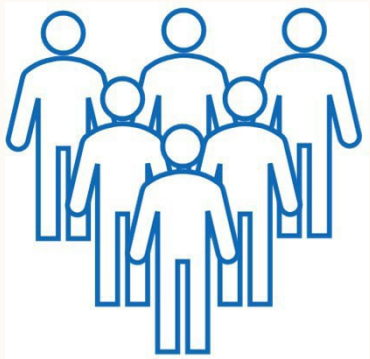
THE “OTHER” DEMENTIAS:
AN INTRODUCTION TO NON-ALZHEIMER’S DISEASE

Dementia is:

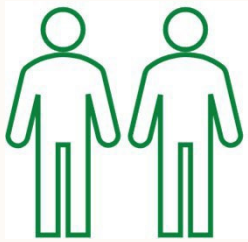
- Cognitive decline that has impaired one's daily activities or resulted in loss of functioning at work or at home.
- Not due to illness, medication effects, or a psychiatric disorder.
- A substantial decline from one's presumed pre-illness baseline on neuropsychological testing
- A description, not a diagnosis

Dementia is a syndrome often (but far from always) associated with a neurodegenerative disease



Alzheimer's
50%-70%

Vascular
20%-30%



Lewy Body
10%-25%

Frontotemporal
10%-15%

Advisory Council on Alzheimer's Research, Care and Services, 2016

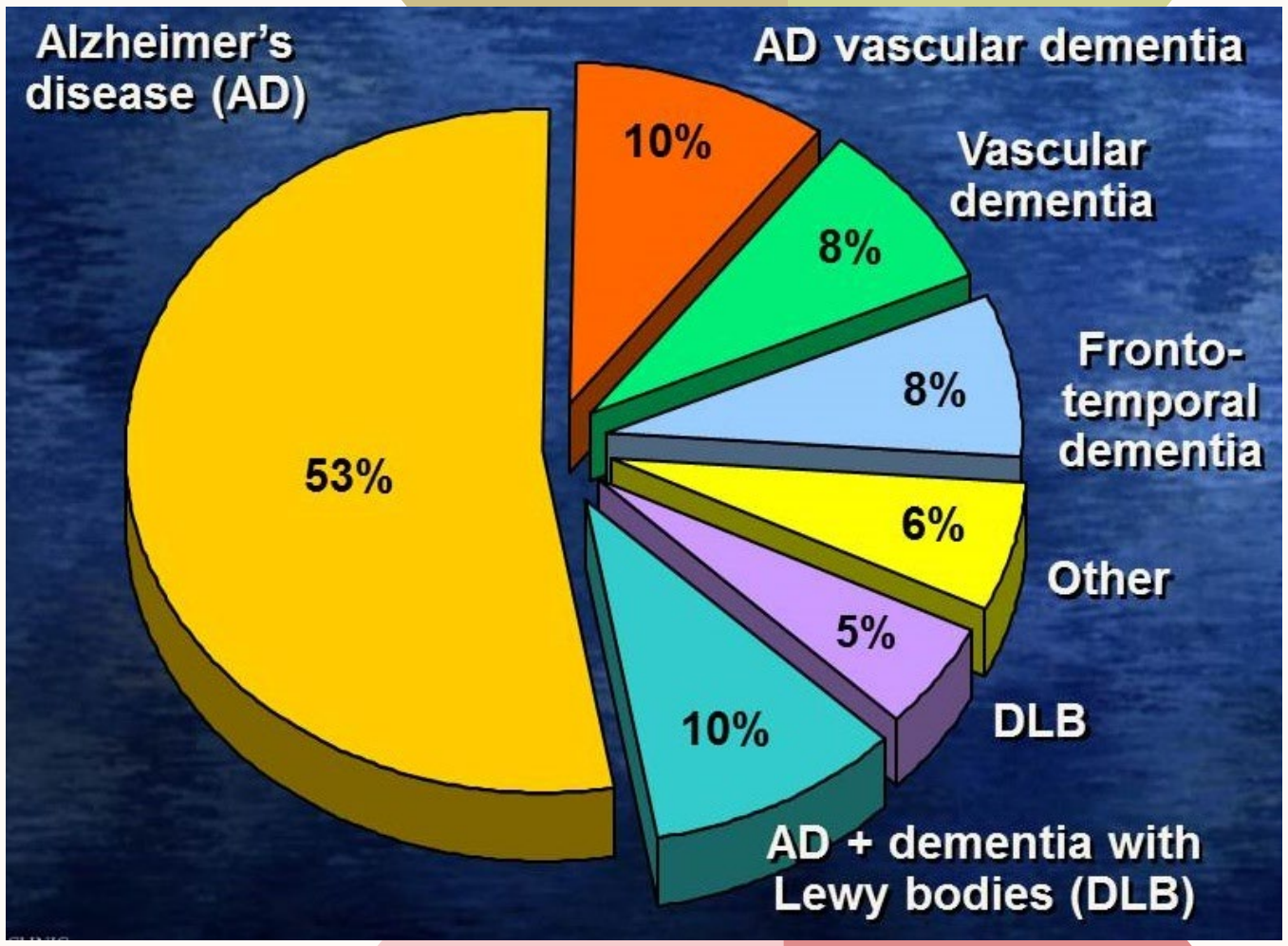
AGENDA

Lewy Body Disease

Frontotemporal Dementias

Vascular Dementia

Mixed Dementias



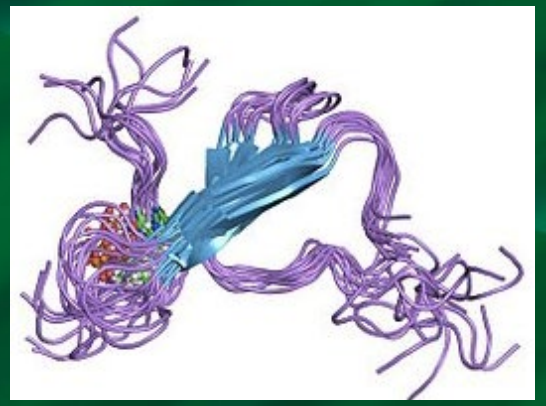
Not discussed today: LATE Disease

https://aspe.hhs.gov/

What do all neurodegenerative diseases have in common?

They are all proteinopathies

- Normal cell proteins change their folding pattern to gain toxic activity or lose normal function



- Disease is triggered because the misfolded proteins stick to each other after changing their shape, and collect in distinct brain areas/neuron types.
- “Prion-like” (pseudo-infectious) cell-to-cell transmission
- Most of the proteinopathies cause more than one type of dementia

Beta-amyloid

Phospho-tau

Alpha-synuclein

TDP-43

Prion protein

FUS

Lewy Body Diseases: Some Terminology

Clinical syndromes

- Parkinson's disease with dementia (PDD)
- Dementia with Lewy bodies (DLB)
- Prodromal Dementia with Lewy Bodies (aka MCI of the Lewy Body type)

