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# Alzheimer's Disease Update:
## Differentiating Cognitive Impairment with Aging, Medical Illness, and Alzheimer's disease

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UAB Neurology

# Disclosures

- Research support (paid to UAB):
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- Stock holdings
  - Doximity

## Off-label use

- Off-label uses of marketed products: antidepressant medications for sleep

# Learning Objectives

By the end of the session a learner should be able to:

- Identify cognitive deficits associated with uncomplicated aging and common illness states
- Describe characteristics of subjective cognitive decline that predict future progression
- Effectively employ imaging and biomarker testing in assessment of cognitive impairments
- Communicate appropriate expectations for pharmacological treatments directed at patients with Alzheimer's disease.

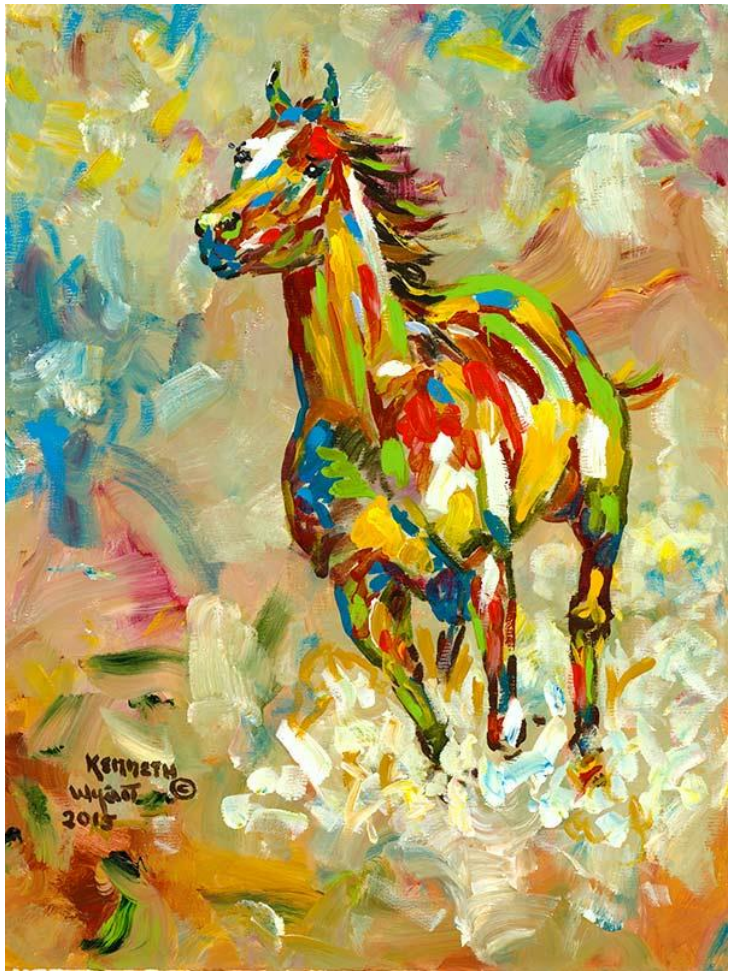
# Core questions in approaching the person with cognitive concerns

- Is the problem age-related or pathological?
- If pathological, how is the brain affected
  - Function (“software”)
  - Structure (“hardware”)
- Is dementia present?
- Is the problem reversible?
- Are specific tests or treatments available?

# Short-term memory loss

## A horse of many colors

- Patients  - and health care providers - lump many problems together as *“short term memory loss”*
- It can mean any or all of these:
  - Distractibility
  - Slowed recall
  - Impaired word finding
  - Difficulty recalling names
  - Route finding problems
  - Actual memory formation failures

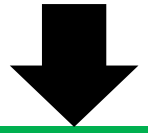



A horse of a different color
Kenneth Wyatt, 2015

# Definitions:
# Severity of cognitive loss

# Defining Subjective Cognitive Decline: Major features

- Self-experienced persistent decline in cognitive capacity unrelated to an acute event
  - Observation of decline by others is not required
- **Normal performance** on clinical testing
- Sometimes described as “The Worried Well”



Unimpaired | MCI | Dementia

# Subjective cognitive decline (SCD) and prognosis

- Most people don't decline, but (with 4 or more years of follow-up)
  - Objective deficits emerge in 27%
  - Dementia occurs in 14%
  - SCD precedes dementia by ~10 years
- Some characteristics increase the risk for decline (SCD Plus)

***Panel*: Features that increase the risk of cognitive decline (SCD plus)**

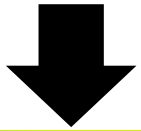
- Subjective decline in memory irrespective of function in other cognitive domains[5,14]
- Onset of SCD within the past 5 years[24,25]
- Onset of SCD at 60 years and older[4]
- Concern (worry) associated with SCD[14,26]
- Persistence of SCD over time[23,27,28*]
- Seeking of medical help[6,29*]
- Confirmation of cognitive decline by an observer[30,31,32]

*Not part of the original SCD plus features.[4] SCD=subjective cognitive decline.

Jessen F, et al *Lancet Neurol* 2020; 19: 271-78

# Defining Mild Cognitive Impairment
## The front door to dementia

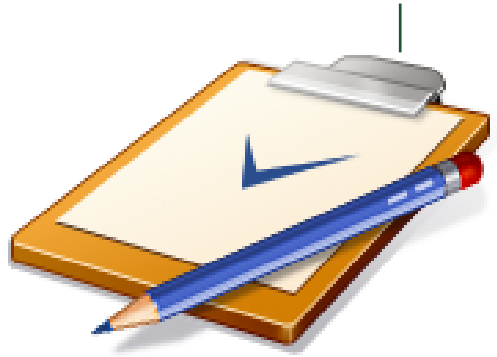
- Concerns for a change in cognition reported by patient or informant or clinician
- **Objective impairment** in ≥ 1 cognitive domain
  - Typically including memory
- **Preserved independence in functional abilities**
  - May have mild problems performing complex functional tasks (bill paying, meal prep, shopping)
  - May take more time, be less efficient, and make more errors
- Not demented



Albert et al, Alzheimer's & Dementia 2011; 7:270-9;
Morris JC , Arch Neurol 2012

Unimpaired | MCI | Dementia

# Defining Dementia



- **Cognitive losses that interfere with usual activities**
- **Decline from a previous level of function**
- Not delirium or psychiatric disorder
- Diagnosed by history and exam (**not a test score or biomarker**)
- Involves at least 2 cognitive domains:
  - Memory
  - Reasoning and judgment
  - Visuospatial
  - Language
  - Personality, behavior, comportment

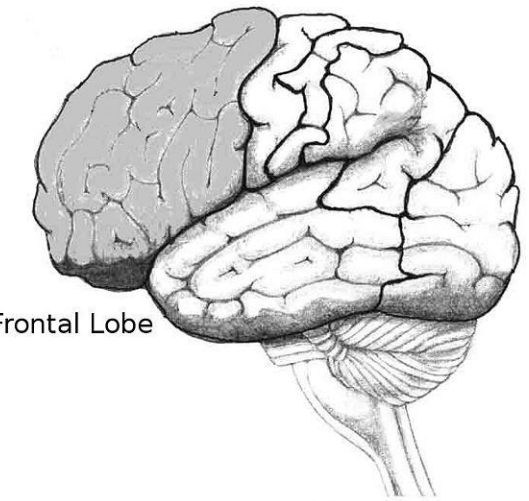
Alzheimer's and Dementia, April 2011

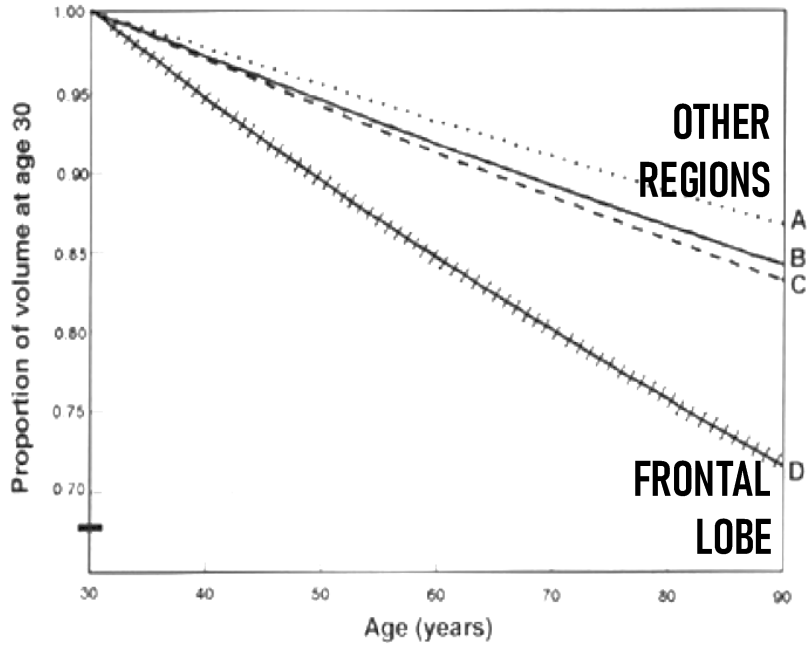
Unimpaired → MCI → Dementia

# What happens to the brain and memory with aging?

# Age-Related Changes on Mental Function

- The frontal lobes show the most age-related atrophy (~30%), resulting in:
  - Loss of mental speed
  - Reduced cognitive flexibility
  - Variable effects on memory
    - Preserved recall of old information
    - Reduced recall of newly learned material
- Minimal effect on everyday skills

