepsis, admitted to a hospital, and becomes agitated on day #2, with aggressive behavior, despite non-Rx strategies such as reorienting by staff, familiar home objects/clocks around, quieter/darkened room overnight, and a 1:1 sitter
- Which of the following medications is not an agent of choice in this particular patient?
  - **Ativan**
  - **Haldol**
  - **Trazodone**
  - **Valproic acid, IV**

QUESTION 3B

- The same 62 yr. old man with DLB develops urosepsis, admitted to a hospital, and becomes agitated on day #2, with aggressive behavior, despite non-Rx strategies such as reorienting by staff, familiar home objects/clocks around, quieter/darkened room overnight, and a 1:1 sitter
- Which of the following medications is not an agent of choice in this particular patient?

  – **Haldol**

Table 4. Pharmacologic Treatment of Delirium.

Class and Drug	Dose	Adverse Effects	Comments
Antipsychotic			
Haloperidol	0.5–1.0 mg twice daily orally, with additional doses every 4 hr as needed (peak effect, 4–6 hr) 0.5–1.0 mg intramuscularly; observe after 30–60 min and repeat if needed (peak effect, 20–40 min)	Extrapyramidal symptoms, especially if dose is >3 mg per day Prolonged corrected QT interval on electrocardiogram Avoid in patients with withdrawal syndrome, hepatic insufficiency, neuroleptic malignant syndrome	Usually agent of choice Effectiveness demonstrated in randomized, controlled trials[20,37] Avoid intravenous use because of short duration of action
Atypical antipsychotic			
Risperidone Olanzapine Quetiapine	0.5 mg twice daily 2.5–5.0 mg once daily 25 mg twice daily	Extrapyramidal effects equivalent to or slightly less than those with haloperidol Prolonged corrected QT interval on electrocardiogram	Tested only in small uncontrolled studies Associated with increased mortality rate among older patients with dementia
Benzodiazepine			
Lorazepam	0.5–1.0 mg orally, with additional doses every 4 hr as needed*	Paradoxical excitation, respiratory depression, oversedation	Second-line agent Associated with prolongation and worsening of delirium symptoms demonstrated in clinical trial[37] Reserve for use in patients undergoing sedative and alcohol withdrawal, those with Parkinson's disease, and those with neuroleptic malignant syndrome
Antidepressant			
Trazodone	25–150 mg orally at bedtime	Oversedation	Tested only in uncontrolled studies

Statistically significant, clinical significance unclear

? 

* Intravenous use of lorazepam should be reserved for emergencies.

Dementia with Lewy Bodies

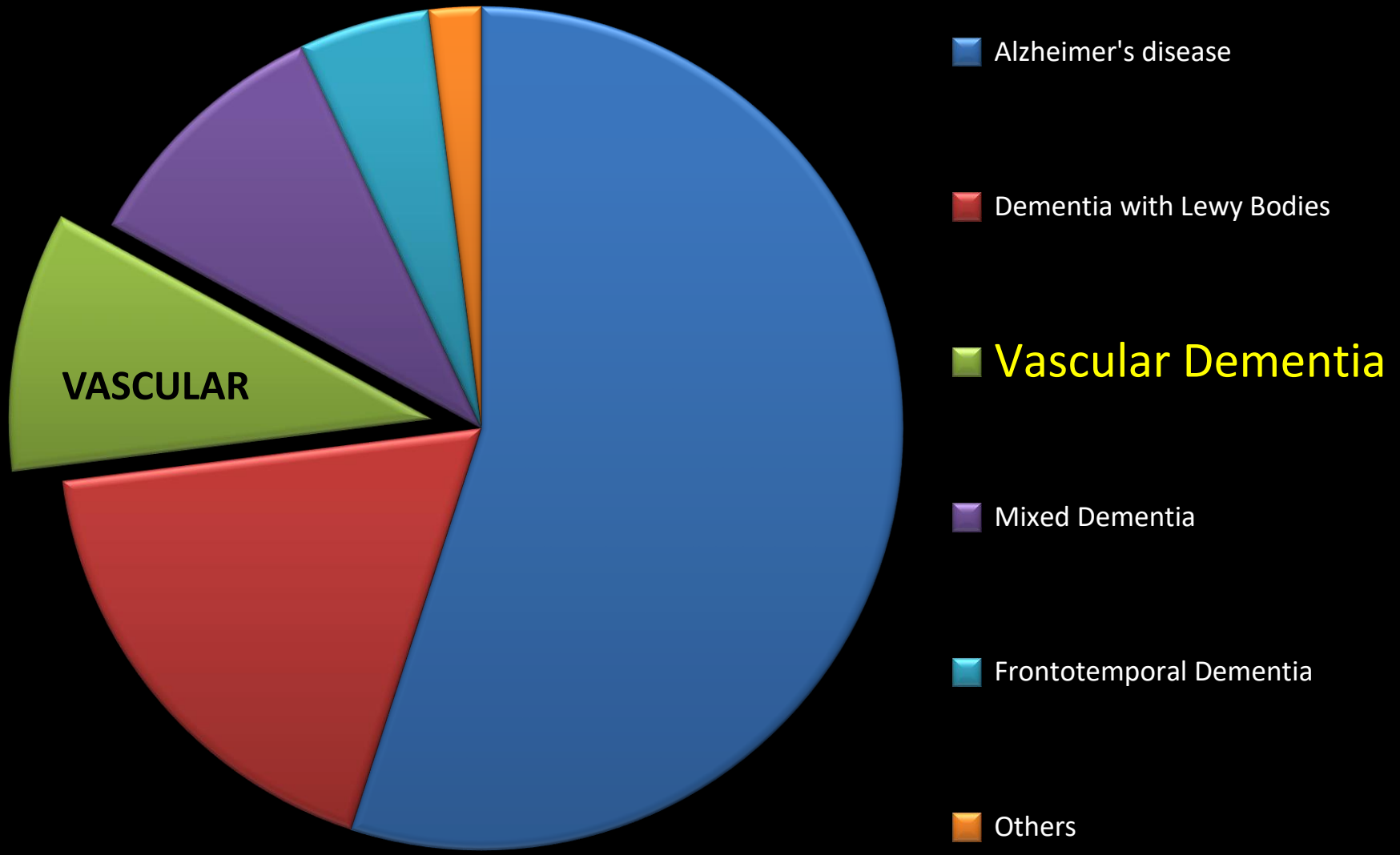
- Supportive features
  - **Severe sensitivity to anti-psychotic agents**
  - Autonomic dysfunction
  - Repeated falls & postural instability
  - Syncopal episodes or transient unresponsiveness
  - Hallucinations in other modalities
  - Systematized delusions
  - Apathy, anxiety, depression

Parkinson's Disease Dementia (PDD)

- Dementia occurs in the setting of established parkinsonism
- "1 year rule"
  - parkinsonian motor features are present for more than 1 year before the onset of cognitive decline
- Symptoms similar to DLB

- Parkinson’s medications can help reduce symptoms but can also cause increased confusion and hallucinations
- Usually good response to cholinesterase inhibitors

All Age Groups

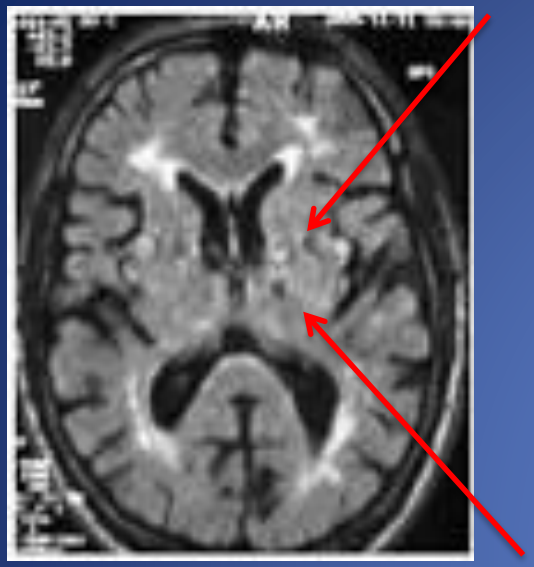


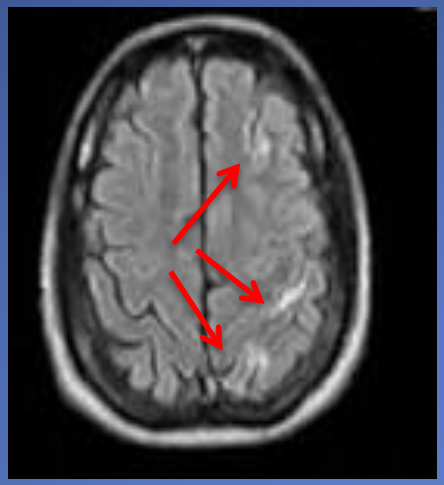
Vascular Dementia (VaD)

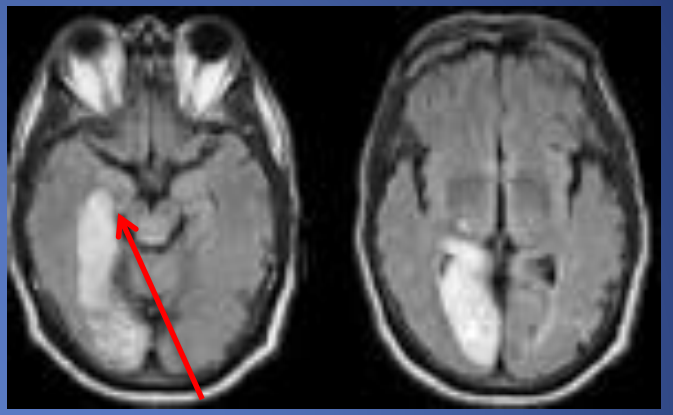
- May be overdiagnosed
- Not a single disease but a group of syndromes
  - Underlying cause is cerebrovascular disease in some form
  - Different pathophysiologic mechanisms
  - Variety of clinical manifestations
- Classified in many different ways