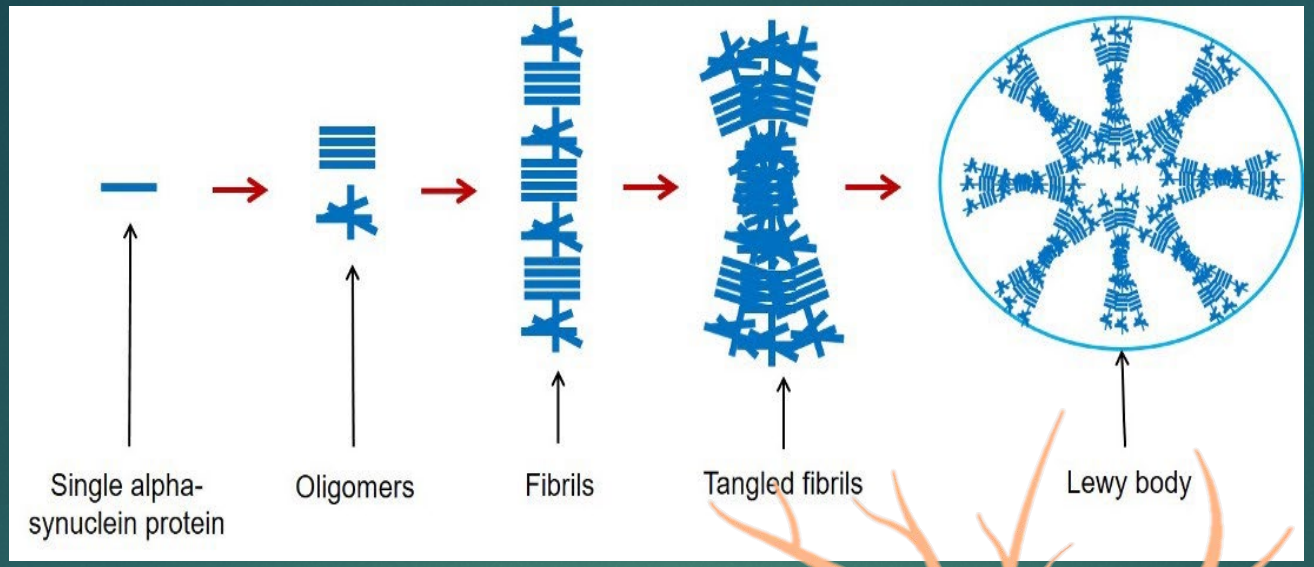
} Lewy Body Dementias

parkinsonism

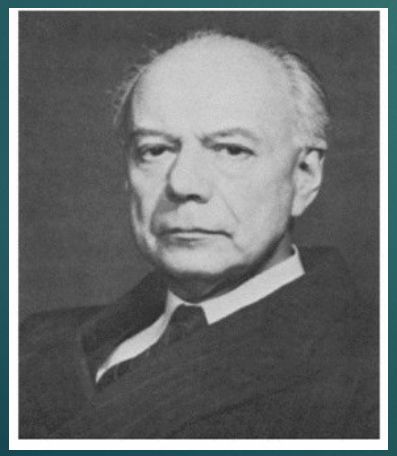
↓ 1 year

dementia

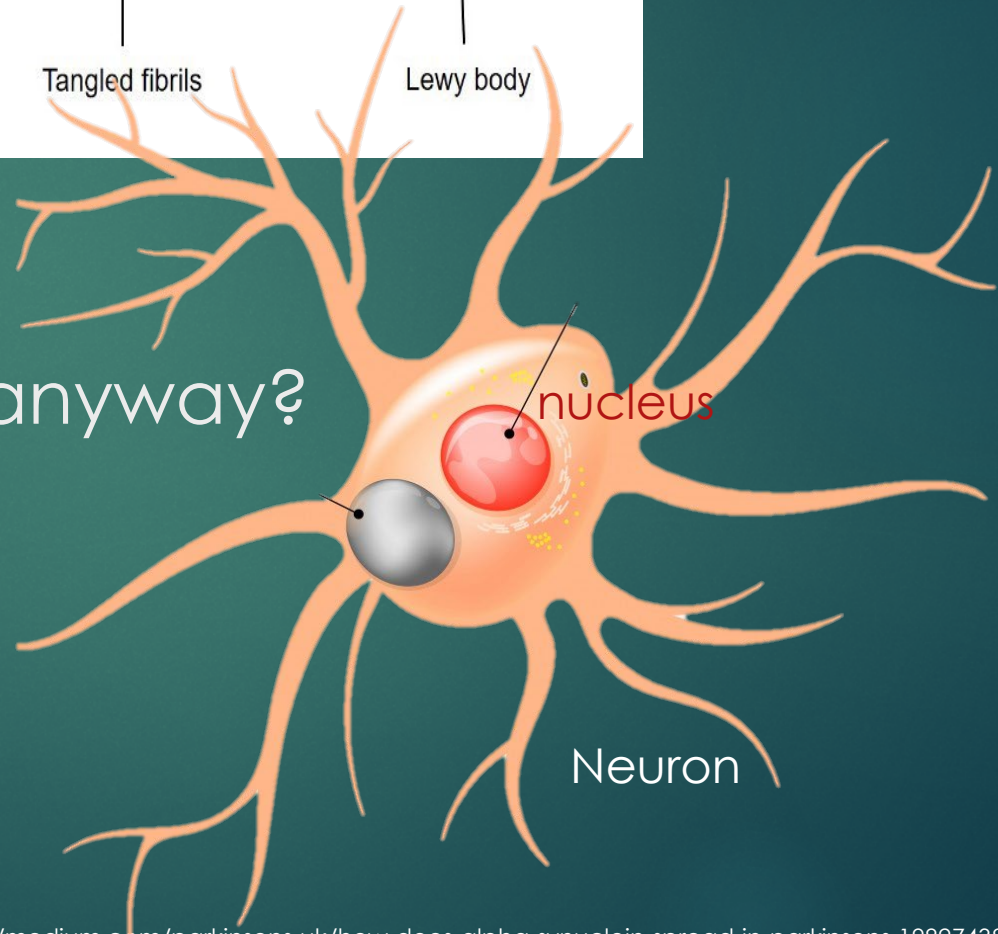
Advances in dementia with Lewy bodies
Melissa J. Armstrong
https://doi.org/10.1177/17562864211057666



What is a Lewy Body anyway?



Frederic Lewy, 1885-1950

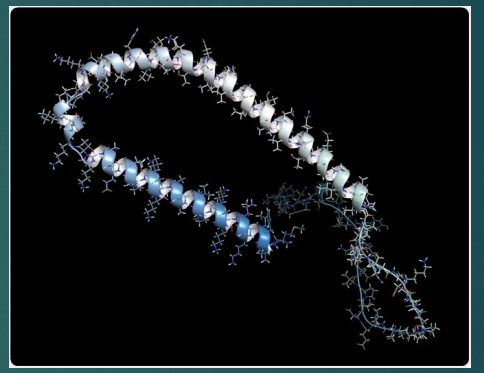


https://medium.com/parkinsons-uk/how-does-alpha-synuclein-spread-in-parkinsons-1982743840c

Pathologically-defined disease

Lewy body disease
Parkinson's disease

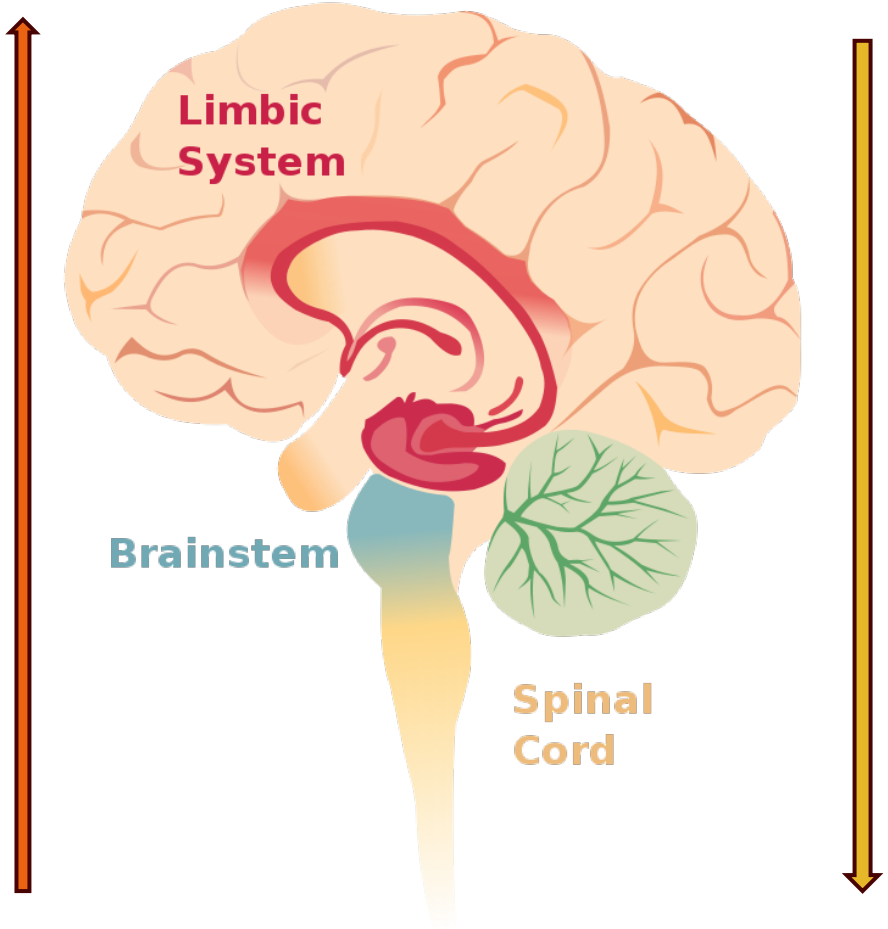
"Synucleinopathy"



Alpha synuclein is a neuronal protein that regulates neurotransmitter release, discovered in 1991

Parkinson's with dementia

Dementia with Lewy Bodies



LEWY BODY DISEASE IS:

- A specific disease that can cause dementia
- A neurodegenerative disease that causes loss of neurons over time. Always progressive but rate is very variable
- Associated with abnormally high levels of a neuronal protein, alpha-synuclein
- Frequently has a transitional state of Mild Cognitive Impairment (MCI)
- When MCI is accompanied by an LBD biomarker: MCI-due-to-LBD
- Now understood to start up to 20 years before someone gets cognitive decline, **BUT some symptoms from an early stage are likely**
- Not everyone with LBD has dementia