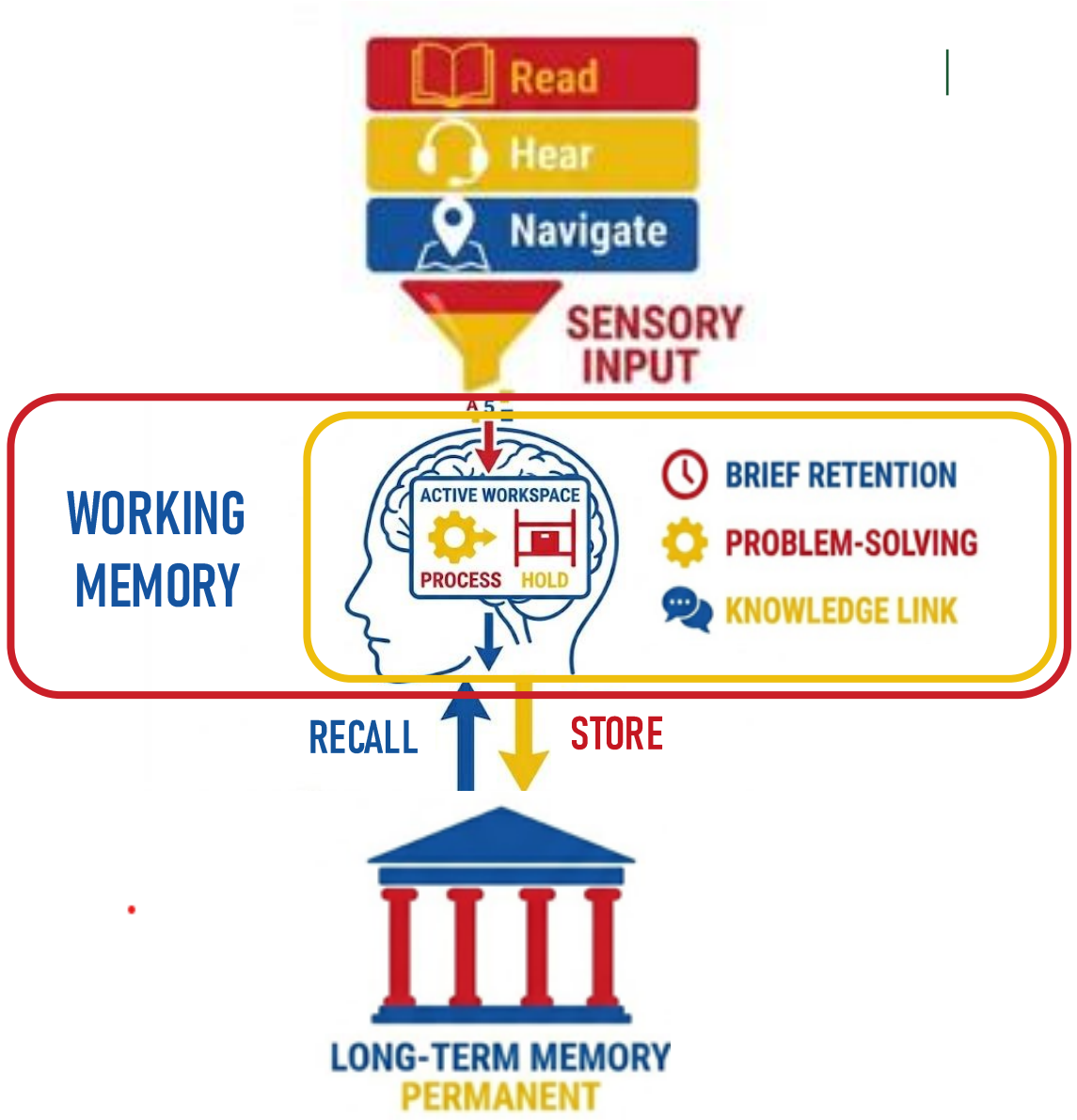


# Working Memory

*The brain's active workspace*

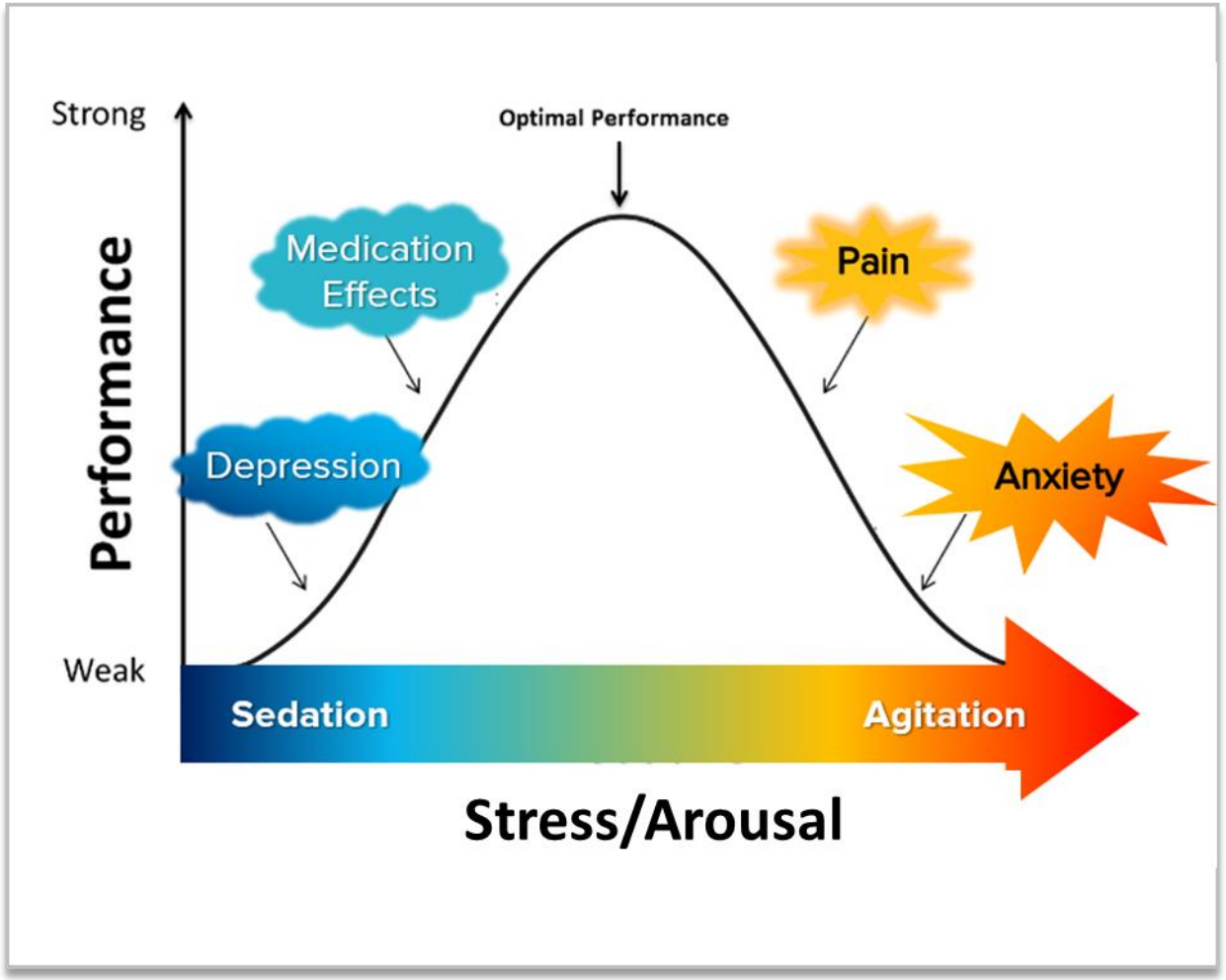
- Working memory
  - Dynamic gateway between sensory awareness and stored knowledge
  - Fixed capacity (5-7 "slots")
  - Stimuli that occupy those slots reduce capacity for other processing
    - Pain, fatigue, anxiety, etc



# General medical conditions and cognition

# Do the complaints really reflect a neurologic (structural) disorder?

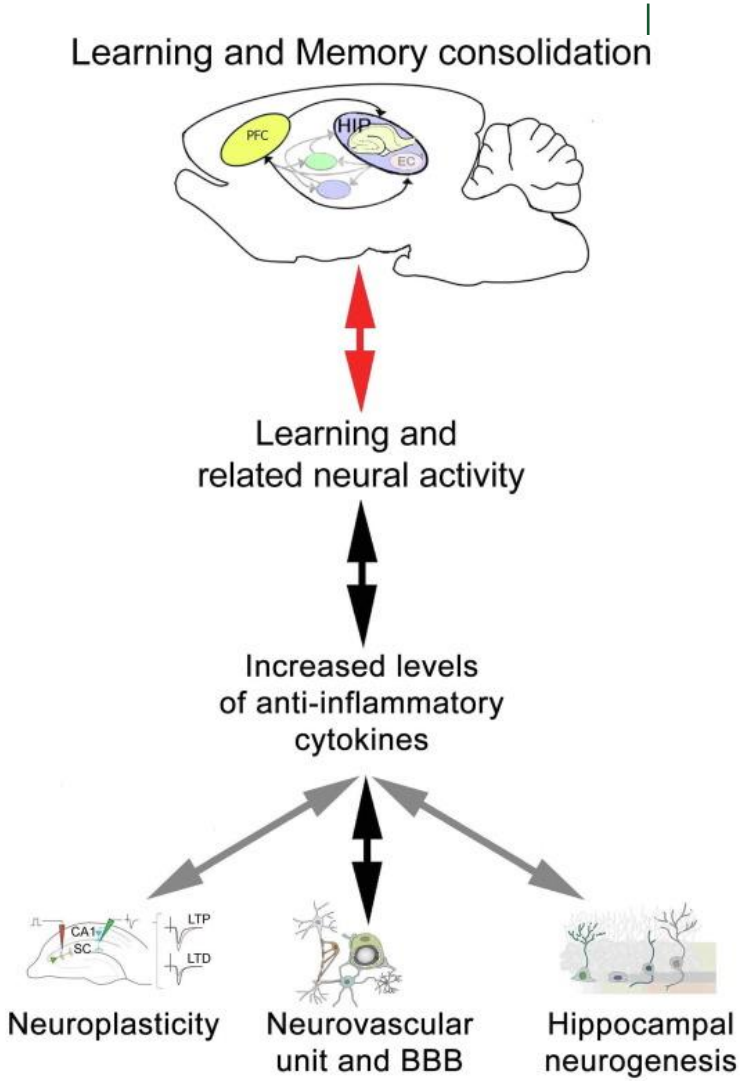
- Be aware of “software” syndromes
  - Meds
  - Mood (includes anxiety or depression)
  - Pain
  - Sleep
- Patients will have Memory ***Complaints,*** but
- ***Observed Deficits*** in:
  - Attention
  - Concentration
  - Working Memory
  - Executive Function