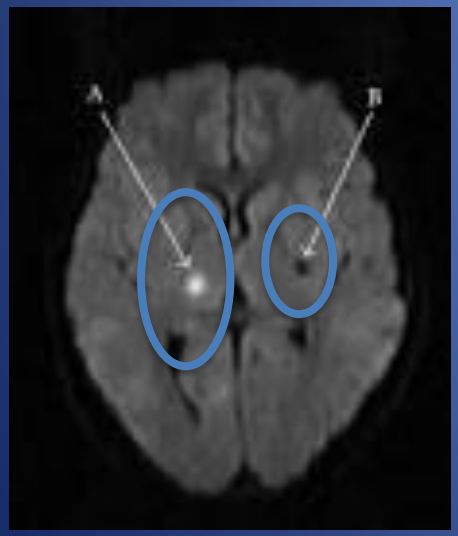
Cerebral Infarcts

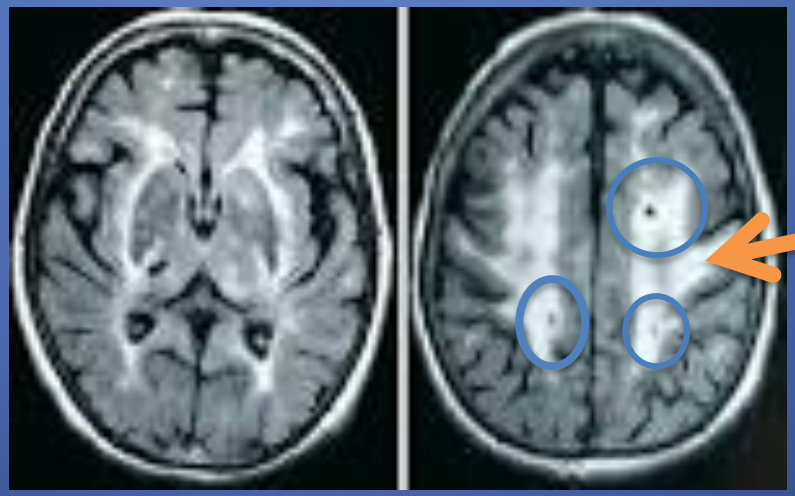
Different strokes (in different folks)









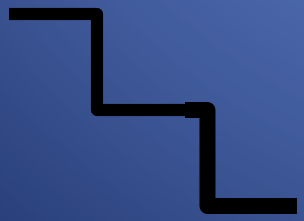


Extensive white matter change

Vascular Dementia

Post stroke dementia due to strategic infarcts

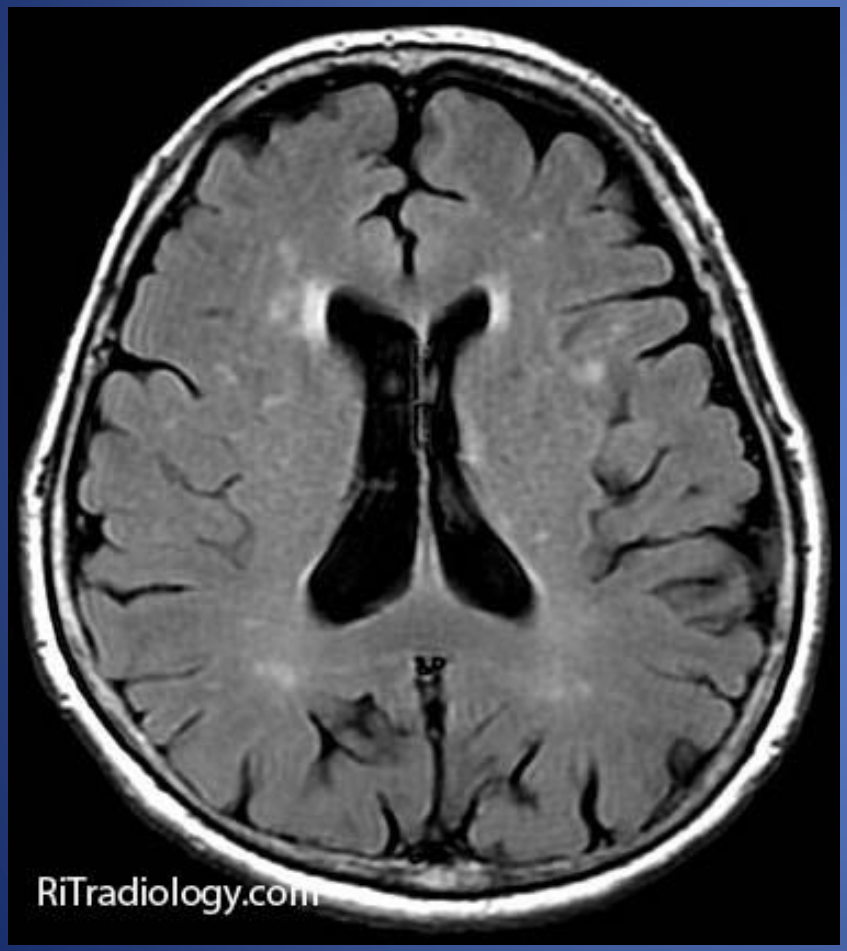
- Often present with a clinical stroke/abrupt onset
- Deficits are specific to the areas affected
- Stepwise decline

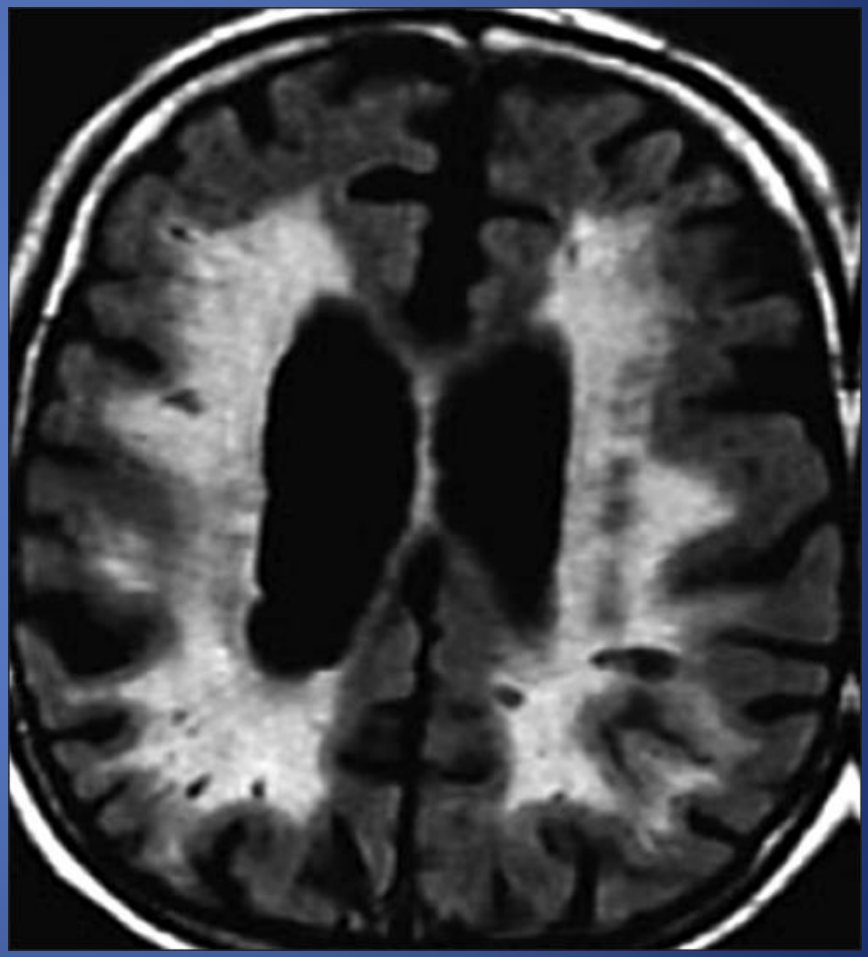


White Matter Disease and Lacunar Infarctions

- Usually need “severe” “extensive” or “confluent” white matter changes to affect cognition
- Need “well placed” or multiple small lacunar strokes to affect cognition