Core Clinical Features for DLB Diagnosis

DEMENTIA (OBLIGATORY) +

2 OR MORE OF:

PARKINSONISM

VISUAL HALLUCINATIONS

COGNITIVE FLUCTUATIONS

REM SLEEP BEHAVIOR DISORDER

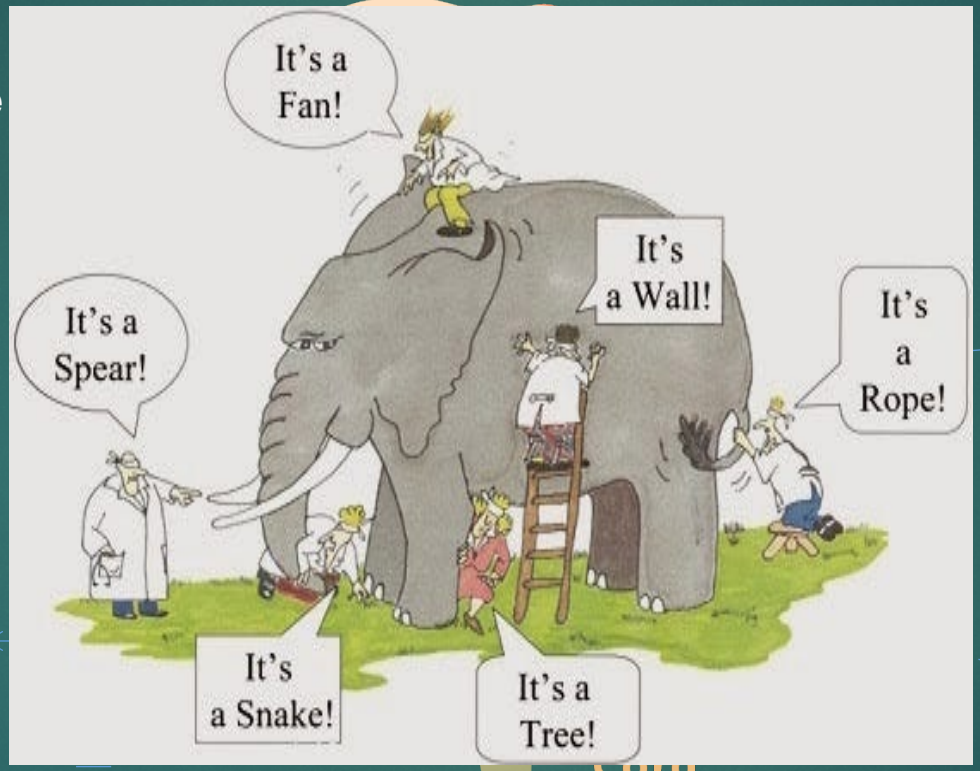
Neurology. 2017 Jul 4; 89(1): 88–100.
doi: 10.1212/WNL.0000000000004058

Diagnosis and management of dementia with Lewy bodies
Fourth consensus report of the DLB Consortium

Ian G. McKeith, MD, F Med Sci,[✉] Bradley F. Boeve, MD, Dennis W. Dickson, MD, Glenda Hal

The Many Faces of DLB

Smell/taste changes



Cognitive impairment
Visual hallucinations

Parkinsonism

Sleep and mood changes

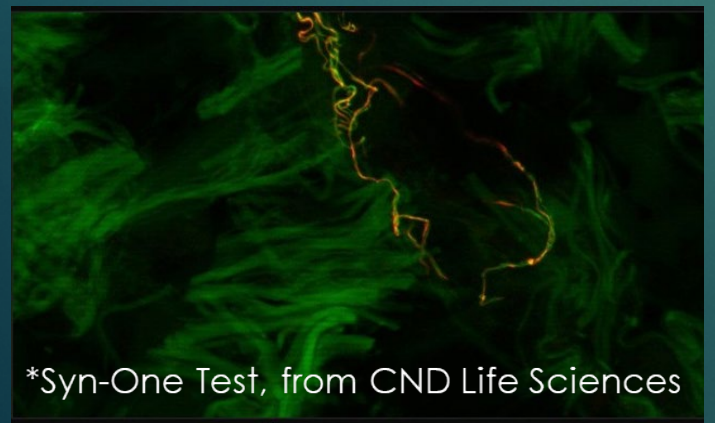
Constipation
Sexual dysfunction
Urinary incontinence

Blood pressure changes

New Diagnostic Methods that directly detect abnormal alpha-synuclein

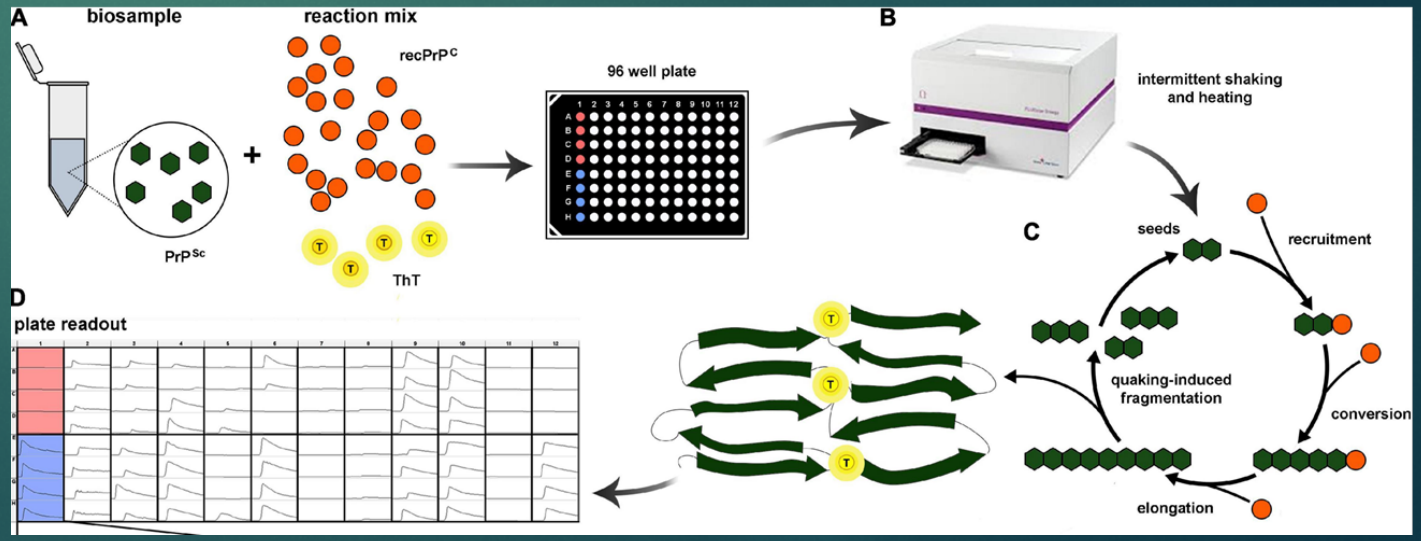
Skin biopsy

- Covered by Medicare
- Skin punch biopsy from 3 sites: neck, upper calf and ankle
- Detect and visualize abnormal alpha-synuclein in skin nerve fibers by immunofluorescence



Lumbar puncture

- Not yet covered by Medicare
- From cerebrospinal fluid
- Detect and visualize abnormal alpha-synuclein by real-time quaking-induced conversion (RT-quic) and immunofluorescence



The U.S. Based

DIAMOND Lewy™ Management Toolkit

Management Overview and Symptom Management Summaries

LBDA
LEWY BODY DEMENTIA ASSOCIATION

Used with permission from Newcastle University and Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust.

Available to download at lbda.org

Lewy body dementia: Management Overview

- Identify key problems under domain headings such as cognition; gait, balance and movement; hallucinations; fluctuations; behavior and mood; sleep, and autonomic system dysfunction.
- Establish which problems have high priority for treatment.
- Discuss benefits and risks of treatment.
- Be aware that symptom response is variable and that benefits in one might be at the cost of worsening of others
- Individual treatments may have global benefits e.g. cholinesterase inhibitors.

COGNITIVE

Non-pharmacological

- cognitive stimulation, use of memory aids, increased social interaction and stimulation, and exercise.

Pharmacological

- **Cholinesterase inhibitors** first-line.
- **Memantine** second line.

NEUROPSYCHIATRIC

Psychosis

- Non-pharmacological includes orientation, validation, reassurance, distraction.
- May respond to **cholinesterase inhibitors** especially visual hallucinations.
- Be cautious in the use of antipsychotics.
- **Quietiapine and clozapine** are least apt to worsen parkinsonism. ⚠

Mood

- Use of **social interventions** may enhance mood.
- SSRIs or SNRIs first line ⚠
- Avoid agents with significant anti-cholinergic side effects. Avoid antipsychotics for non-psychotic mood disorders

SLEEP

Insomnia

- Work on **sleep hygiene.**
- **Review all medications** that could be affecting sleep.
- **Melatonin** 1 hour prior to bedtime

⚠ **Cautious consideration for other sleep aids**

REM-sleep behavior disorder

- Consider **non-pharmacological** as first-line and only treat if troublesome.
- **Melatonin is first line**

⚠ **Clonazepam** may help although **possible** side effects

Motor related sleep disturbances

- May be improved with long-acting levodopa.