# Inflammation and working memory

## A common link across age and illness

- Inflammatory states undermine working memory
  - Mediated by **pro-inflammatory** cytokines
  - Exaggerated by underlying neural dysfunction
    - Age, cerebrovascular disease, incipient neurodegeneration, etc.
- **Anti-**inflammatory cytokines increase during learning and memory
- Inflammation is likely a significant contributor to cognitive decline in multiple conditions
  - post-operative cognitive dysfunction
  - delirium

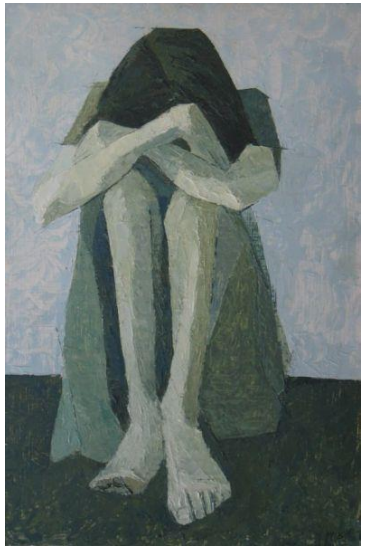



Sergey G, et al. 2021 (https://www.sciencedirect.com/science/article/pii/S0306452221004139)
Balldin VH, et al. Int J Alzheimers Dis. 2012;2012:703871. doi: 10.1155/2012/703871.

# Specific “software” syndromes that affect working memory

# Depression

- Present in up to 50% of memory clinic referrals[1]
  - Anxiety is often concurrrent
- Older adults (especially men) often do not express sadness[2]
  - Apathy, withdrawal, agitation/irritability, and cognitive changes predominate.
- Typical cognitive changes:
  - Attention/working memory impairments
  - Psychomotor slowing
- Resultant symptoms
  - Reduced new memory formation
  - Poor or slow recall of older information



Depression II, 1975 (oil on board),
Marion Patrick (1940-93)

1. Kosteniuk JG et al. Dement Geriatr Cogn Dis Extra. 2014 ;4:209-20
2. Kockler M, Heun R Int J Geriatr Psychiatry, 2002;17:65-72.

# Cognitive outcomes after depression treatment

- Cognitive symptoms in depression usually improve with return to normal mood
  - Improved mood may not result in full restoration of cognition
- Residual cognitive difficulties
  - Subjective feelings of reduced capability
  - Impaired decision-making
  - Adverse consequences on social function
- Tendency to “give up” on cognitively effortful tasks
  - On testing they are likely to say ***“I can’t”***
- In contrast, Alzheimer’s patients often persist while failing on tasks
  - Seem surprised when they are unable to complete them

Depression II, 1975,
Marion Patrick

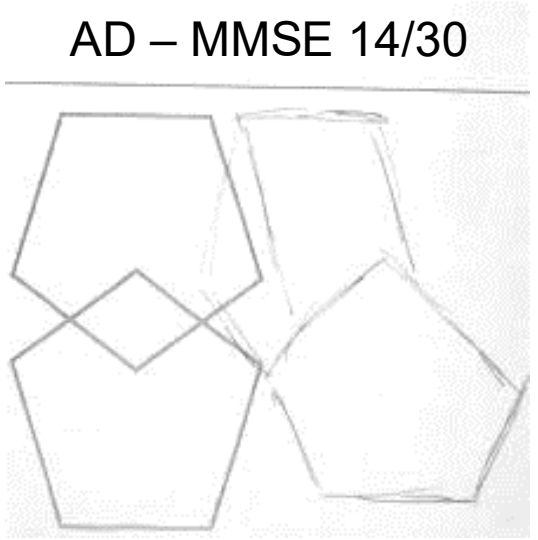
# “Giving up” on cognitive tasks

*Learned helplessness*

Depression – MMSE 23/30

Early Quitting

AD – MMSE 14/30



http://site.macleans.ca/longform/alzheimers/

Persistent/Perseverative

# Chronic pain and cognition


http://www.justinziegler.net/wp-content/uploads/2015/03/Depositphotos_7849283_s-002.jpg

- Emotional distress predicts cognitive complaints better than reported pain severity[1]
  - e.g., ***suffering*** is a better predictor of dysfunction than pain itself

- Common correlates of pain magnify cognitive impairments
  - Somatic preoccupation
  - Sleep disturbance
  - Fatigue

1. Hart RP et al .*Curr Pain Headache Rep* 2003;7:116-26

# Sleep and cognition

- Older adults with poor sleep report problems with[1]
  - Memory
  - Motivation
  - Concentration
  - Decision-making
- Sleep apnea has long term consequences
  - May accelerate the cognitive effects of brain aging
  - Associated with increased white matter disease burden


http://sleepandcognitionlab.org/

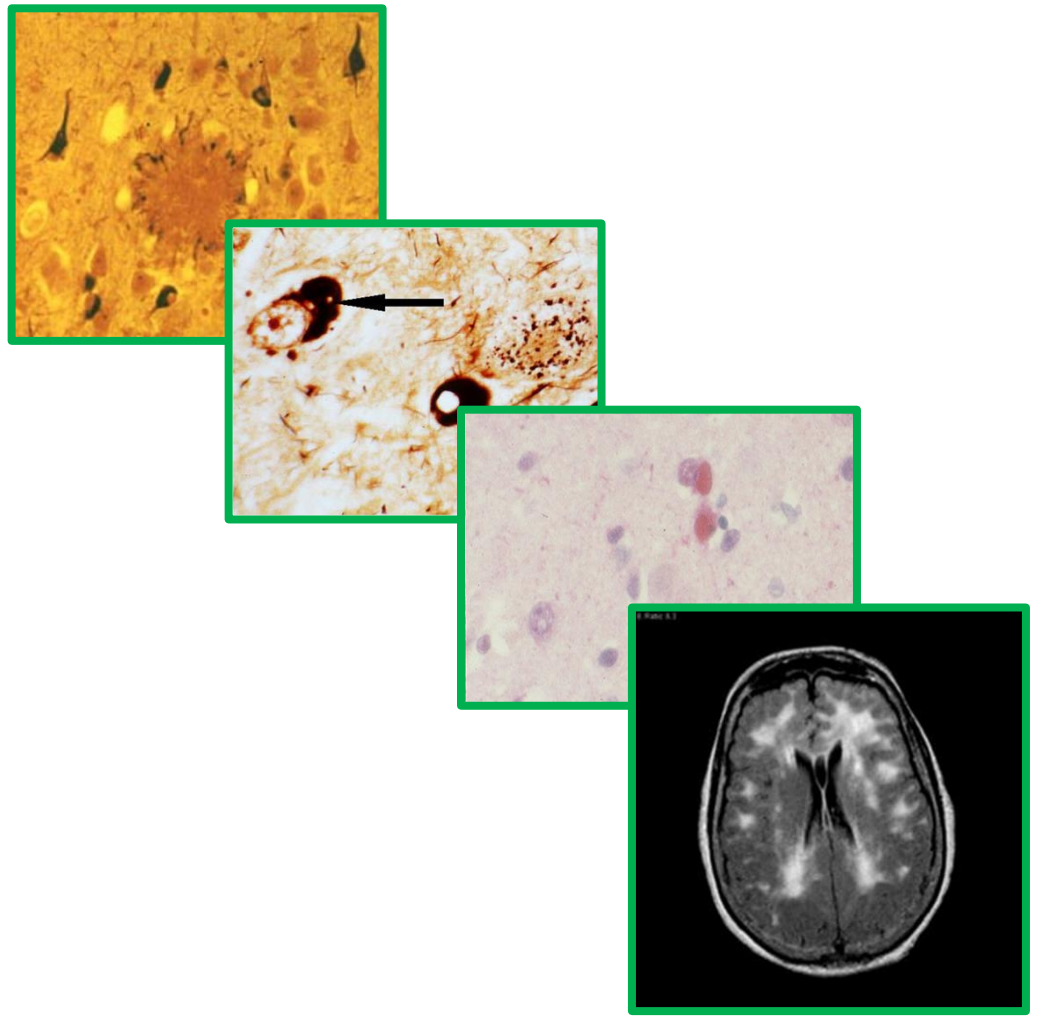
1. Nebes RD et al. *J Gerontol B: Psychol Sci Soc Sci* 2009;64B:180-7
2. Sforza E, Roche F. *Front Neurol* 2012;3:87

# Structurally-mediated cognitive disorders

# Structural diseases causing dementia

*The big four of "Hardware" issues*

- Alzheimer's disease
  - Proteinopathy: Amyloid, Tau
  - Clinical: Poor Memory Formation & Time Orientation
- Frontotemporal lobar degeneration
  - Proteinopathy: Tau, TDP
  - Clinical: Behavior & Social Conduct Changes
- Dementia with Lewy Bodies/Parkinson's
  - Proteinopathy: Synuclein
  - Clinical: Early Hallucinations, REM Sleep Behaviors
- Vascular Brain Injury
  - Vascular lesions
  - Clinical: Mental Slowing, MRI positive