White Matter Disease

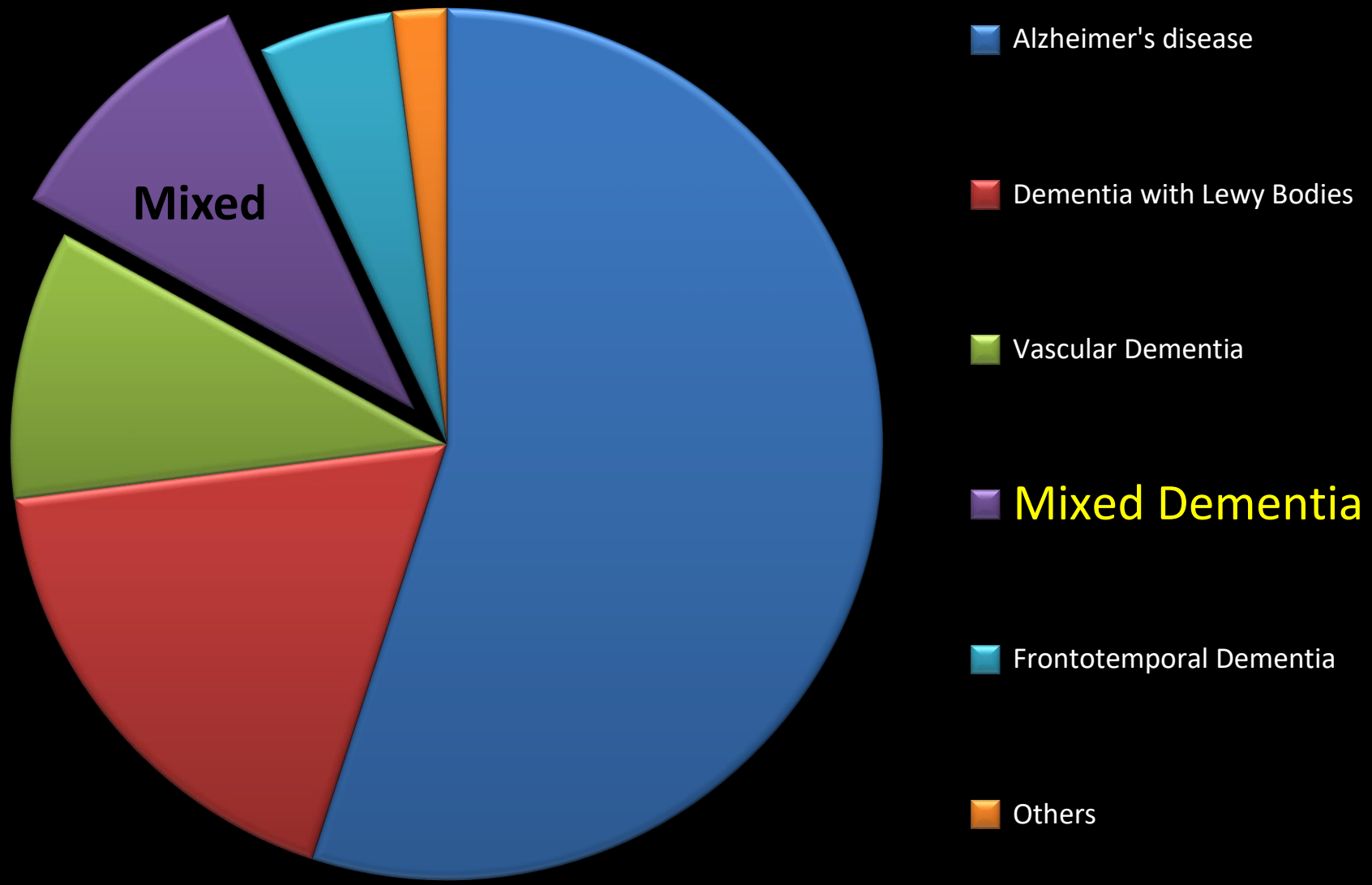


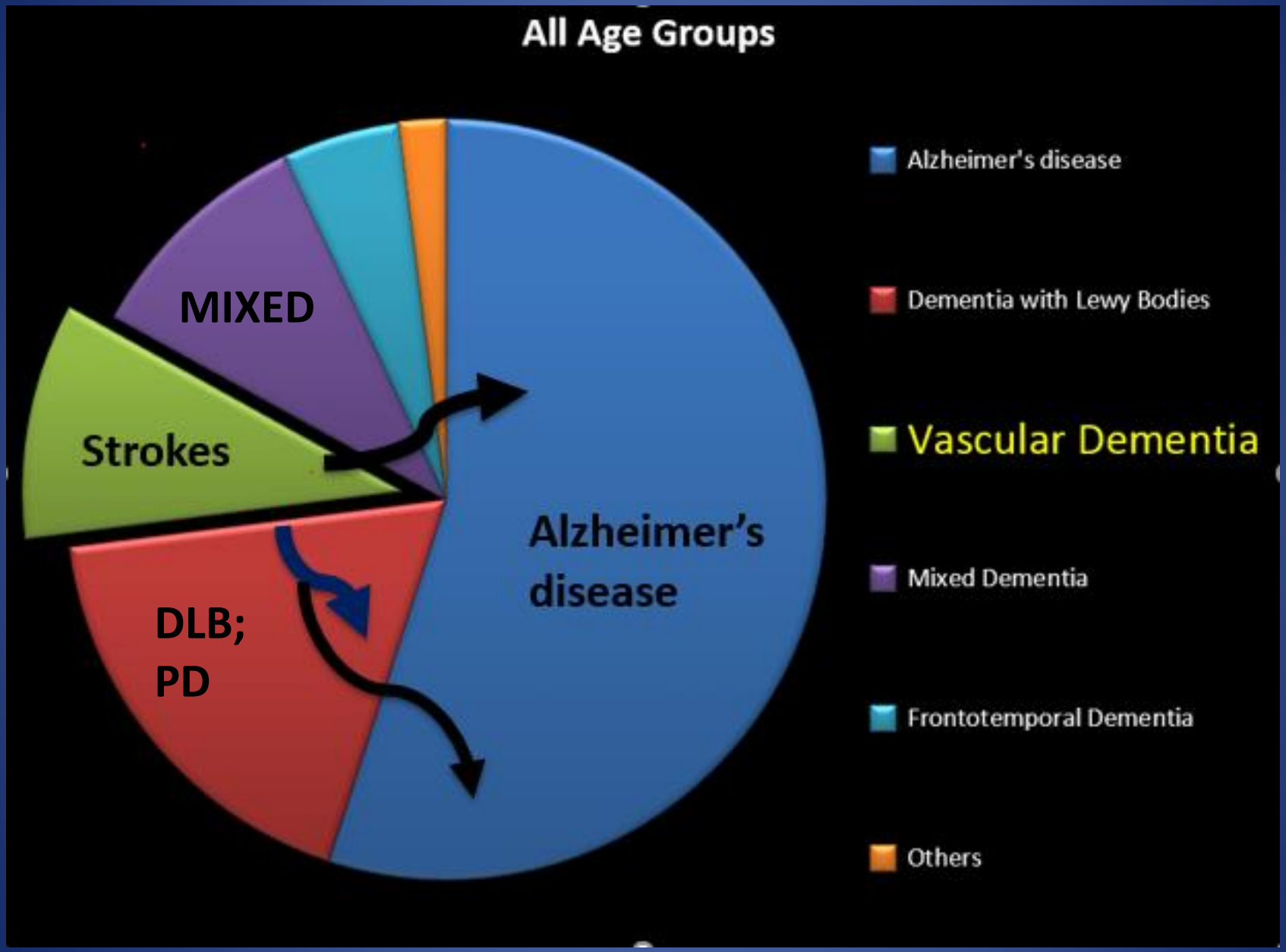


Clinical Features Consistent with a diagnosis of VaD

- Early gait disturbance
- Early urinary symptoms not explained by urologic disease
- Abnormal executive functioning (planning, sequencing, etc)
- Personality and mood changes
- Pseudobulbar palsy
- Psychomotor retardation