Other

Evaluation for OSA

AUTONOMIC

Orthostatic hypotension

- **non-pharmacological** management e.g. compression stockings, fluid/salt intake, stand slowly.
- pharmacological e.g. fludrocortisone, midodrine, droxidopa

✕ Reduce/remove exacerbating drugs e.g. antihypertensives.

Constipation

- **Hydration and fiber intake.**
- **Stool softeners or mild laxatives like polyethylene glycol**

Gastroparesis

- **Non-pharmacological: smaller, more frequent meals**

✕ **Avoid** using metoclopramide.

Urinary dysfunction

- **Non-pharmacological** first-line e.g. pads, sheath catheter etc.

Pharmacological: based on etiology. Consideration for referral to Urology. Agents like, Mirabegron can be considered. Botox may be considered for overactive bladder. Avoid centrally acting anticholinergics.

Sexual dysfunction

⚠ **Phosphodiesterase-5 inhibitors** may be considered with caution in men

Sialorrhea

✕ Anticholinergics should not generally be used

- **Botulinum toxin injections** to salivary glands is an effective treatment

MOTOR

- Preferred pharmacological treatment of parkinsonism in LBD is **levodopa monotherapy.**
- Use **minimal dose** needed for benefit.

Monitor for potential neuropsychiatric side effects, if present:

✕ **Withdraw in order, one at a time:** anticholinergic drugs, amantadine, selegiline, dopamine agonists and catechol-O-methyltransferase inhibitors.

- Remember that LBD patients may exhibit exaggerated responses to medications.
- Severe antipsychotic sensitivity can occur in up to 50% of patients therefore use antipsychotic agents with caution.
- Review the need for drugs which can affect brain function and/or cause sedation and falls (see Beers List).
- Minimize anticholinergic burden as this may worsen cognition and behavior, and counteract cholinesterase inhibitors.

Frontotemporal Lobar Degeneration

No clean mapping of proteinopathy/mutation with clinical syndrome

Phospho-tau TDP-43 FUS

- Behavioral variant Frontotemporal Dementia (“Pick’s disease”)
  - Sometimes with motor neuron disease (“Lou Gehrig’s disease”)
- Progressive Semantic Dementia
- Progressive Non-Fluent aphasia
- Progressive logopenic aphasia (shared with Alzheimer’s)
- Corticobasal Degeneration (shared with Alzheimer’s)

Behavioral Variant Frontotemporal Dementia Clinical Features

- Personality change of "frontal lobe" type:
  - apathy, disinhibition, irritability, loss of empathy & sympathy
- "Dysexecutive syndrome" type cognitive loss: poor judgement, logic and reasoning
- Mood symptoms; depression, emotional dysregulation
- Speech/language disorder; mutism, aphasia
- Age of onset typically a decade+ younger than AD.
- Often, more rapid progression than AD

- A 62-year-old financial planner became progressively more aloof, exhibiting increased insensitivity to others. On one occasion he abandoned his two 3-year-old grandchildren at night a block from their house, believing they could return home on their own.
- One to 2 years later, he started to behave in a sexually inappropriate manner toward different women, to eat voraciously (subsisting on junk food, pizza, and ice cream), to drink wine heavily, and to misuse medications such as diazepam (up to 30 mg a day). On several occasions, even after being explicitly told not to do so, he entered his neighbor's garage and stole liquor. The patient lacked any insight into the inappropriateness of his actions. Family members reported that he also showed impaired decision making and problem solving in daily life situations, eg, shuffling boxes around without purpose during a family move.
- Standard neuropsychological test scores were within the average range apart from mild impairments in verbal generation and a complex executive task requiring a combination of set-shifting and verbal response inhibition.
- Despite his quite preserved cognitive skills, his emotion recognition for faces and voices was impaired, as was his ability to detect sarcasm and deception, and to adopt another person's perspective.

Language-predominant forms of frontotemporal dementia

Progressive Nonfluent Aphasia and Logopenic (fluent) Aphasia

- Nonfluent: progressive loss of speech output, effortful, *agrammatic* speech, impaired repetition and naming, milder comprehension deficits
- Logopenic: speech fluent but empty. More comprehension problems than Nonfluent but less than Semantic
- Many patients eventually develop a true dementia, but often takes >5 years
- https://youtu.be/XJyRpPjT-jk?list=PL6gus3T87-y3Eze-2VhCmhtqCynphdJ_h (to 1:05)

Semantic Dementia

- Empty, circumlocutory speech with frequent word mistakes. Comprehension is very impaired.
- Poor knowledge of the meaning of words- lose understanding of what something is
- Syntax, grammar and repetition are comparatively preserved
- Slightly older age of onset than FTD/PPA
- https://youtu.be/fkKrsbwQvrE?list=PL6gus3T87-y3Eze-2VhCmhtqCynphdJ_h&t=66

Corticobasal Syndrome Clinical Features

Distinctive clinical feature: progressive, asymmetric limb stiffness and apraxia

Cortical

- Apraxia
- Myoclonus
- Cortical sensory loss (can't tell where being touched)
- "Alien limb: phenomenon
- Aphasia
- Visuospatial deficits

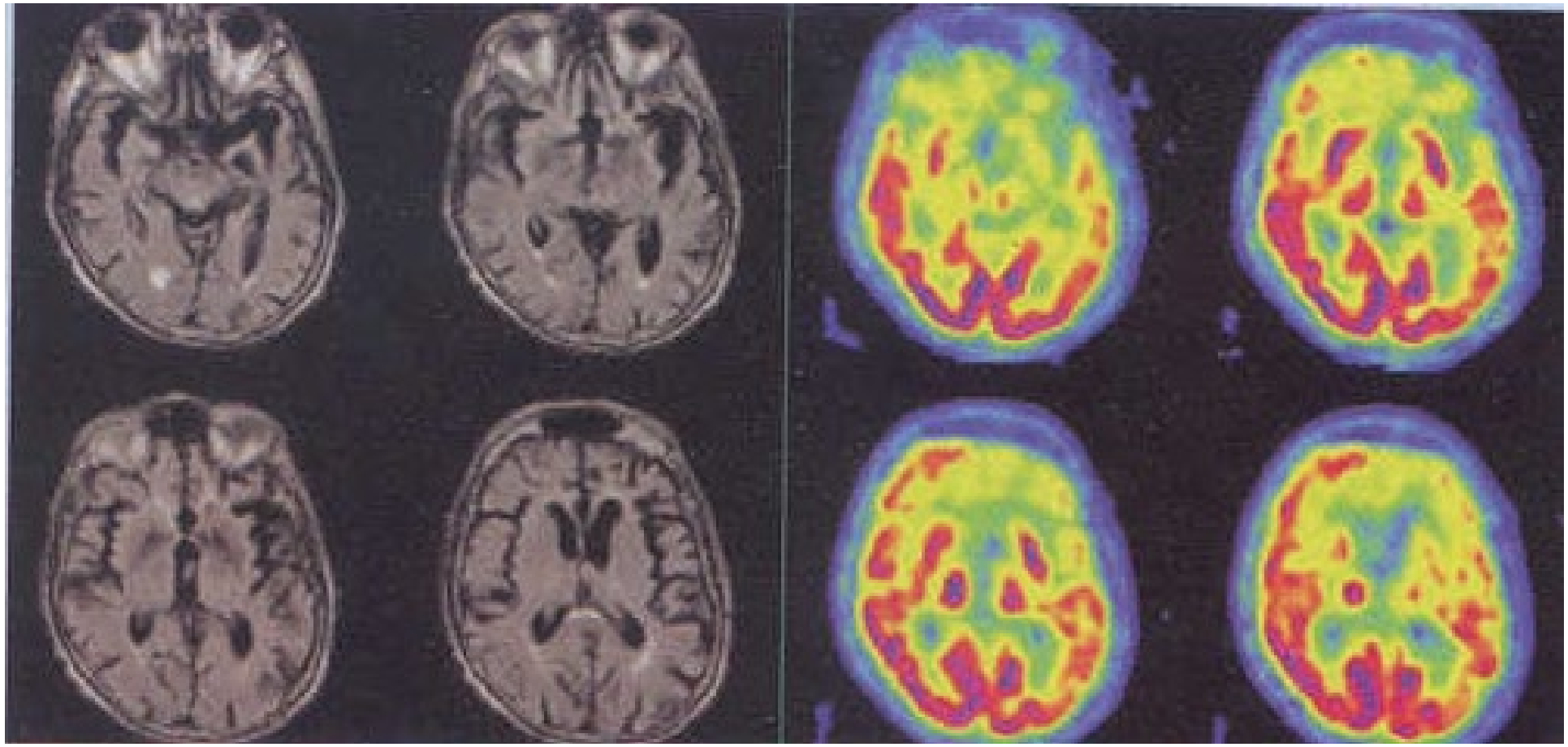
Basal

- Rigidity
- Sometimes tremor
- Limb Stiffness
- Fisted hand

https://youtu.be/5GgZjhSEoQI?list=PL6gus3T87-y3Eze-2VhCmhtqCynphdJ_h

Apraxia:
Inability to carry out skilled motor movements (e.g. flipping over a coin in one's hand) not due to weakness, pain or other incoordination but because the learned "motor program" is damaged