# Practical approaches to assessment

# Differential Diagnosis: reference point

## Core symptoms of Alzheimer-type dementia by history

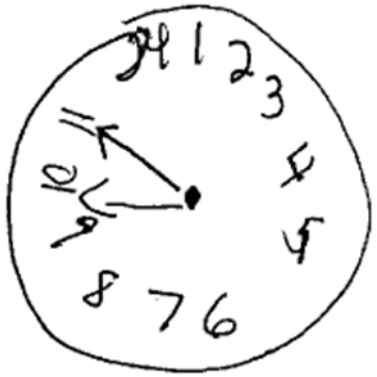
- **Amnesia** for recent events and activities
- Supported by:
  - **Anomia**
  - **Apraxia**
  - **Agnosia**
- Causing:
  - **ADL losses**
- Masked by:
  - **Anosognosia**
  - **Apathy**

Not just conversations, birthdays, and appointments

Reduced function in work or home roles

Low concerns or poor insight about the issues

# Practical Approach to Cognitive Assessment
## Mini-Cog



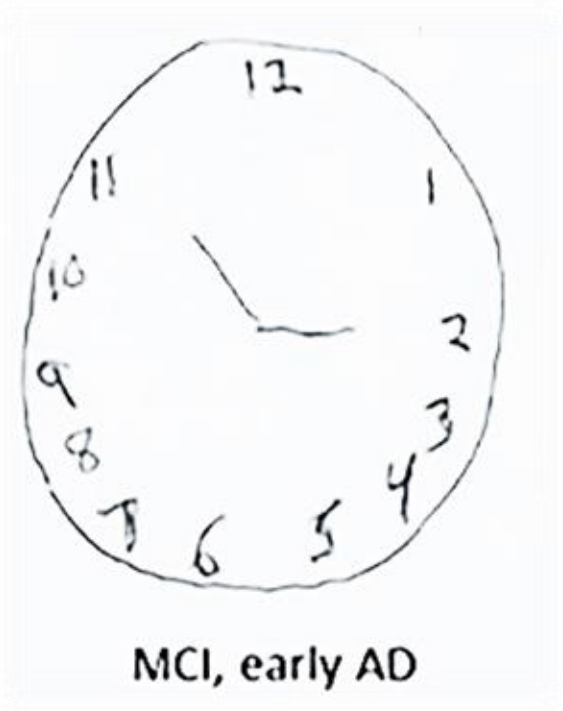
1. Repeat 3 Items
2. Clock Drawing Test
3. Recall 3 Items

Mini-Cog for detection of dementia
- Sensitivity 99%,
- Specificity 93%

Borson S, et al. *Int J Geriatr Psychiatry*. 2006;21:49-355
Callahan CM et al. *Med Care*. 2002 Sep;40:771-81.

# Using cognitive test *data*, not *scores*

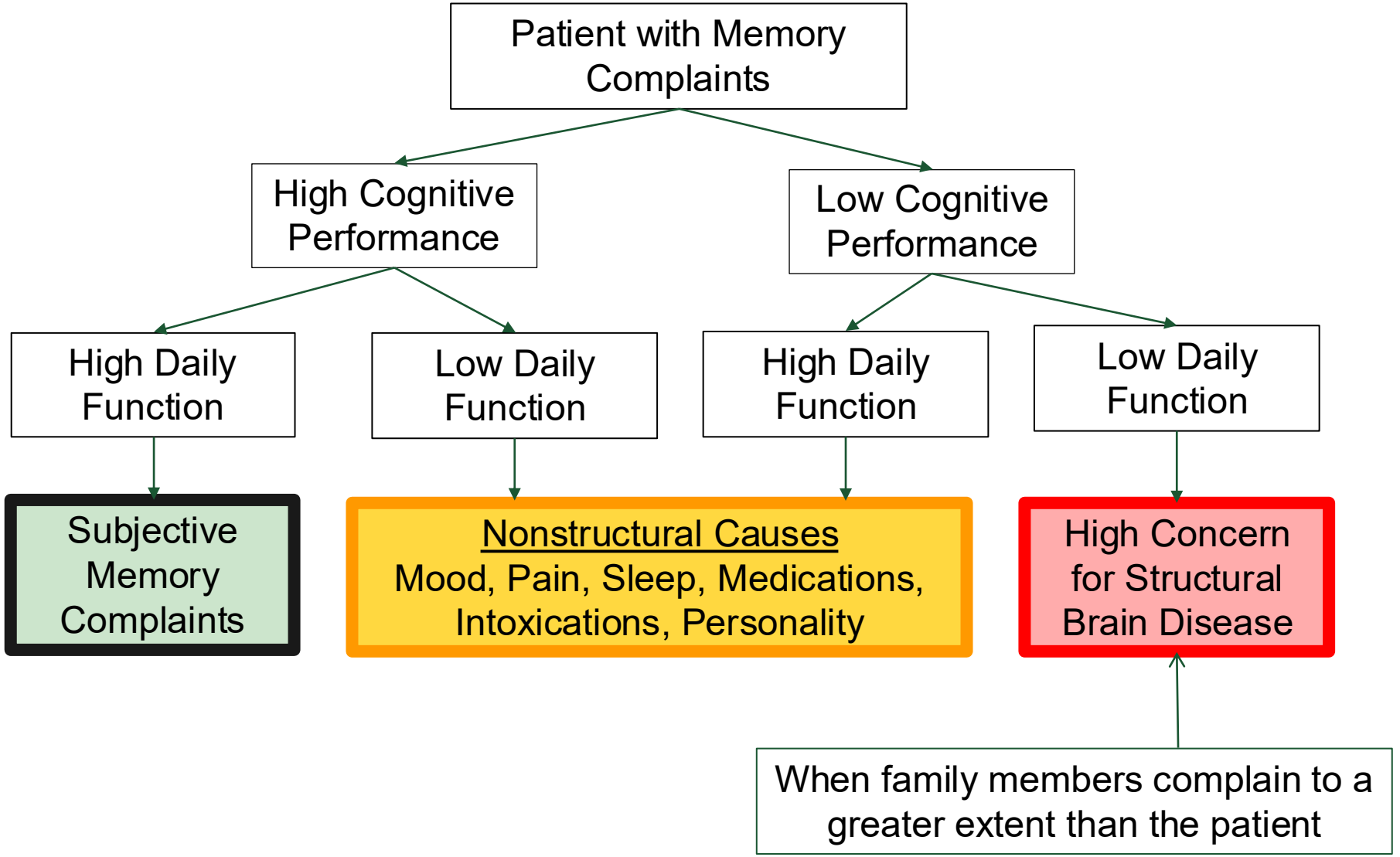
- Overall MMSE score is not sensitive to early AD
- Errors on “Memory” tasks are nonspecific
  - Sensitive to attention, executive function, motivation, etc.
- Loss of *Orientation to Time* is very suggestive of AD pathology




**Take Home:** Consider assessing memory complaints with **Mini-Cog** plus **Orientation to Day/Month/Year**

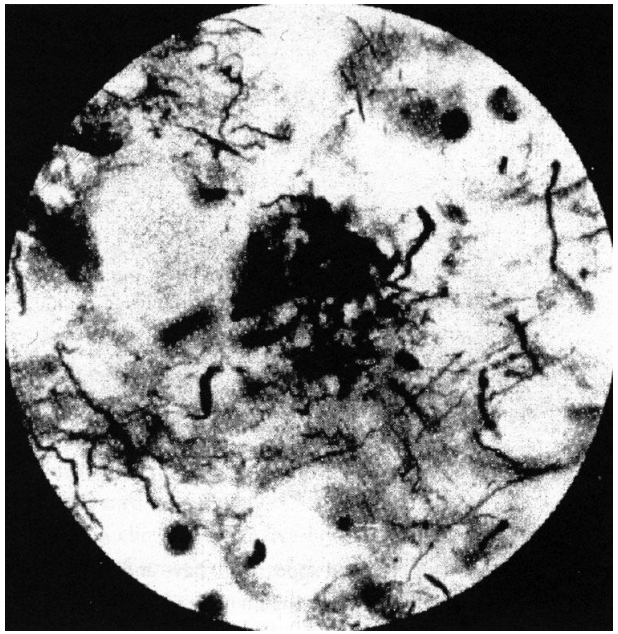
Arevalo-Rodriguez I, Cochrane Database Syst Rev. 2021 Jul 27;7(7.
Choe YM, e al Neuropsychiatr Dis Treat. 2020 Jul 24;16:1767-1775.