All Age Groups



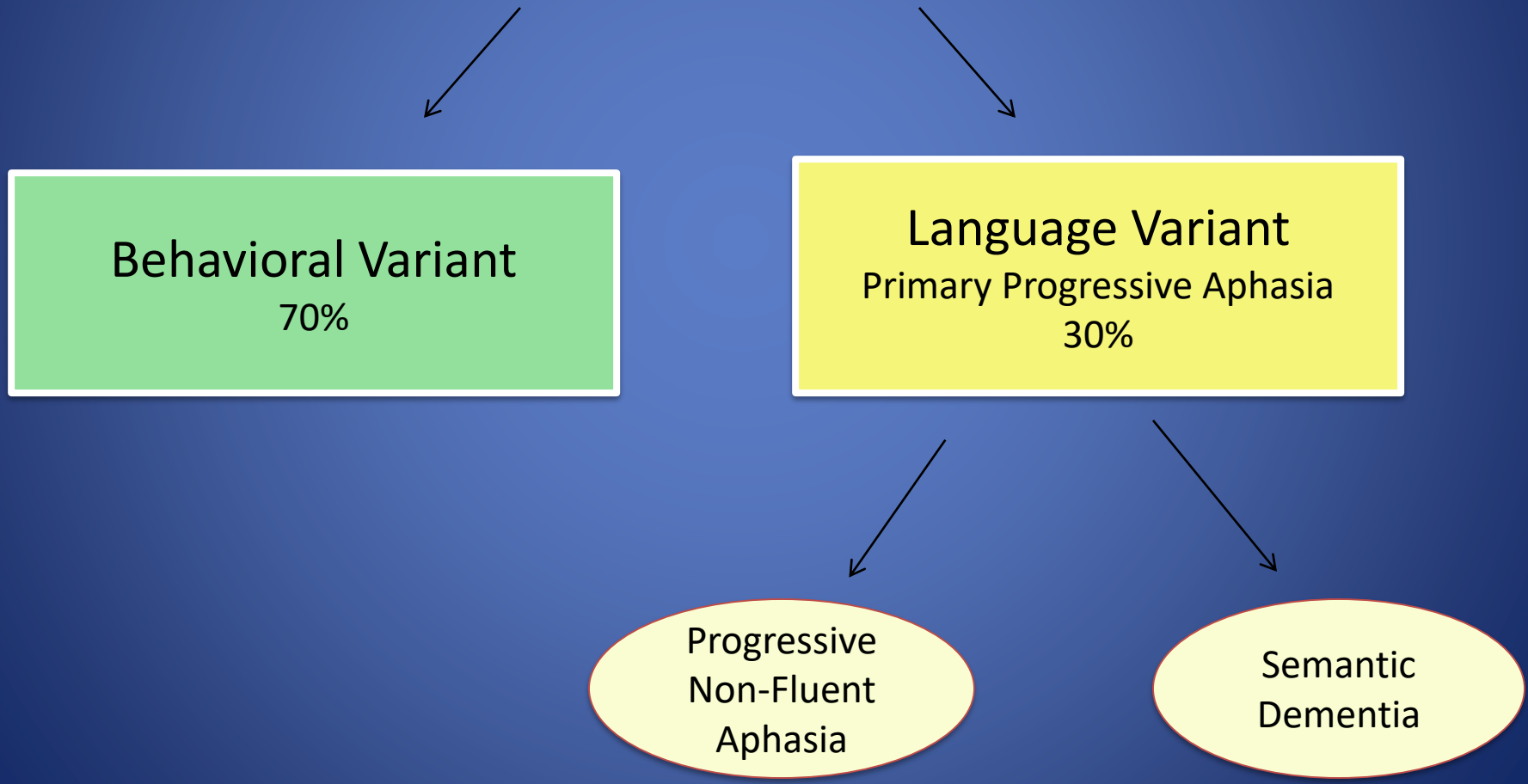

All Age Groups
MIXED
Strokes
DLB;
PD
Alzheimer's disease
Alzheimer's disease
Dementia with Lewy Bodies
Vascular Dementia
Mixed Dementia
Frontotemporal Dementia
Others

Mixed Dementia

- Refers to the co-occurence of 2 diseases (usually AD and VaD pathology; many with DLB have mixed pathology with AD)
- Can be difficult to distinguish which process is “more important”
- 1/3 of patients diagnosed with VaD will have AD pathology (meet the path definition of AD) at autopsy

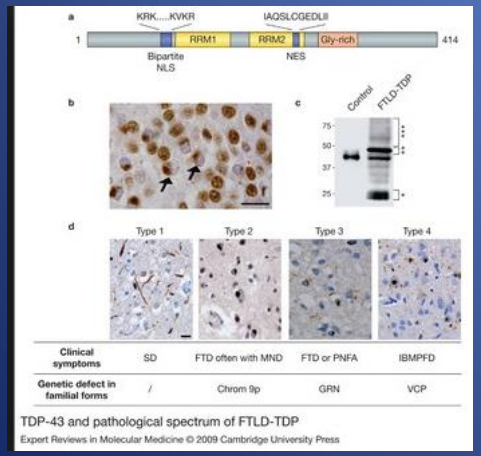
(Alzheimer Dis Assoc Disord. 1999)

Frontotemporal Dementia (FTD)



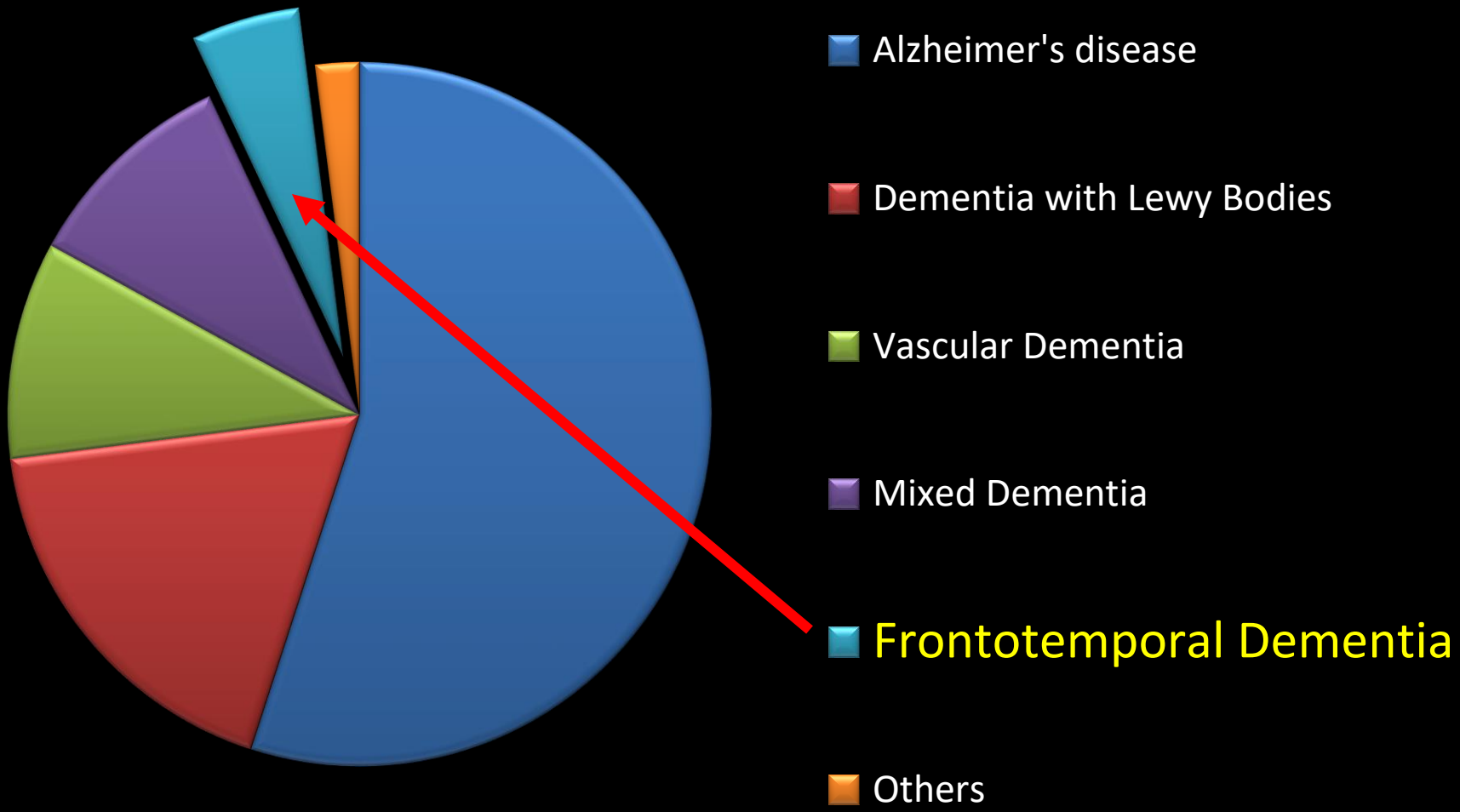
Frontotemporal Dementias (FTD)

- Typical onset is < 65 years
- More commonly a reason for dementia in those younger than 65
- 3 main clinical syndromes
- Diverse pathology