MRI and FDG-PET of typical FTD



Off-label use of FDA-approved drugs for symptoms

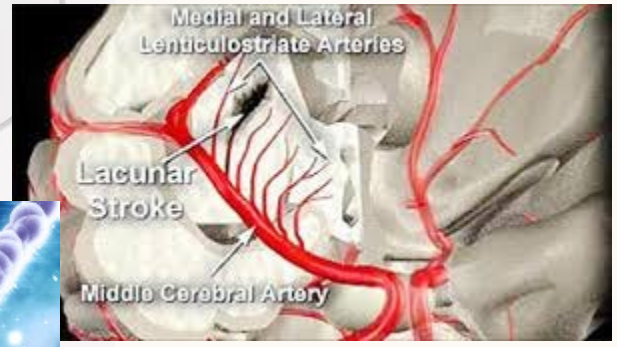
- Cholinesterase inhibitors do not improve any aspect of any form of FTLD (inc. PSP). ***DO NOT USE***.
- Memantine MAY help cognitive, though not behavioral symptoms in bvFTD and PPA
- Small, uncontrolled studies of SSRIs (paroxetine, trazodone, citalopram, fluvoxamine) suggest a modest benefit on the NPI (neuropsychiatric inventory). Needs replication.
- Aripiprazole, quetiapine, olanzapine have each shown benefit on NPI (agitation and inappropriate behaviors) in small, open-label studies.
- Case reports of valproic acid and lithium being used successfully. The latter is being tested more rigorously now.

VASCULAR DEMENTIA

A cognitive loss syndrome attributable to some combination of:

