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Cognitive Impairment with Aging, Medical Illness, and Alzheimer's disease

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UAB Neurology

Disclosures

- Research support (paid to UAB):
  - Eisai, Genentech/Roche, Janssen
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  - Eisai, Lilly, NFL Concussion Settlement Program, Premier Inc.
- Stock holdings
  - Doximity

Off-label use

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

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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.

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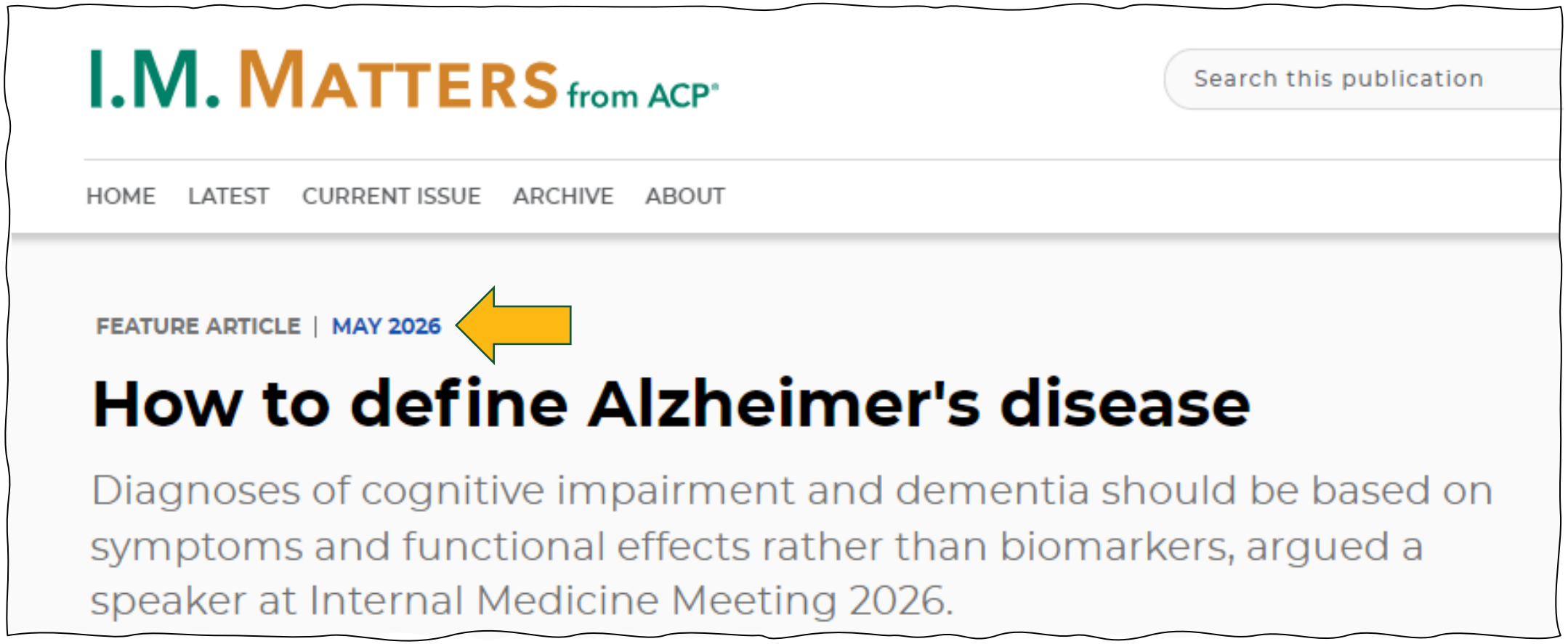
In the news…



Referring to:
Eric Widera, MD, FACP; Professor of Medicine (Geriatrics), UCSF

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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?