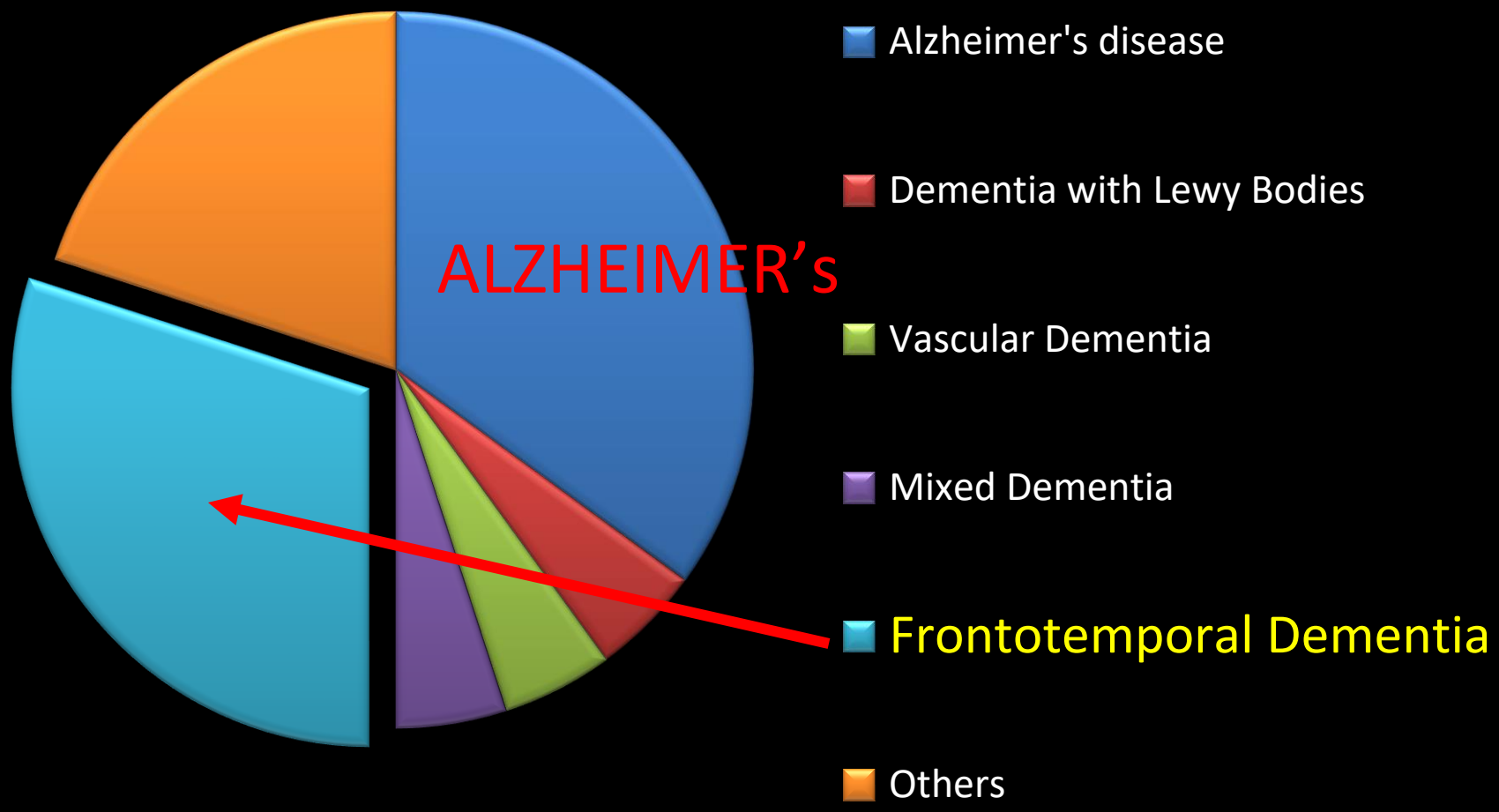


TDP-43 and pathological spectrum of FTLD-TDP

All Age Groups

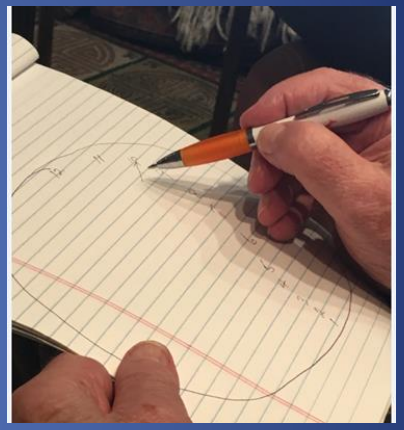


Under Age 65


ALZHEIMER’s
Alzheimer's disease
Dementia with Lewy Bodies
Vascular Dementia
Mixed Dementia
Frontotemporal Dementia
Others

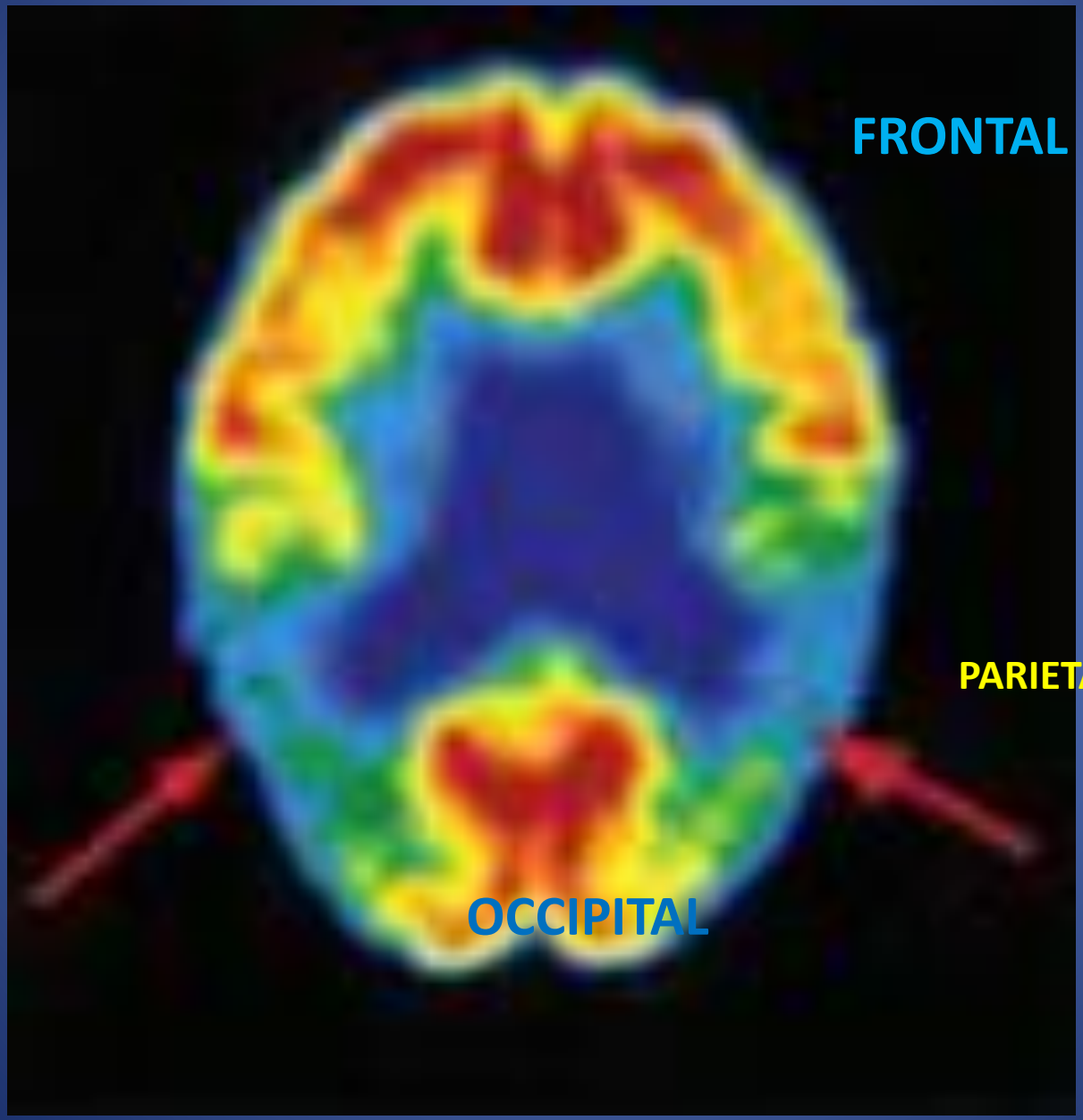
Appropriate Evaluation of a patient with dementia

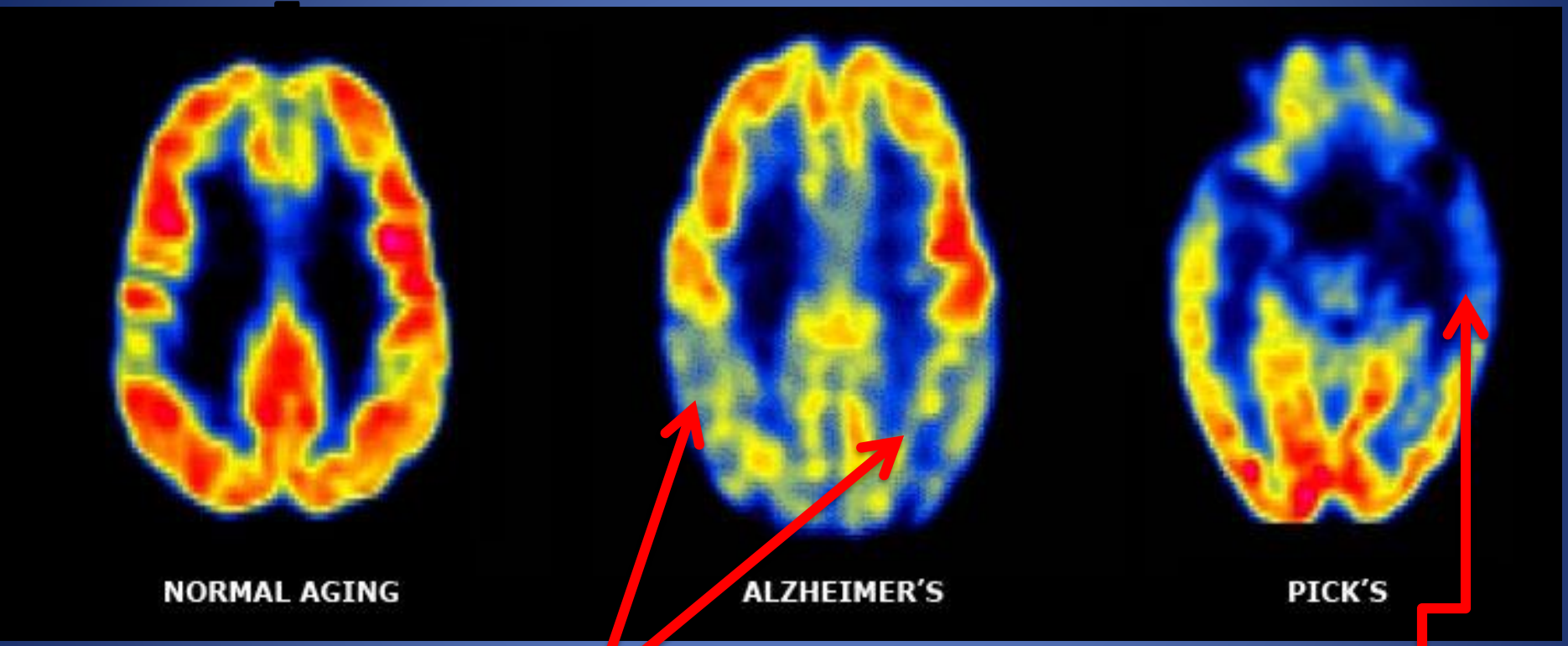
- Screening metrics: MMSE, MoCA, Clock drawing



- Lab work to rule out reversible causes
  - **CBC, CMP**
  - **TSH level, reflex to TFT's**
  - **Vitamin B12 level**
  - ESR (sedimentation rate), in occasional cases
  - RPR (no longer routinely done, only if at increased risk)
  - Selectively: HIV, MMA if B12 level intermediate, FTA&CSF VDRL/cell count if suspected neurosyphilis
- Brain MRI (CT, if MRI not safe or feasible)
- **FDG-PET, selectively: differentiate between AD and FTD**