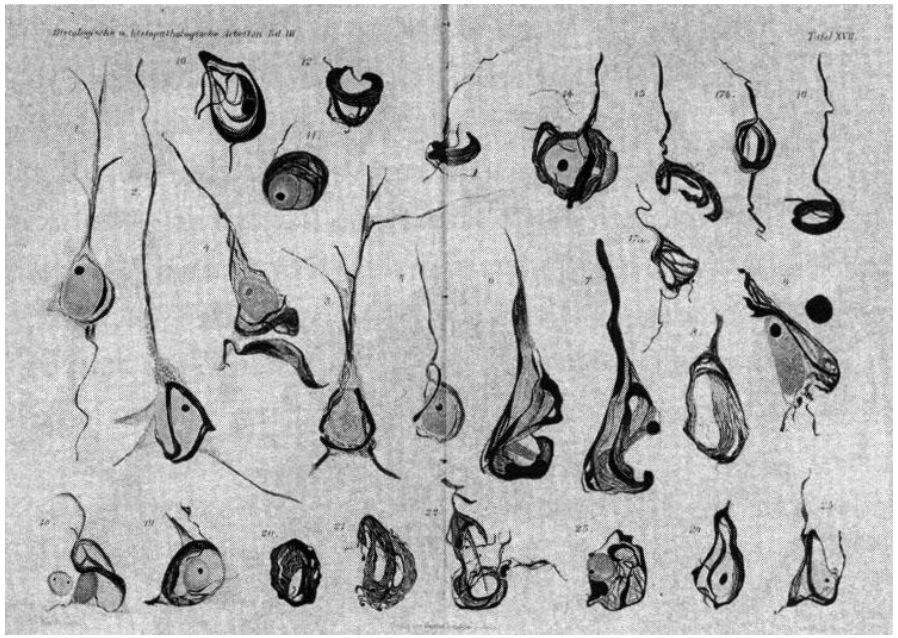
# Using Daily Function in Differential Diagnoses



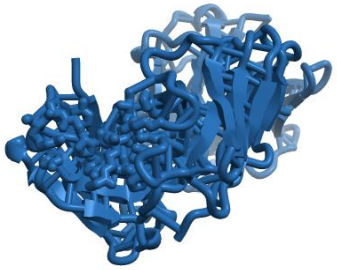
# **Alzheimer's disease**
Evolving concepts; Emerging treatments

# Defining Alzheimer’s disease - 1906



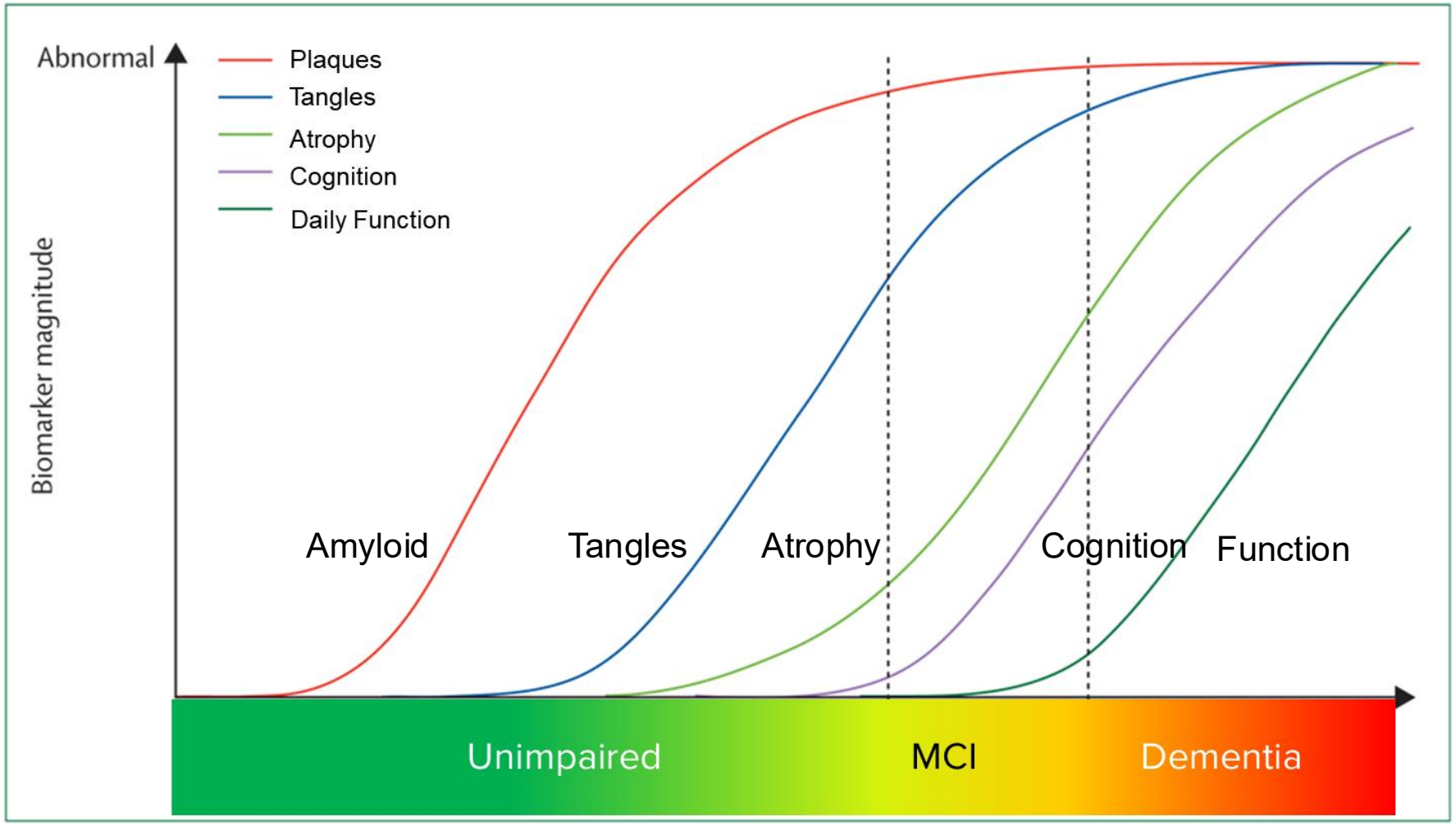


# Defining Alzheimer’s disease - 2024



# Alzheimer's re-envisioned in the 21st Century

## Alzheimer pathology accumulates before cognitive decline



# Biomarker diagnosis of AD

# New Guidance on AD Biomarkers- 2025 Best practices:

- A Blood Based Biomarker test *should not be obtained* before a comprehensive clinical evaluation by a health care professional
- Clinicians should consider the pre-test probability of Alzheimer's disease pathology for each patient when deciding whether or not to use a BBM test.

| Cognitively Unimpaired | |
|---|---|
| Age | % Amyloid Positive |
| 50-59 | **2.7** |
| 60-69 | **18.3** |
| 70-79 | **32.1** |
| 80-89 | **41.3** |

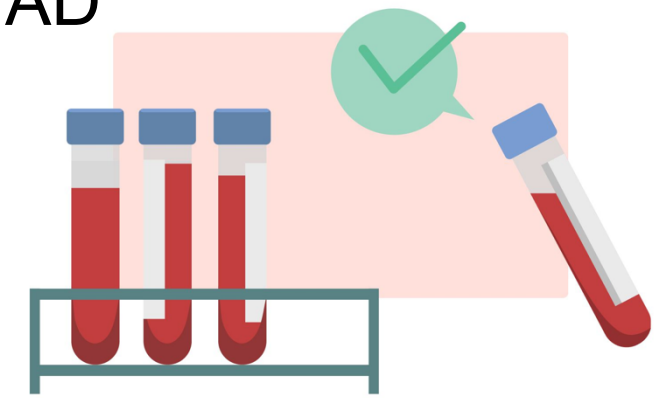
https://aaic.alz.org/releases-2025/clinical-practice-guideline-blood-based-biomarkers.asp

# Blood-based biomarker “confirmation” of AD

- Blood Based biomarkers are appropriate when considering AD
  - Single stand-alone tests remain nondefinitive in clinical populations
  - Common medical conditions (CKD, OSA) can elevate pTau biomarkers

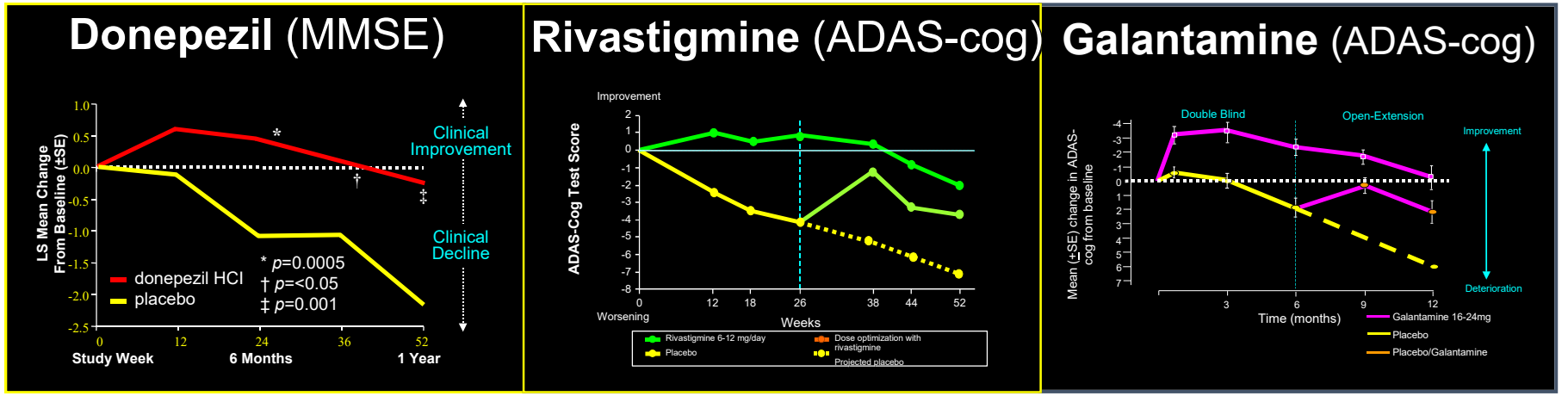
- Available tests assess amyloid status, not neuronal loss (tangles)