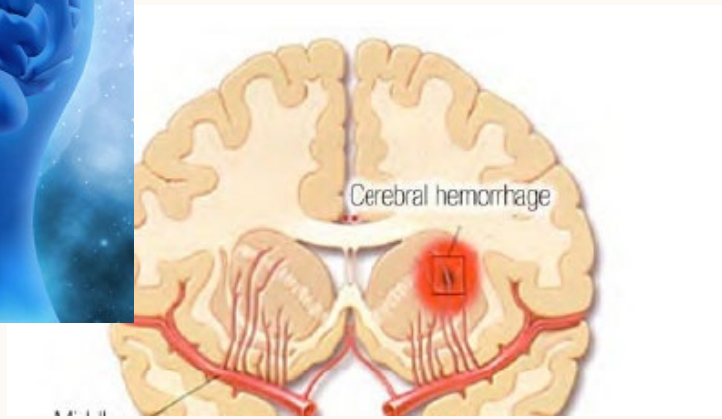
- thromboembolic stroke

- small vessel lacunar stroke

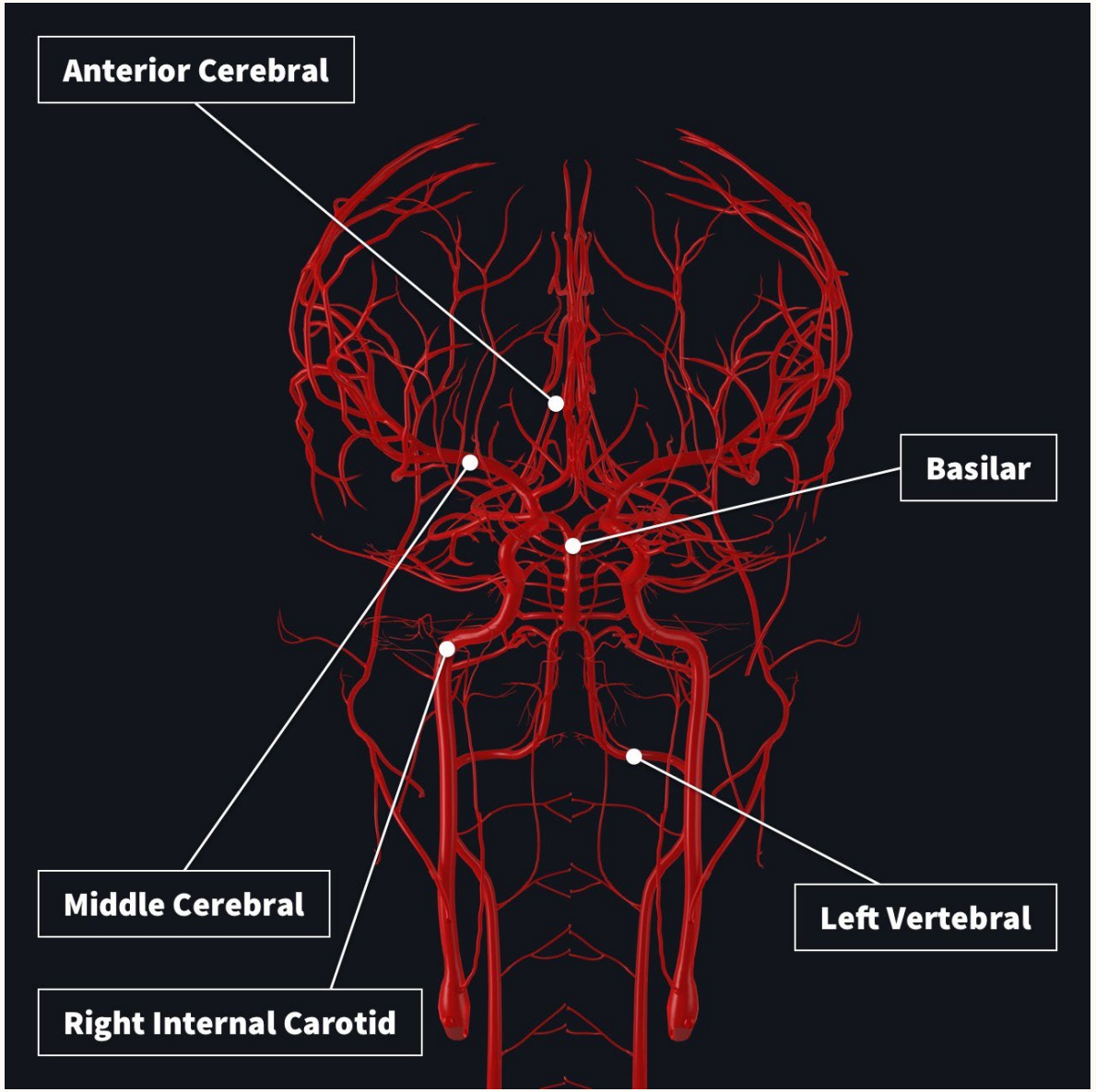


- chronic ischemia with neuronal loss

- hemorrhages: both within and outside the brain

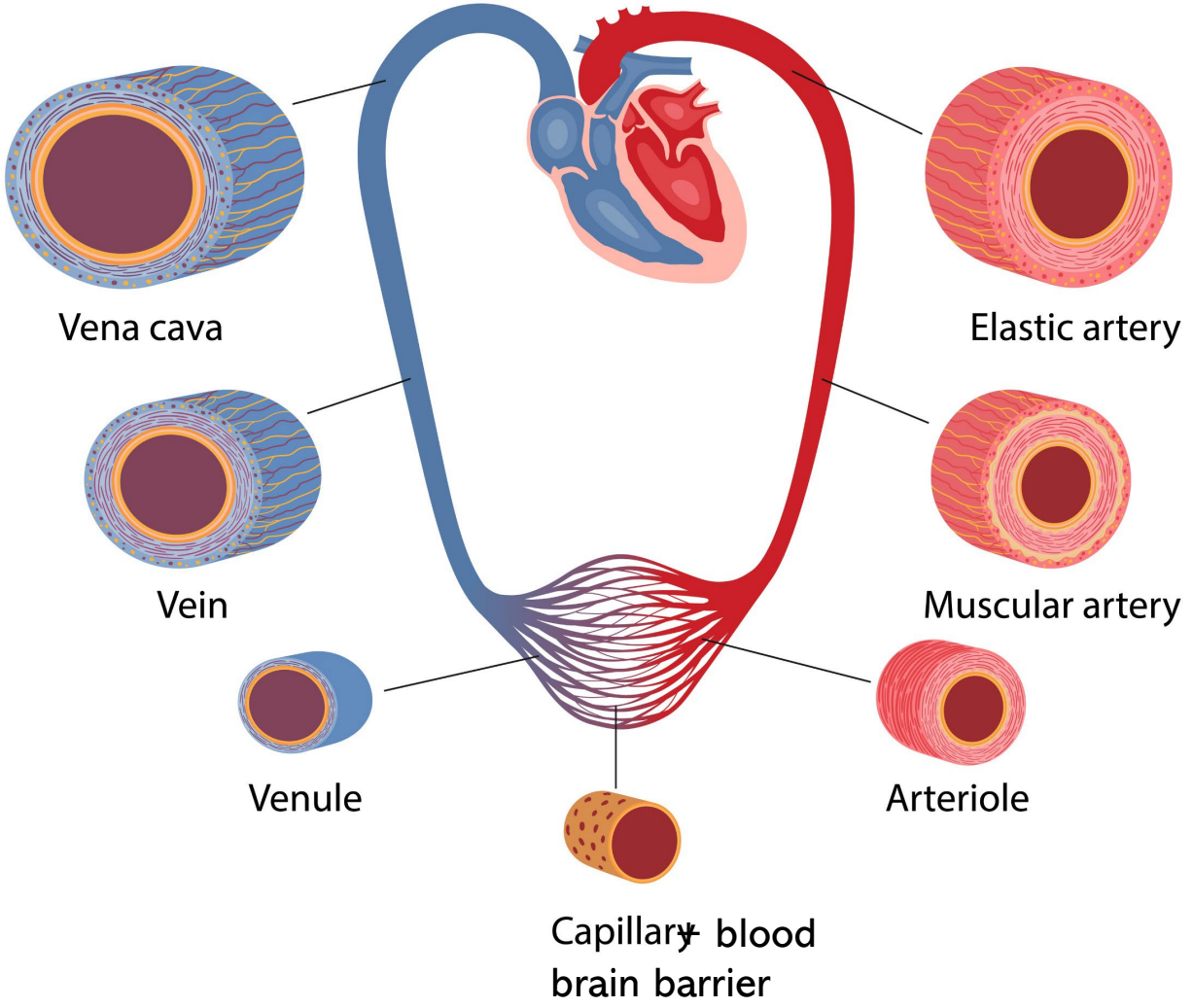


GLASS BRAIN (3D) VIEW



https://3d4medical.com/blog/blood-supply-to-the-brain

Blood vessels types



Source of emboli + atherosclerosis

athero- and arteriosclerosis

Ischemic small vessel disease

TYPES OF VASCULAR DEMENTIA

- **Large/medium vessel disease:** Multi-infarct dementia
- **Small vessel disease:** Subcortical Vascular Dementia
- **Mixed dementia:** neurodegenerative + vascular *or* ischemic + hemorrhagic

FEATURES OF VASCULAR DEMENTIA

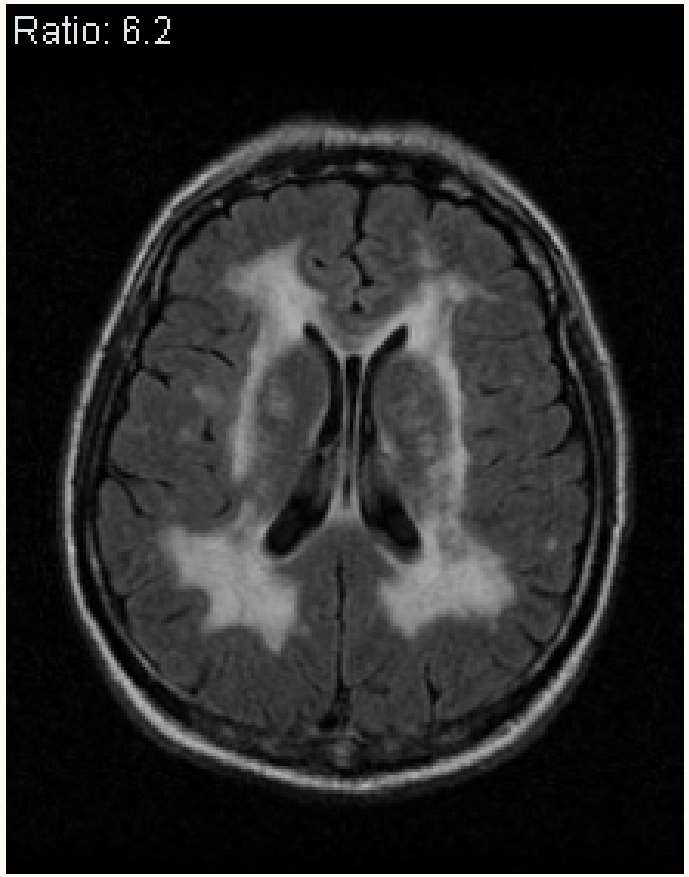
Cognitive

- Cognitive slowing: "processing speed"
- Attentional Problems
- Dysexecutive syndrome
- Variable degree of memory loss
- Language problems if L-sided

Non-cognitive

- Depression
- Gait and balance impairment
- Urinary frequency/incontinence
- Personality changes
- Confusion and agitation

SUBCORTICAL ISCHEMIC VASCULAR DEMENTIA



- Used to be called “Binswanger’s Disease”
- No good consensus on diagnostic criteria
- Decline is insidiously progressive, not stepwise
- Often no physical abnormalities, unlike after a stroke
- Most common associated impairments are gait disturbance and urinary incontinence

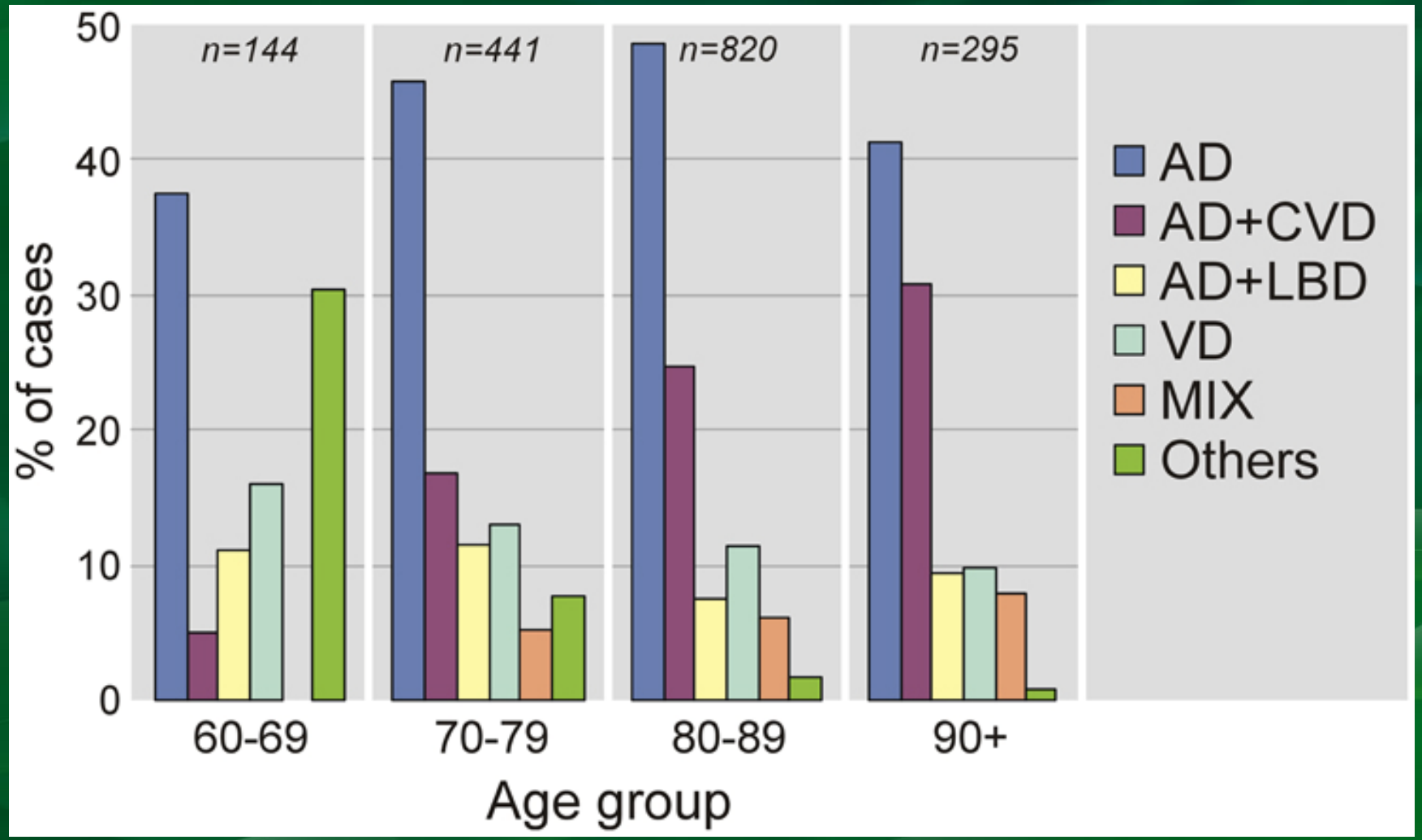
TREATMENT

- No role for cholinesterase inhibitors or memantine in “pure” VCI
- Goal is to slow progression through effective control of vascular risk factors:
  - Systolic Blood Pressure <=120, based on SPRINT-MIND*
  - Smoking cessation, LDL cholesterol <80, eliminate insulin resistance
- Low-dose aspirin and/or cilostazol**
- Aerobic exercise: 30+ min daily
- Mediterranean or MIND diet
- Eliminate most ultra-processed foods
- Sufficient sleep; treat sleep apnea