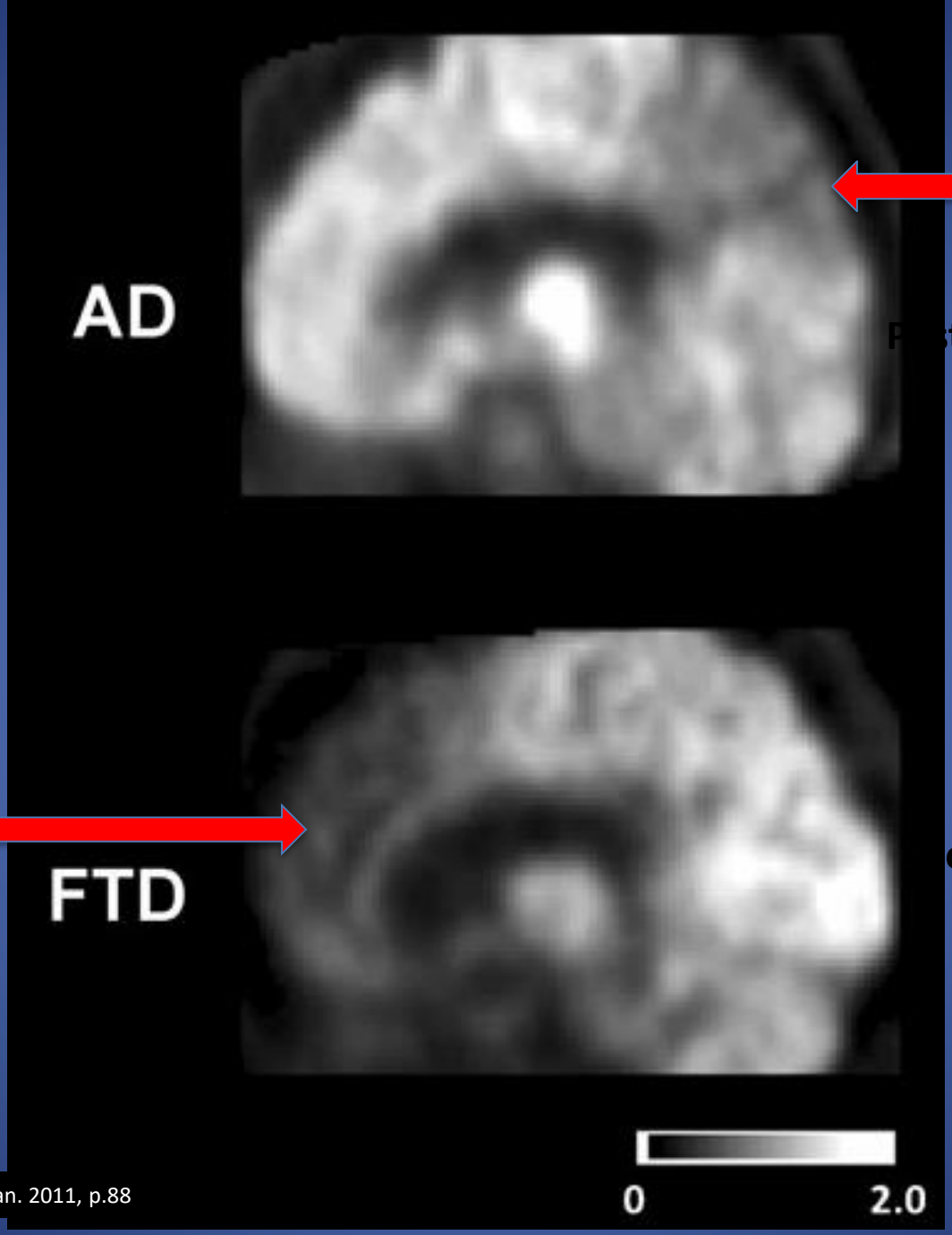
FDG (Fluoro-Deoxyglucose) PET SCAN





Lower Metabolism of glucose

FTD



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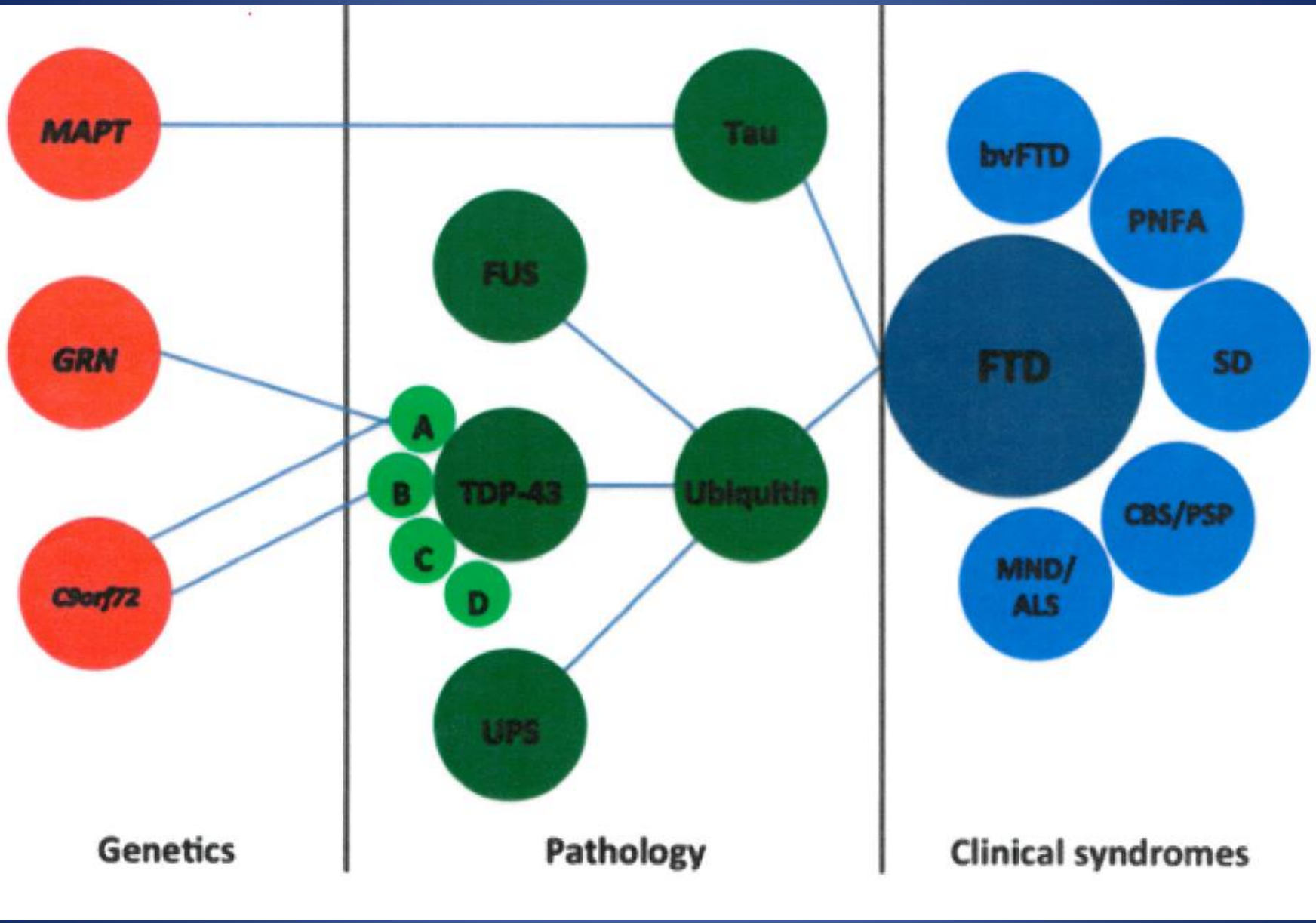

MAPT
GRN
C9orf72
Tau
FUS
A
B
C
D
TDP-43
Ubiquitin
UPS
bvFTD
PNFA
FTD
SD
CBS/PSP
MND/
ALS
Genetics
Pathology
Clinical syndromes