- Current tests more reliably **exclude**, rather than confirm AD pathology



# Treatment of AD Symptoms

# Cholinesterase Inhibitors
## Cognitive Efficacy



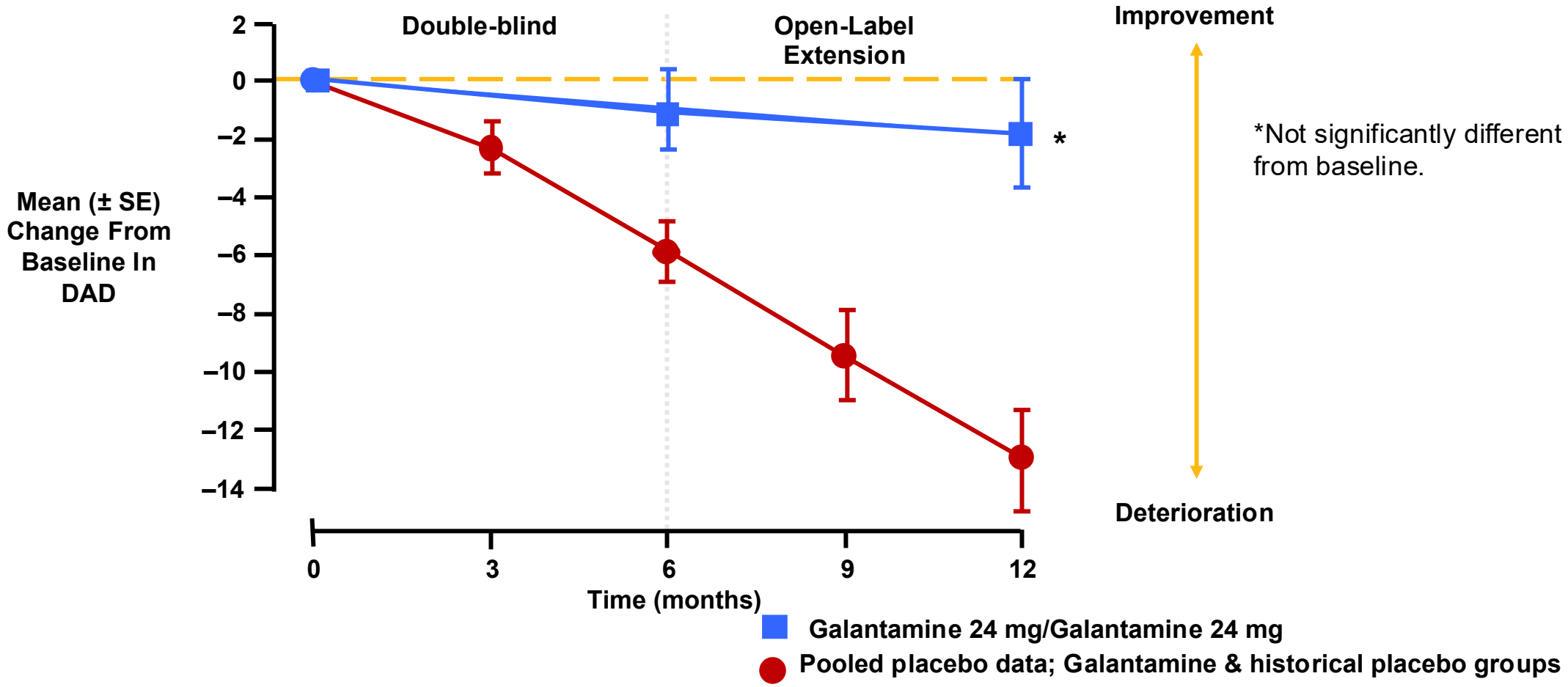

At the end of one year, all three agents show no statistically significant decline from baseline on cognitive tests in mild-moderate AD dementia

**Note:** Memantine is not labeled for MCI or mild-stage dementia

Geldmacher DS *Continuum* 2024;30(6):1823-1844

# Cholinesterase Inhibitors

## Efficacy on daily function (mild-moderate AD)



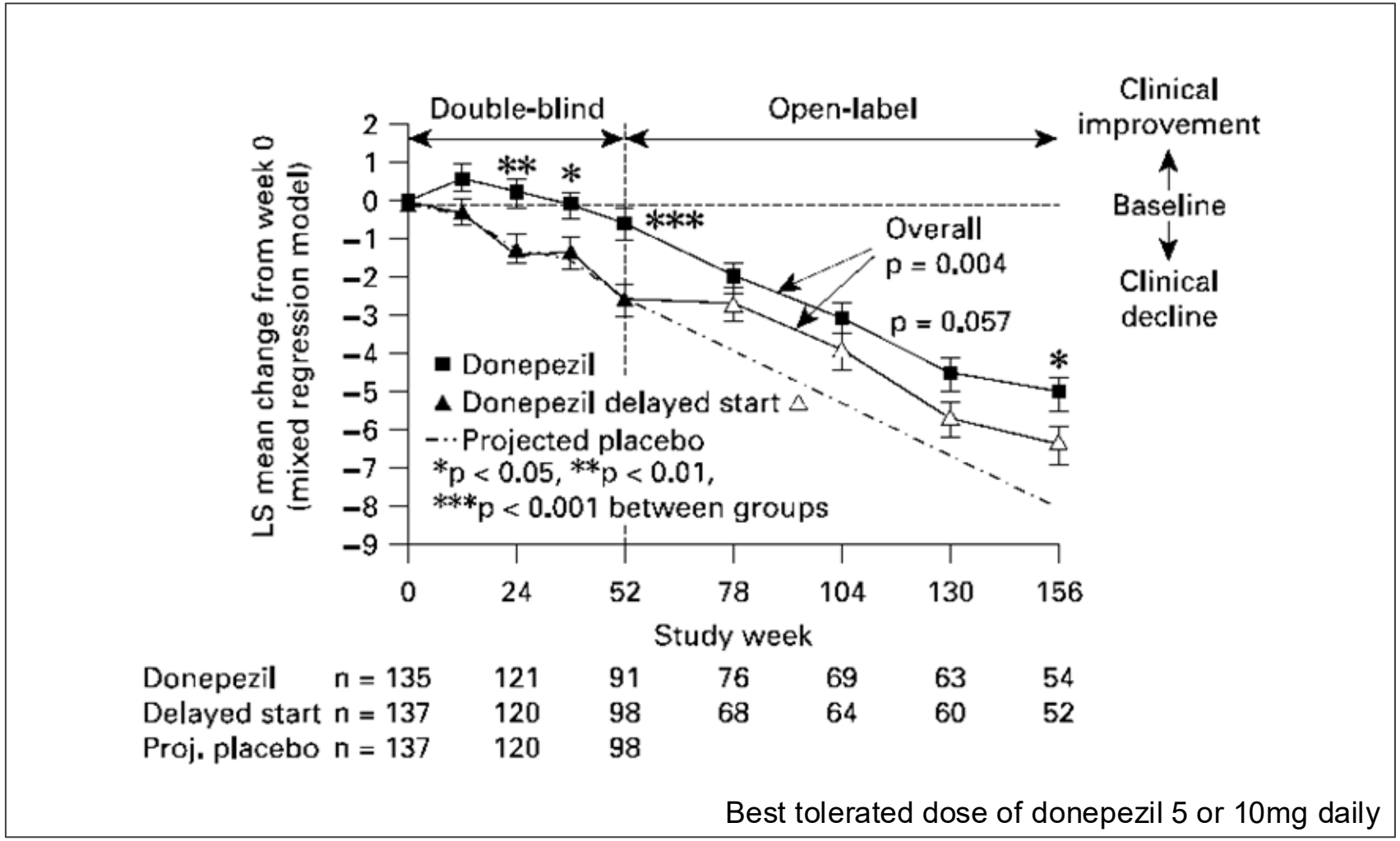

Raskind et al. *Neurology.* 2000;54:2261-2268.

# Cholinesterase Inhibitors
## Safety and Tolerability

- In the community setting (open-label prescriptive use),
  - 14% of AChEI patients reported adverse effects over 9 mos.
- Across all double-blind, randomized, placebo-controlled trials
  - GI complaints are most frequent, higher than seen in community use
    - Nausea (31%), vomiting (21%), diarrhea (15%)
    - Most occur during initiation and rapid dose titration
  - Syncope and its complications (1.75x) are significant and meaningful
- Direct comparison studies:
  - Fewer patients experience GI effects on donepezil than oral rivastigmine (DBRPC)
  - No major differences between conventional-release galantamine and donepezil (open-label)
- Slower dose titration is associated with fewer adverse effects.