**Class C evidence only

*JAMA. 2019;321(6):553-561. doi:10.1001/jama.2018.21442

Mixed Dementias

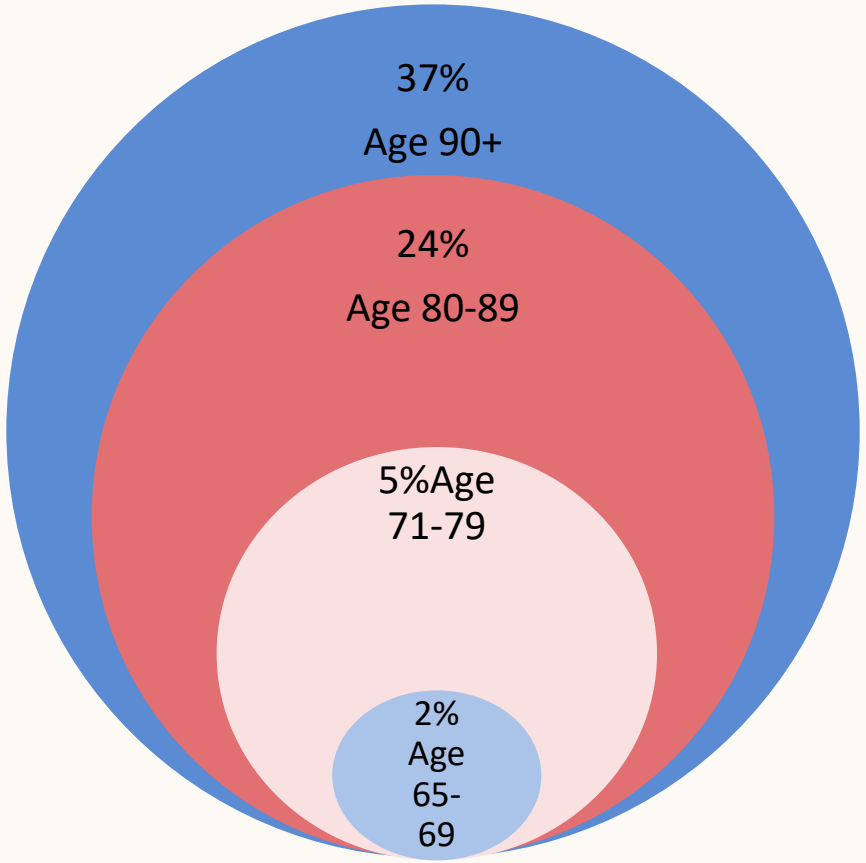


Jellinger, Front. Aging Neurosci., 10 April 2013 | doi: 10.3389

U.S. DEMENTIA BY THE NUMBERS:

8 M … but if you add in MCI, 16 M

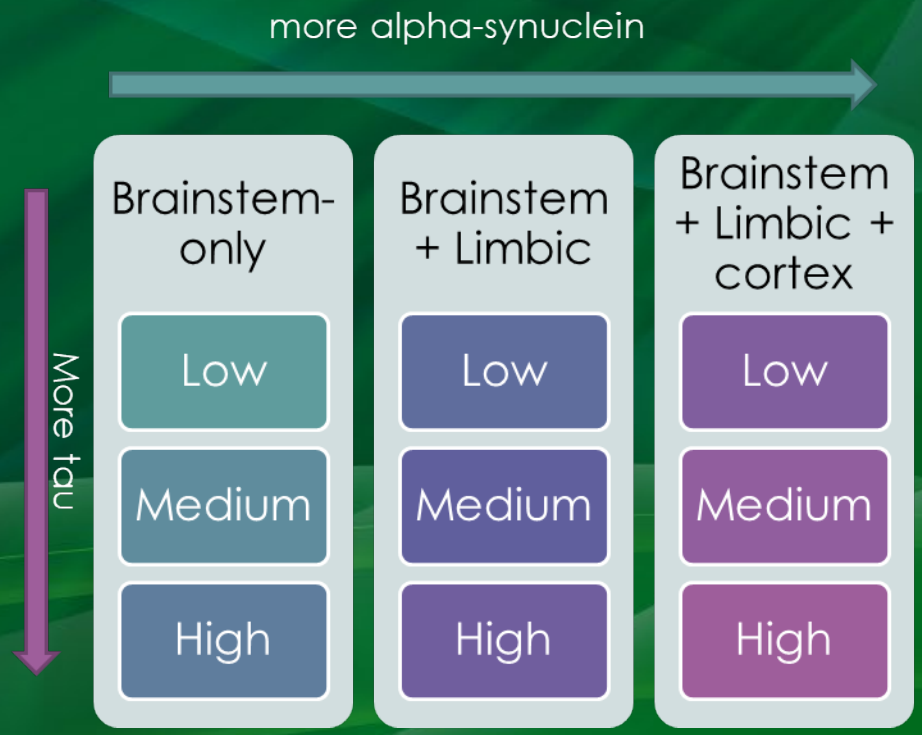
5% of population is living with cognitive impairment



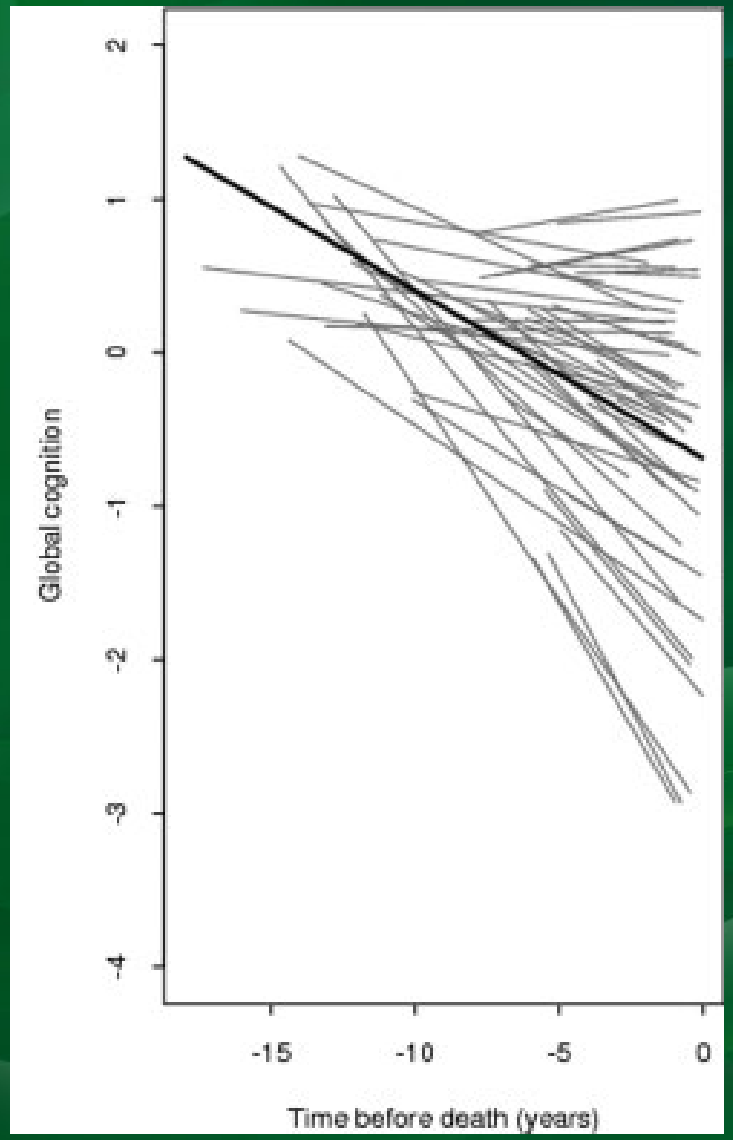
After age 90, >1/3 have dementia, >60% have cognitive impairment… but < 1/2 have AD as the sole cause

“Mixed” DLB and Alzheimer’s disease

- Autopsy studies indicate that between a third and a half of carefully clinically diagnosed AD show some degree of LB pathology at autopsy and
- Up to 50% of Lewy Body Disease patients have at least some AD pathology
- Mixed disease patients have more severe disease and shorter survival but also depends on extent of each pathology