Behavioral Variant FTD

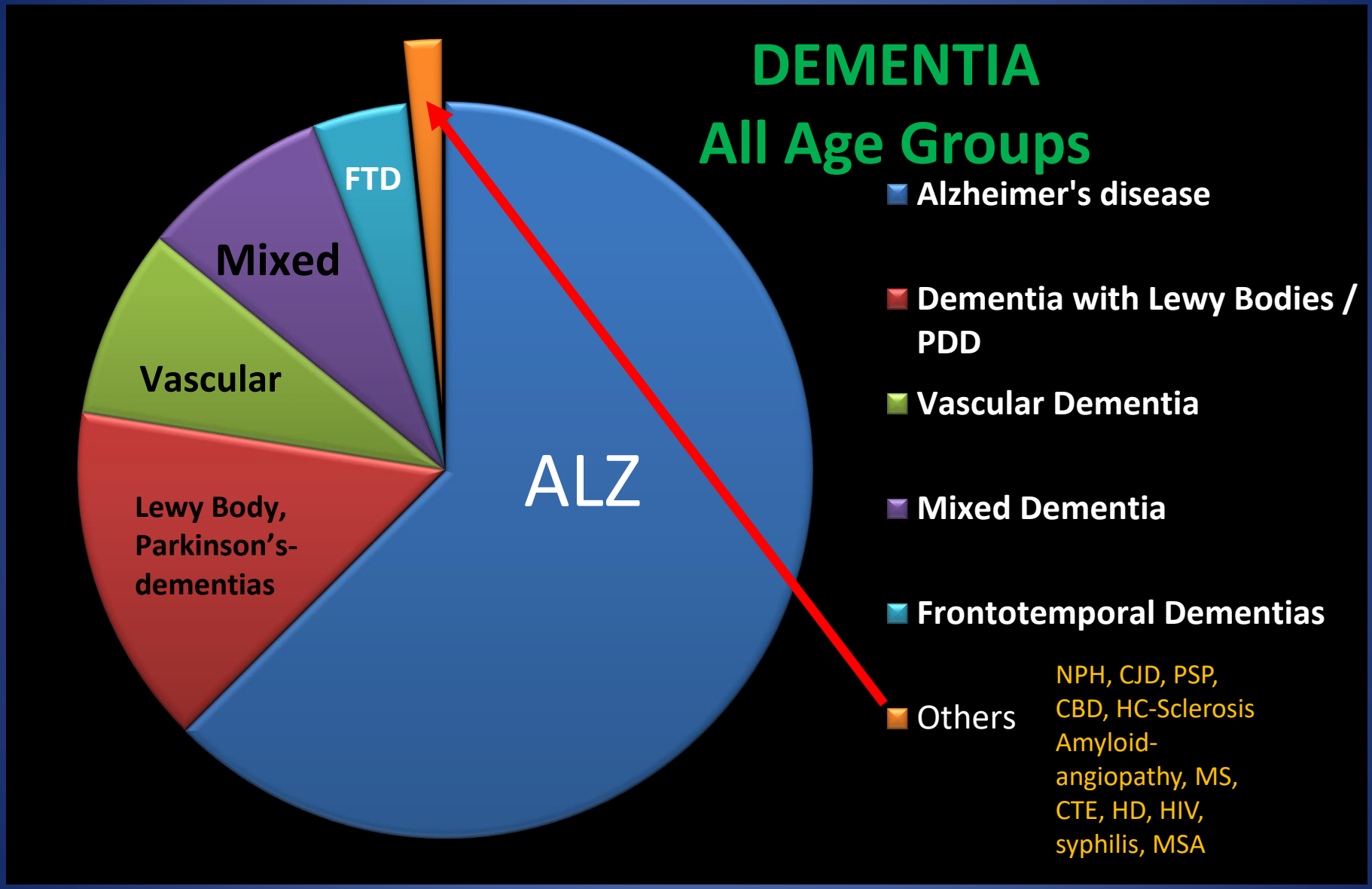
- Insidious onset and slow progression
- Personality change and disordered social conduct are the dominant features at onset
- Memory intact initially
- Lack of insight and empathy
- Decline in personal hygiene

Behavioral Variant FTD

- Mental rigidity and inflexibility
- Hyperorality
- Executive dysfunction OR
- Disinhibition
  - Antisocial and Compulsive behaviors
  - Hoarding
  - Food compulsions

FTD - Language Variant
Primary Progressive Aphasia

- Progressive non-fluent aphasia
  - Expressive aphasia, word finding difficulty
  - Understand but cannot speak
  - Loss of grammar, speech apraxia
- Semantic Dementia
  - Speak fluently but cannot understand meaning of individual words, significant anomia, cannot follow commands adequately

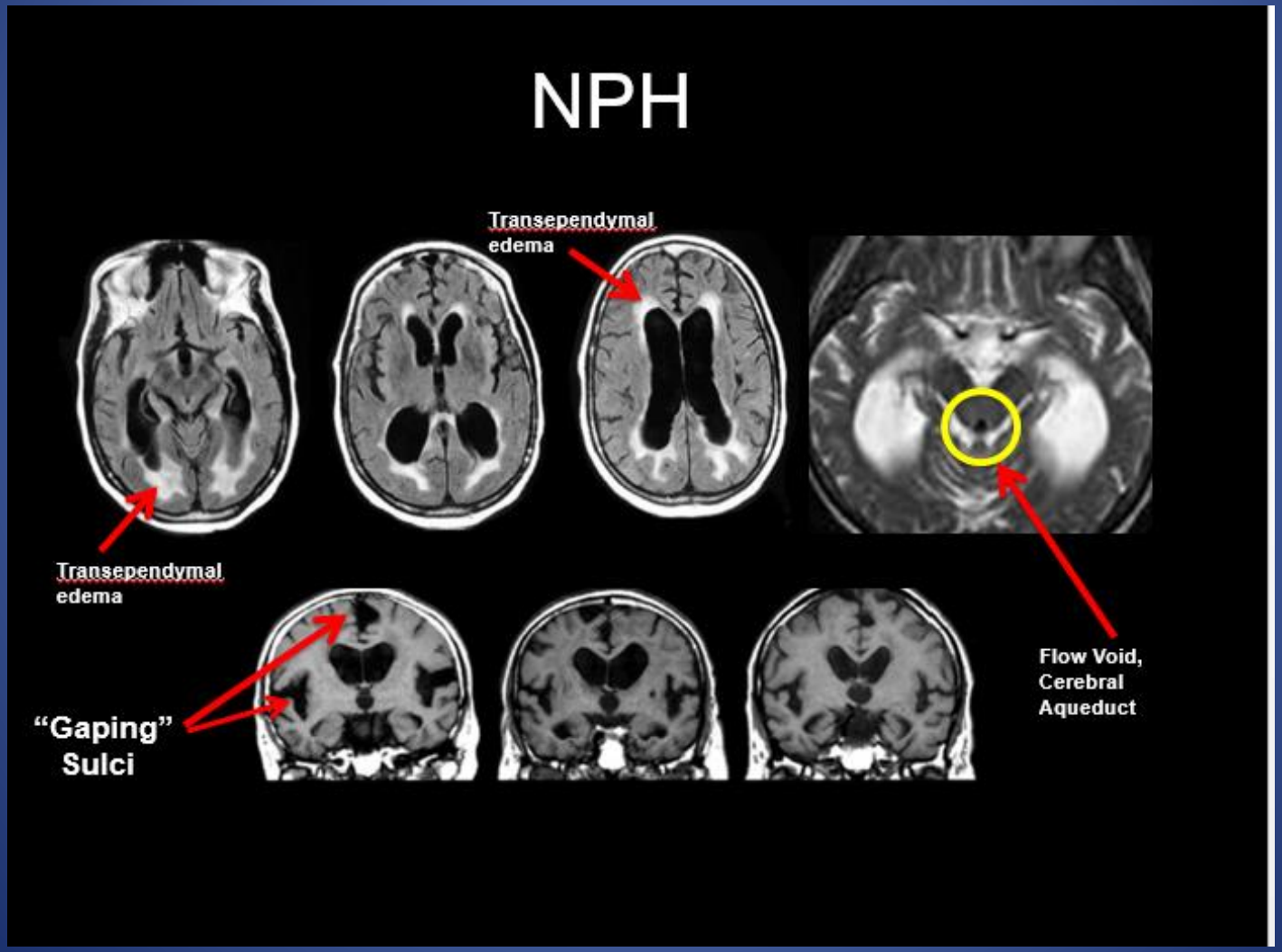

DEMENTIA
All Age Groups
FTD
Mixed
Vascular
Lewy Body, Parkinson's-dementias
ALZ
Alzheimer's disease
Dementia with Lewy Bodies / PDD
Vascular Dementia
Mixed Dementia
Frontotemporal Dementias
Others
NPH, CJD, PSP, CBD, HC-Sclerosis Amyloid-angiopathy, MS, CTE, HD, HIV, syphilis, MSA

“Other” Dementias

- Reversible causes
- Cortical Basal Degeneration
- Progressive Supranuclear Palsy
- **Normal Pressure Hydrocephalus**
- Chronic Traumatic Encephalopathy
- Creutzfeldt-Jacob disease
- Huntington’s disease
- Alcohol
- HIV
- Anoxia

NPH:

Triad of Gait disturbance, urinary incontinence and mild dementia (attention, working memory, exec function impairments, with good memory)



- GAIT:
  - Magnetic; robotic, “glue-footed”, sliding feet along the floor
- BLADDER:
  - Large volumes voided without control or warning
    - ? Less urgency than usual overactive bladder
- Dementia
  - is usually LATER

The main etiologies of secondary NPH were subarachnoid hemorrhage (SAH) in 46.5%, head trauma in 29%, intracranial malignancies in 6.2%, meningoencephalitis in 5%, and cerebrovascular disease in 4.5% of patients

Secondary NPH does indeed exist, and should be differentiated from idiopathic NPH based on outcome and on clinical, pathophysiological, and epidemiological characteristics, but should not be considered as a separate entity.

“Primary” NPH just means the cause or precipitant is unknown! Much less common, compared to secondary

Daou B, Klinge P, Tjoumakaris S, Rosenwasser RH, Jabbour P. Revisiting secondary normal pressure hydrocephalus: does it exist? A review. Neurosurg Focus. 2016 Sep;41(3):E6. doi: 10.3171/2016.6.FOCUS16189. Review. PubMed PMID: 27581318.