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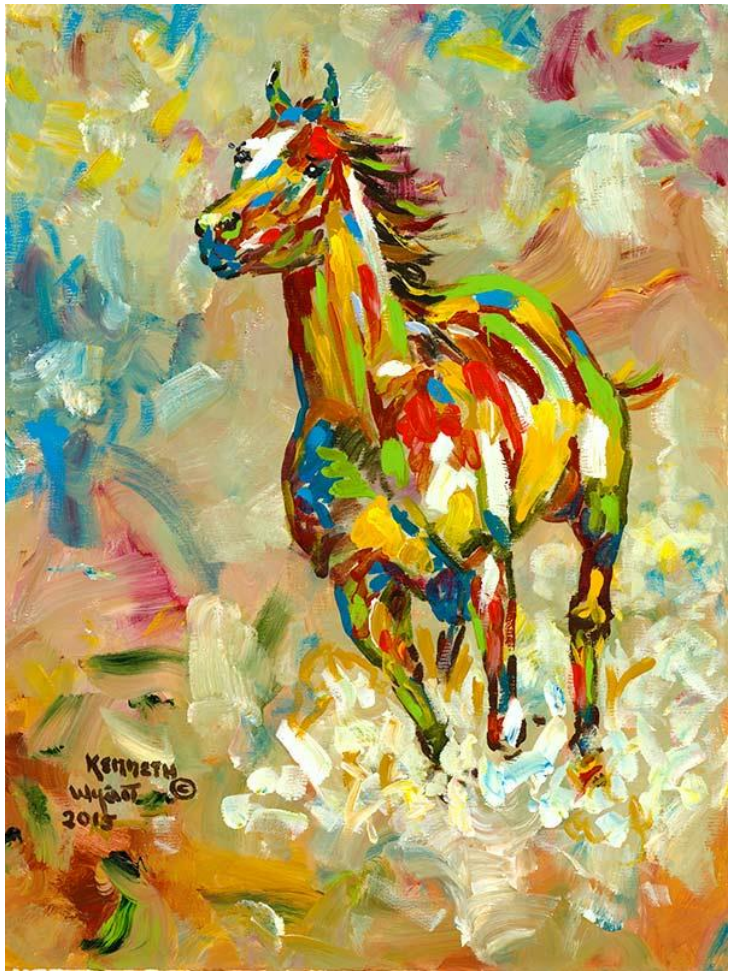
Short-term memory loss

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

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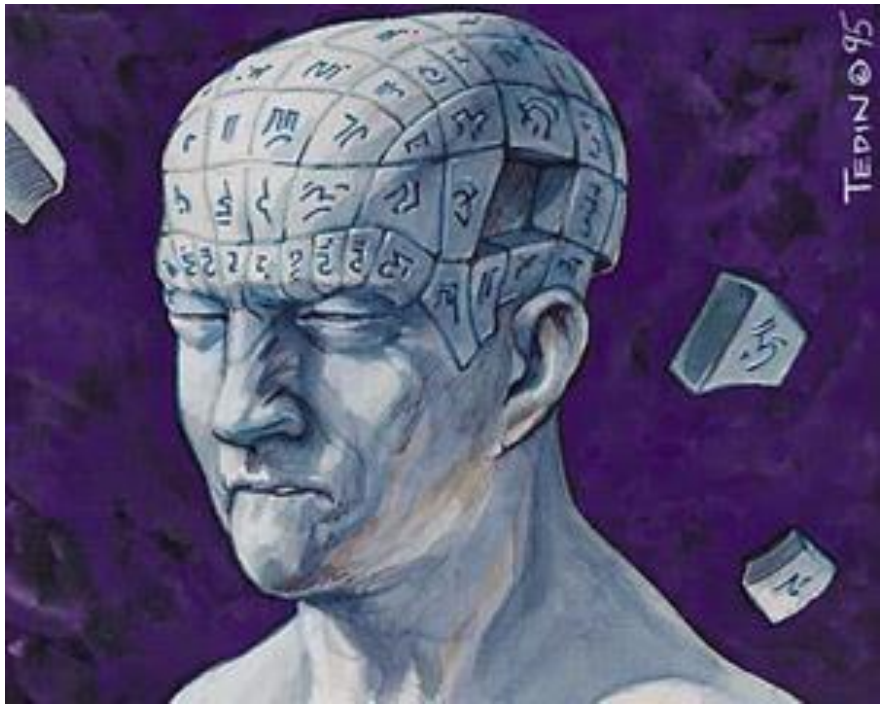
Risk factors for *complaints* of memory loss

- Older age
  - 50-80% of people over age 70 have cognitive complaints but normal testing
- Depressive symptoms
- Less education
- Less exercise
- Hypertension
- Female sex



Chen ST, et al *PLoS One*. 2014 Jun 4;9(6):e98630. doi: 10.1371/journal.pone.0098630. PMID: 24896243.