Geldmacher DS *Continuum* 2024;30(6):1823-1844

# When should I start therapy?
## Effect of delayed treatment on MMSE



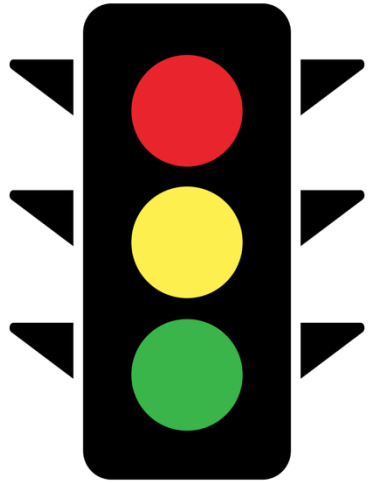

Best tolerated dose of donepezil 5 or 10mg daily

Winblad B et al. *Dement Ger Cog Dis* 2006; 21:353–363 (II-

# Treatment of AD pathology
## Amyloid-targeting therapies

# Lecanemab and Donanemab
## Practical limitations

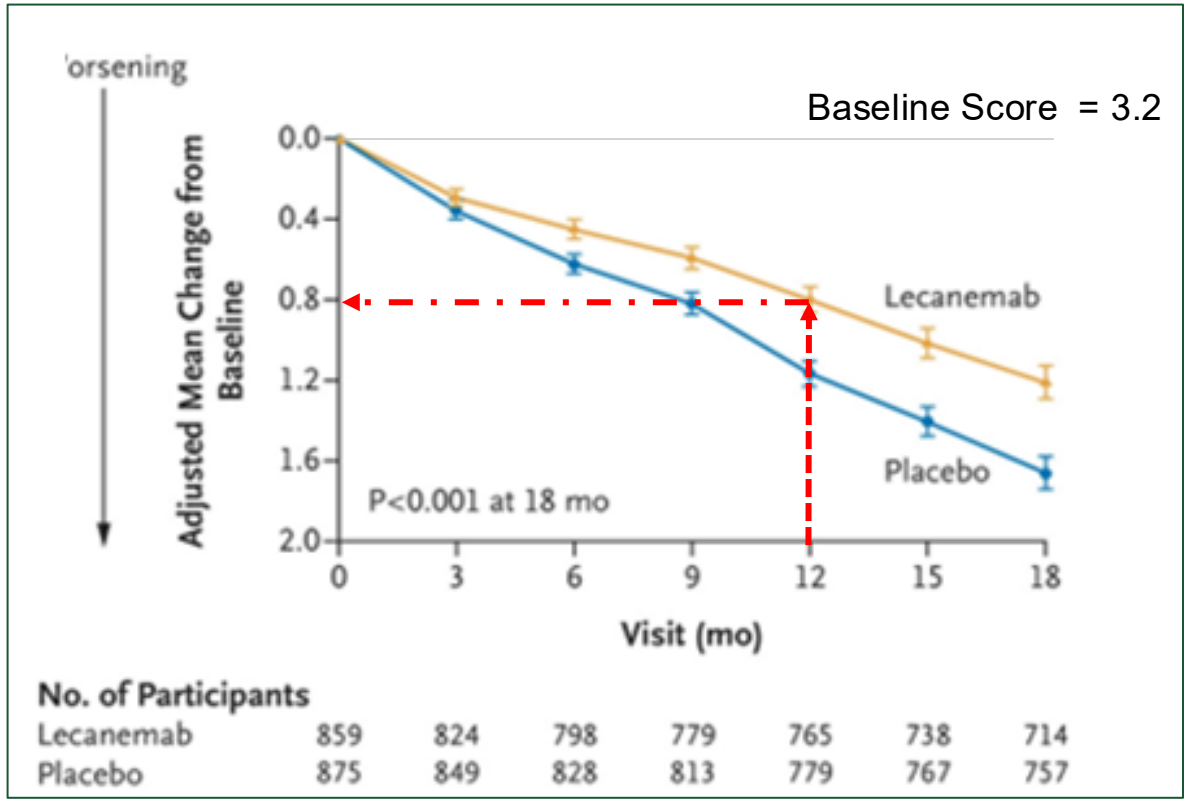
- Indicated only for “Early AD” (MCI and Mild dementia)
  - e.g., MMSE >20
  - Mostly independent in community activities
  - Lower amy;oid burden on PET scans is associated with greater efficacy
- Must be able to tolerate regular MRIs
- No anticoagulation, no other mAb therapies
  - Antiplatelet agents OK
- Must be willing & cooperative with q2week infusions, q4w infusions, or weekly SQ injections x 18 months
- Individual clinical outcomes are generally below the threshold of detectability
  - Benefits are best considered in a time-to-next-stage context



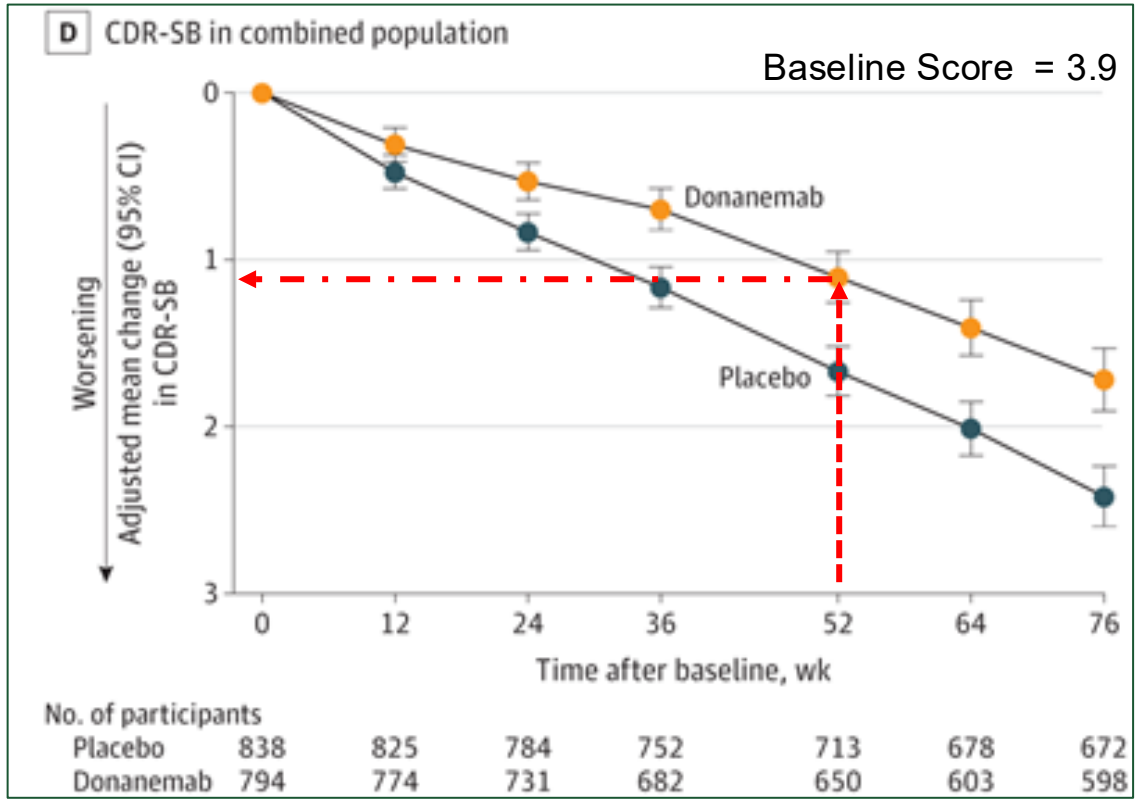
# Clinical outcomes with Amyloid Targeting Therapies