QUESTION 7

- The following feature on an early/mild dementia is a red flag the primary cause is unlikely to be Alzheimer's disease:
  - Executive dysfunction worse than memory
  - Visual hallucinations
  - Prominent gait disturbance
  - Moderately severe word finding difficulty

QUESTION 7

- The following feature on an early/mild dementia is a red flag the primary cause is unlikely to be Alzheimer's disease:
  - **Prominent gait disturbance**

Disease	Age (y) at diagnosis	Progression	Earlier cognitive symptoms	Visual hallucinations	Parkinsonism	REM sleep behavior disorder	Autonomic insufficiency	Dominant presenting symptoms
Alzheimer dementia	Late (> 65) Early (< 65)	Gradual	Early impairment of memory and attention	Rare	Late stages	Rare	Rare	Memory loss, cognitive impairment
Vascular dementia	≥ 60	Sudden, stepwise	Executive dysfunction, deficits depend on location of stroke or lesion	Rare	Depends upon location of stroke	None	None	Sudden onset of cognitive deficits and impairment
Dementia with Lewy bodies	70s [6]	Gradual with fluctuation in cognition	Early Impairment of visual spatial skills and attention Delayed recall is relatively preserved in the beginning	Typical	Within first year	Common	Occasional	Parkinsonism or cognitive impairment
Frontotemporal dementia	Mostly < 65	Gradual	Difficulty with language and executive function or behavioral change	Rare	Sometimes	Occasional	Infrequent	Behavioral changes
Primary progressive aphasia	Around 60	Gradual	Expressive language impairment	Rare	In late stages	None	None	Expressive language impairment
Normal-pressure hydrocephalus	50s–60s	Gradual	Impairment of attention, working memory, verbal fluency and executive function; recognition memory is preserved	Rare	May present as parkinsonism	None	None	Gait impairment with urinary frequency and/or cognitive impairment

Treatments - Medications

Acetylcholinesterase Inhibitors

Donepezil (Aricept™)

Rivastigmine (Exelon™)

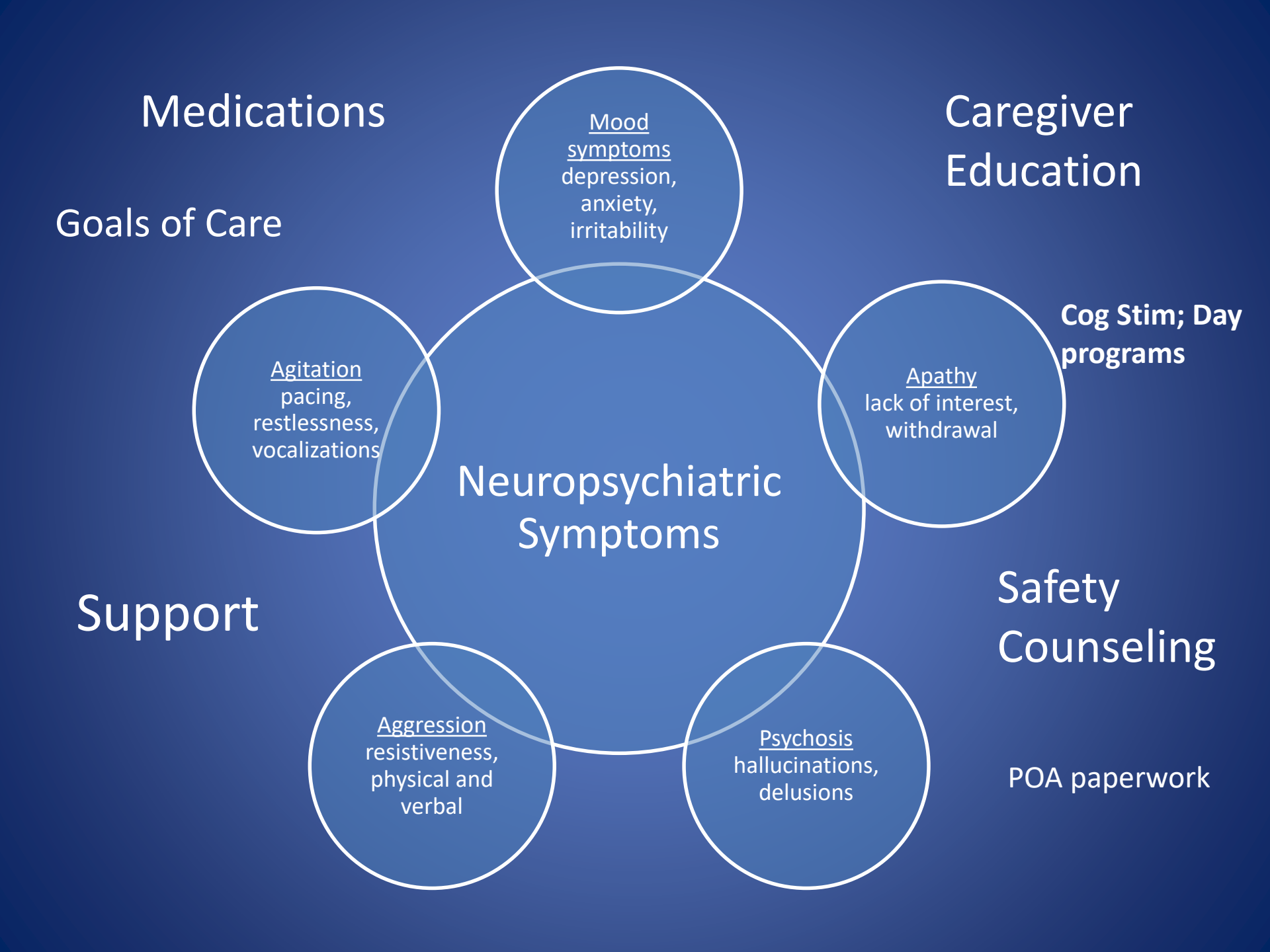
Galantamine (Razadyne™)

NMDA Antagonist

Memantine (Namenda™)

memantine

- NMDA antagonist
- Moderate to severe AD (little help in mild disease)
- Modest benefits
  - Cognition
  - Activities of daily living
  - Behavior
- Immediate release (twice daily) and XR (once daily) forms
  - IR generic in summer of 2015
- Dose needs to be slowly titrated for the first month
- Well tolerated
  - Headache, dizziness, confusion


Medications
Goals of Care
Support
Caregiver Education
Cog Stim; Day programs
Safety Counseling
POA paperwork
Mood symptoms depression, anxiety, irritability
Agitation pacing, restlessness, vocalizations
Apathy lack of interest, withdrawal
Neuropsychiatric Symptoms
Aggression resistiveness, physical and verbal
Psychosis hallucinations, delusions

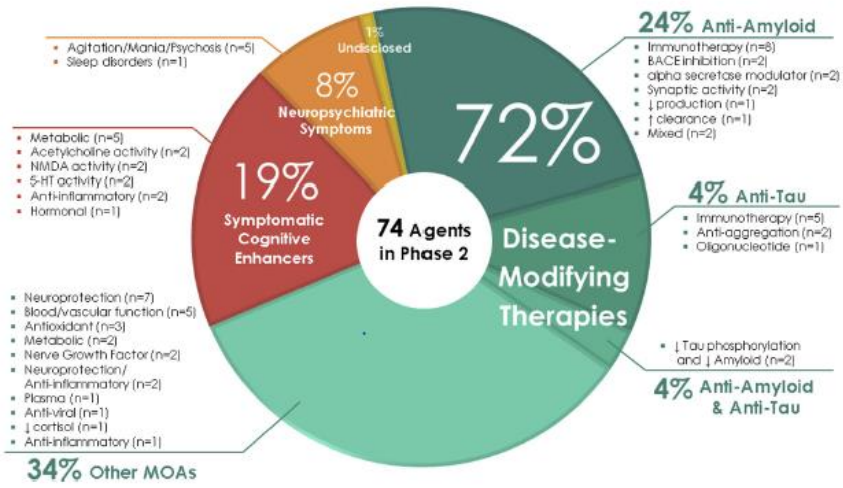


Fig. 3. Mechanisms of action of agents in phase 2.

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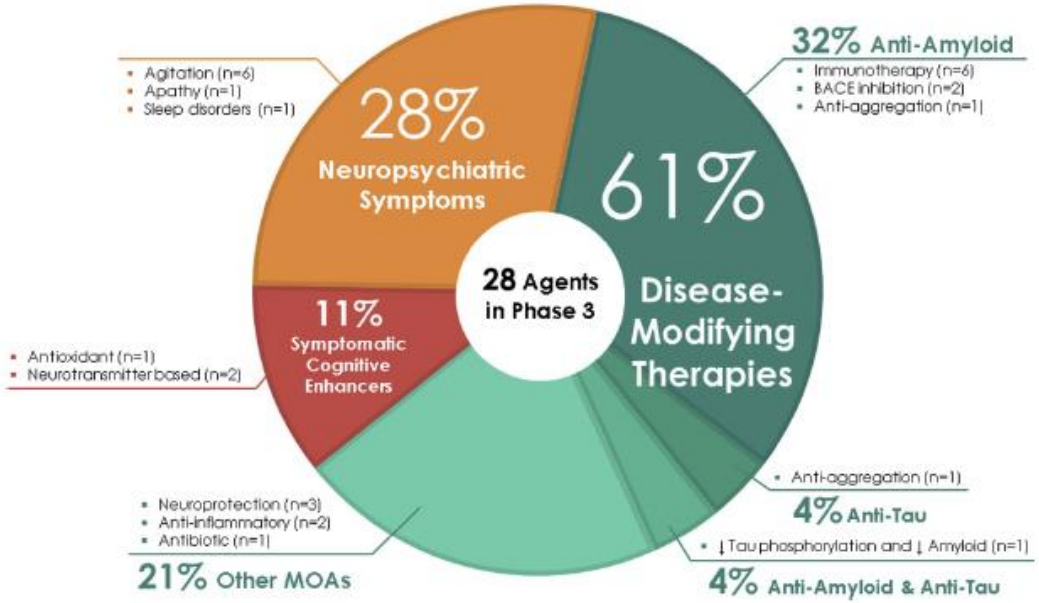

Fig. 2. Mechanisms of action of agents in phase 3.

THE END