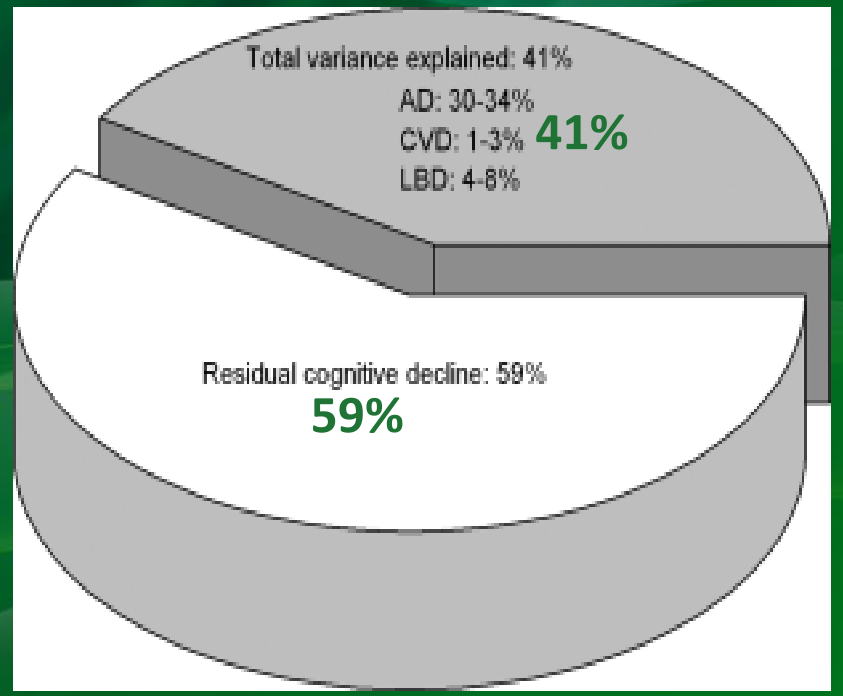
Late life cognitive decline is very variable:



The extent to which variation in cognitive decline is explained by different pathologies including

- amyloid load,
- tangle density,
- macroscopic infarcts
- microinfarcts,
- Lewy bodies

TDP-43 may be one "missing factor"

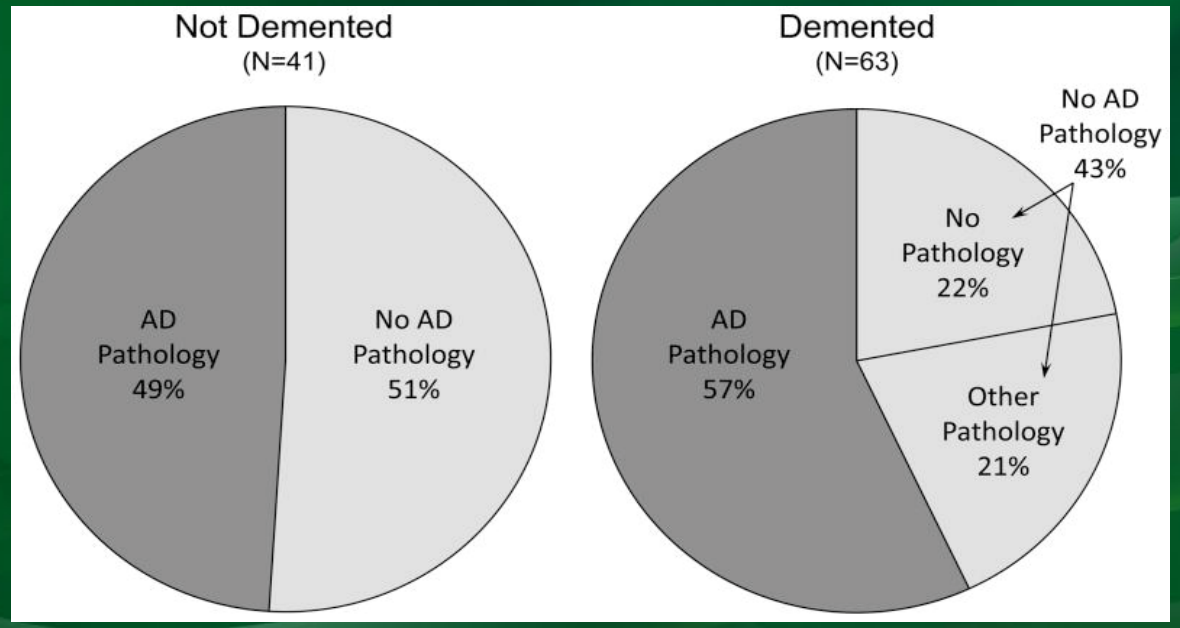


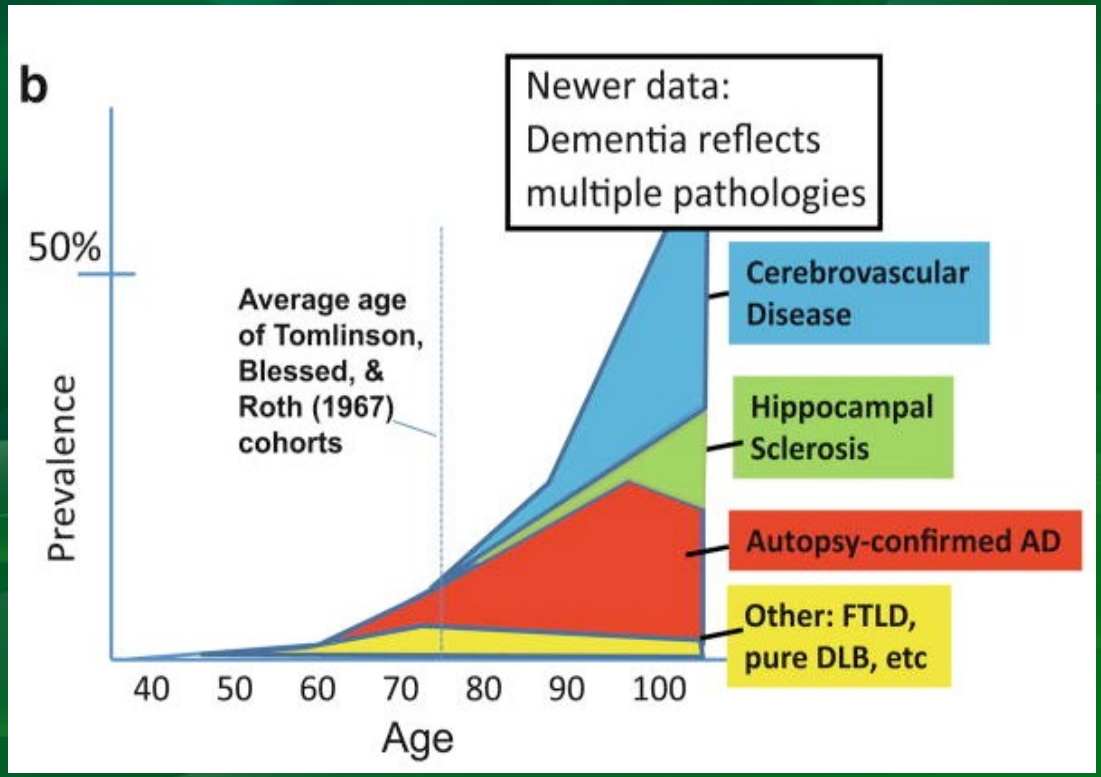
Annals of Neurology
Volume 74, Issue 3, pages 478-489, 10 JUL 2013 DOI: 10.1002/ana.23964

Oldest-old (>85) dementia causes are less frequently AD

Brain diseases *other than pure AD* afflict older human brains and contribute to cognitive impairment:

- Cerebrovascular disease
- AD/VD/LB mixed pathology
- Hippocampal sclerosis (TDP-43 related)





Zarow C et al, Brain Behav. 2012 Jul;2(4)
Nelson et al, Acta Neuropathol 2011
Corrada M et al, Curr Alzheimer Res. 2012 Jul;9(6):

The Punchline: Dementia ≠ AD

- Clinical symptoms map less well onto brain disorder than most textbooks (and neurologists) admit
- Alzheimer's frequently co-exists with additional pathologies that are sufficient to cause dementia in themselves
- Alzheimer's pathology alone is often insufficient to cause dementia during a person's life
- Accurately diagnosing individuals with full-blown dementia is hard enough; diagnostic uncertainty increases substantially in the MCI stage
- New blood, spinal fluid and skin tests are helping increase accuracy of diagnosis, or diagnoses

NC Registry for Brain Health

https://ncbrainhealth.org/

A mailing list to connect people who are interested in getting involved in research with enrolling studies throughout North Carolina

THANK YOU. QUESTIONS?

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