## CDR-SB side by side*

### Lecanemab




### Donanemab




Overall ~25-30% slowing of overall decline over 18 months

*No statistical comparison should be inferred

# Why disease severity matters (donanemab)

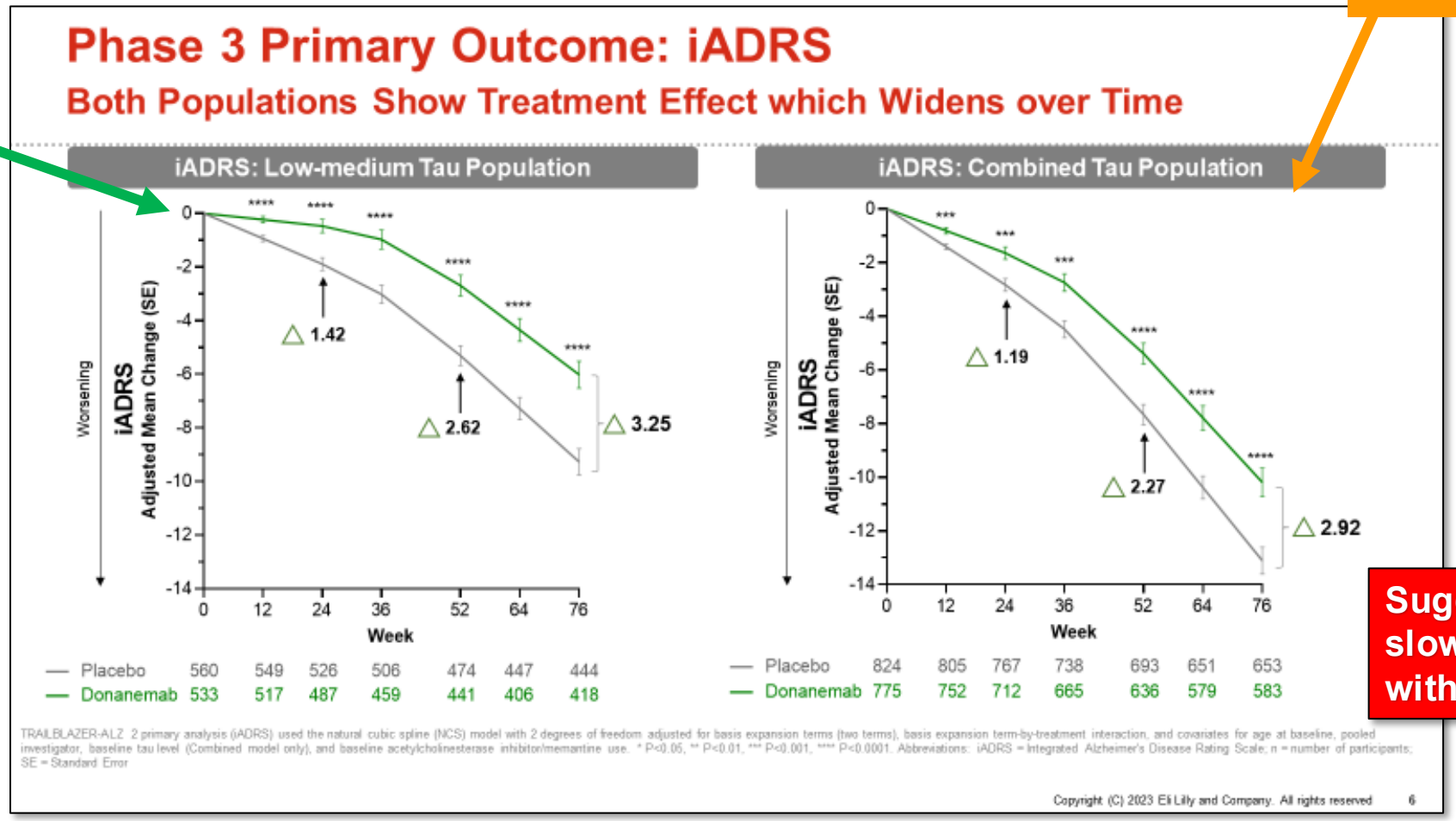
## More tau = less effect

**High tau excluded**

**35% slowing**

**High tau included**

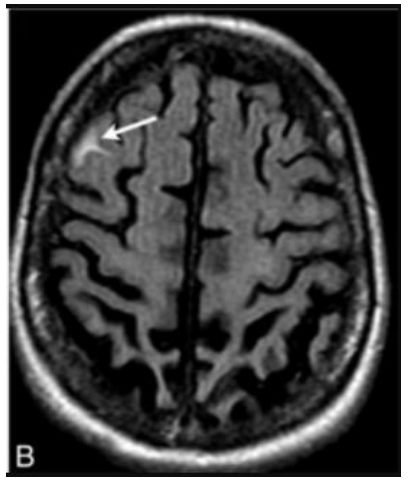
**22% slowing**

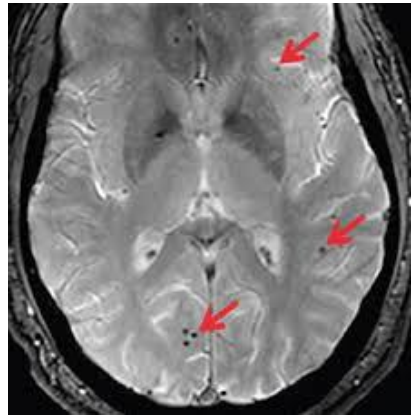



**Suggests about 9% slowing for those with high tau burden**

# Amyloid-Related Imaging Abnormalities (ARIA)

- Two flavors
  - ARIA-E (edema/effusion)
  - ARIA-H (hemorrhage, includes micro- & macro- hemorrhage and siderosis
- Probably related to accumulation of vascular amyloid
- Predictors
  - APOE ε4 Gene dose
  - Evidence of prior bleeds
- Frequently asymptomatic
  - Requires prospective awareness with scheduled MRIs



# ARIA rates in Lecanemab Phase III

## Routine Screening vs. Symptomatic

| | APOE ε4 noncarrier | | APOE ε4 heterozygote | | APOE ε4 homozygote | |
|---|---|---|---|---|---|---|
| | placebo | LEC | placebo | LEC | placebo | LEC |
| ARIA-E total | 0.3 | 5.4 | 1.9 | 10.9 | 3.8 | 32.6 |
| ARIA-E symptomatic | 0 | 1.4 | 0 | 1.7 | 0 | 9.2 |
| ARIA-E serious | 0 | 0.7 | 0 | 0.4 | 0 | 2.1 |
| | | | | | | |
| ARIA-H | 4.2 | 11.9 | 8.6 | 14.0 | 22.1 | 39.0 |
| ARIA-H symptomatic | 0 | 0.4 | 0.2 | 1.0 | 0.8 | 0 |
| ARIA-H serious | 0.3 | 0.7 | 0 | 0.2 | 0 | 1.4 |

**Most Frequent ARIA Symptoms**

- Headache
- Confusion
- Visual changes
- Dizziness
- Nausea
- Gait difficulty

**Events defined as "Serious ARIA"**

- Seizures
- Status epilepticus
- Encephalopathy
- Stupor
- Focal neurological deficits

# ARIA rates in Lecanemab Phase III

## Symptomatic vs. Serious

| | APOE ε4 noncarrier | | APOE ε4 heterozygote | | APOE ε4 homozygote | |
|---|---|---|---|---|---|---|
| | placebo | LEC | placebo | LEC | placebo | LEC |
| ARIA-E total | 0.3 | 5.4 | 1.9 | 10.9 | 3.8 | 32.6 |
| ARIA-E symptomatic | 0 | 1.4 | 0 | 1.7 | 0 | 9.2 |
| ARIA-E serious | 0 | 0.7 | 0 | 0.4 | 0 | 2.1 |
| | | | | | | |
| ARIA-H | 4.2 | 11.9 | 8.6 | 14.0 | 22.1 | 39.0 |
| ARIA-H symptomatic | 0 | 0.4 | 0.2 | 1.0 | 0.8 | 0 |
| ARIA-H serious | 0.3 | 0.7 | 0 | 0.2 | 0 | 1.4 |

**Most Frequent ARIA Symptoms**

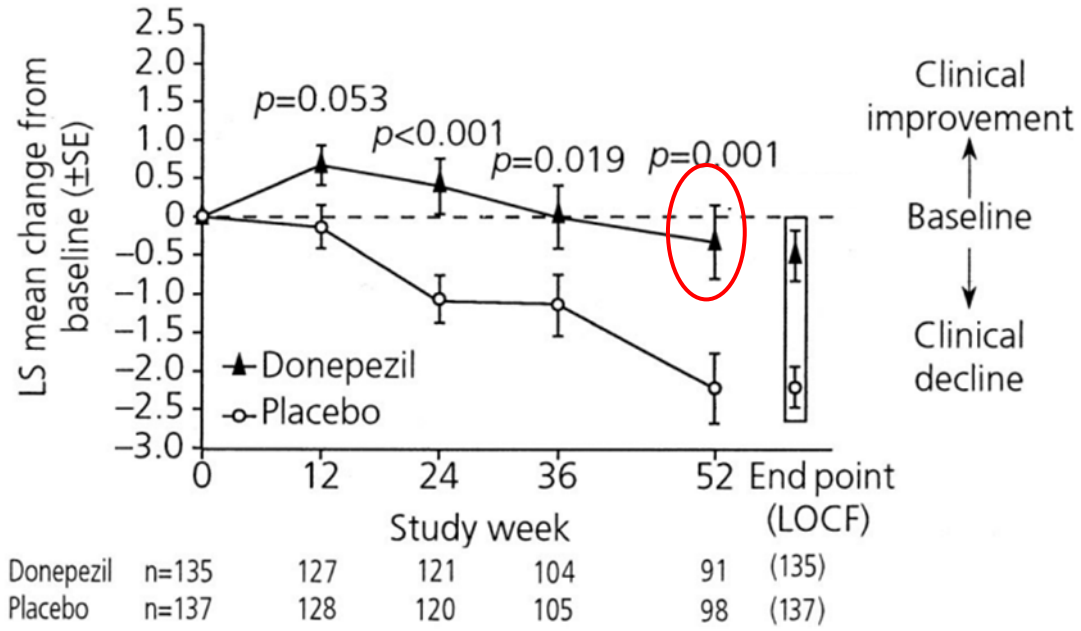
- Headache
- Confusion
- Visual changes
- Dizziness
- Nausea
- Gait difficulty

**Events defined as "Serious ARIA"**

- Seizures
- Status epilepticus
- Encephalopathy
- Stupor
- Focal neurological deficits

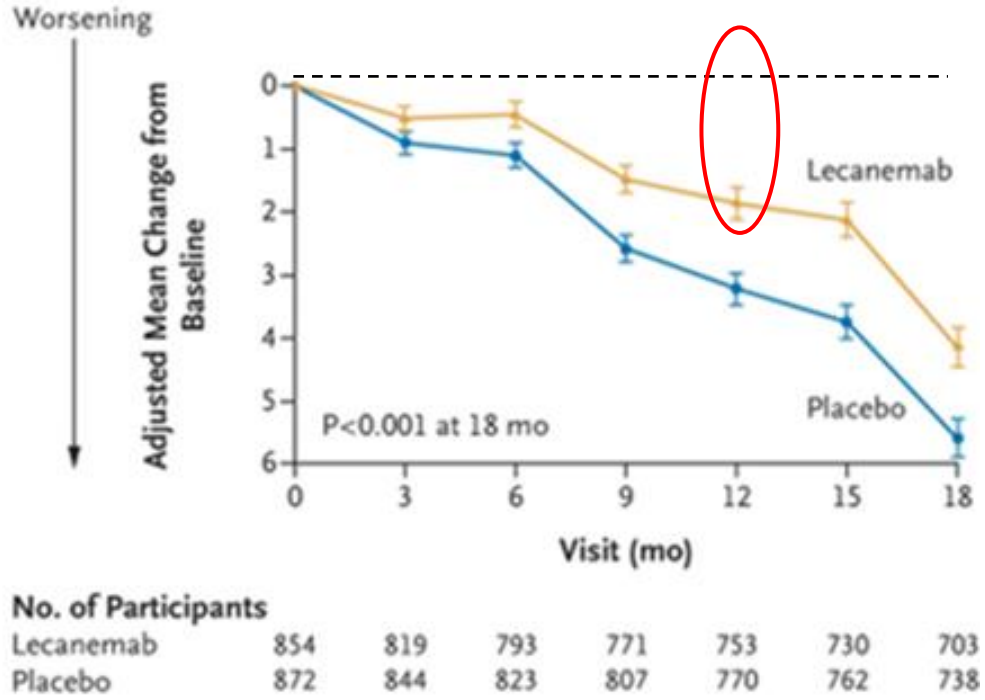
# Comparison: donepezil and lecanemab 1 year data

**MMSE Score**




**Donepezil**

**ADAS-cog13 Score**




**Lecanemab**

# Summary

- Cognition declines with advancing age
  - Slowing typically becomes evident after age 60
  - Daily function is unimpaired
- Many medical illnesses contribute to cognitive complaints (“software”)
  - Working memory is the vulnerable process
  - Inflammation is a common theme
  - Underlying neural dysfunction magnifies the effects of other conditions
- Alzheimer’s disease is highly prevalent among structural causes (“hardware”)
  - Biological diagnosis is available, but nuanced
- Treatments are effective, but warrant expectation management
  - Symptomatic therapies **delay** decline
  - Pathology-modifying treatments **slow** progression
    - Amyloid targeting therapies are very labor-intensive for prescribers

# Questions?