DeCarli C. *Lancet Neurology* 2003;2:15-21

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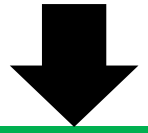
Definitions:
Severity of cognitive loss

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

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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

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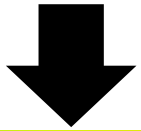
Defining Mild Cognitive Impairment
The front door to dementia

- 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

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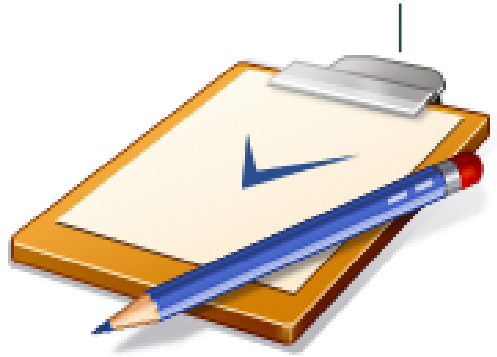
Defining Dementia



- **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

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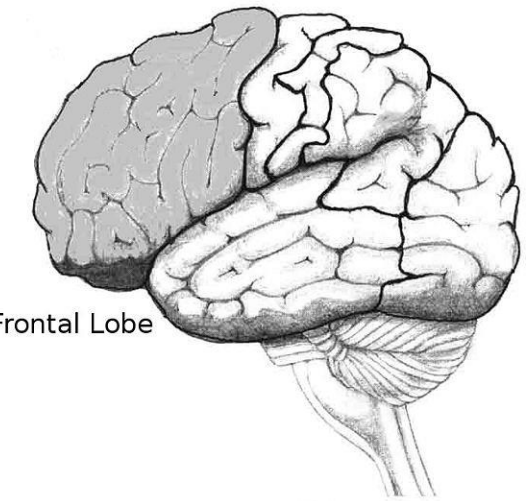
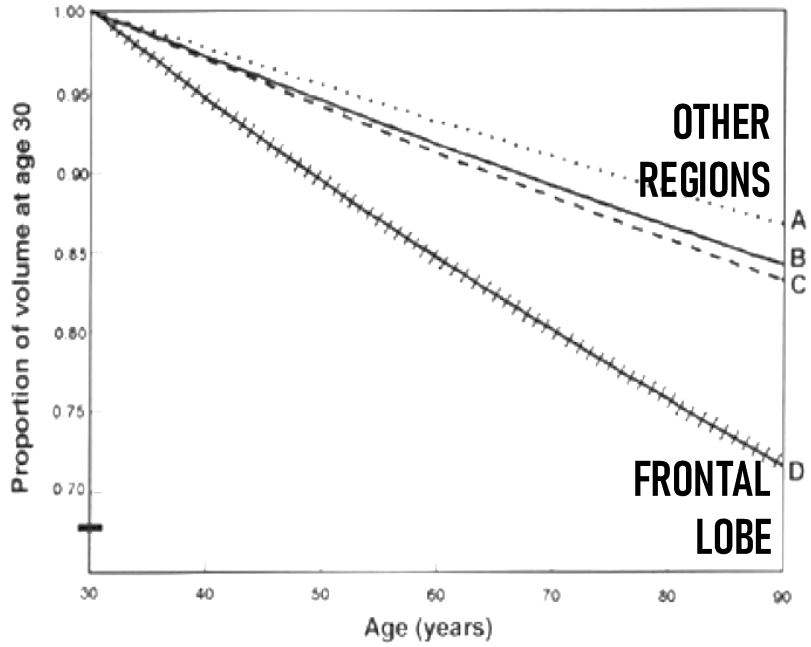
What happens to the brain and memory with aging?

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





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The Personal Computer

Model for the aging brain?

The old computer:

- Cannot retrieve information as quickly
- Slower to switch between programs
- Does not accept newer software well
- Still stores/recalls, e-mails, word-processes, etc.

Old Computer

New Computer

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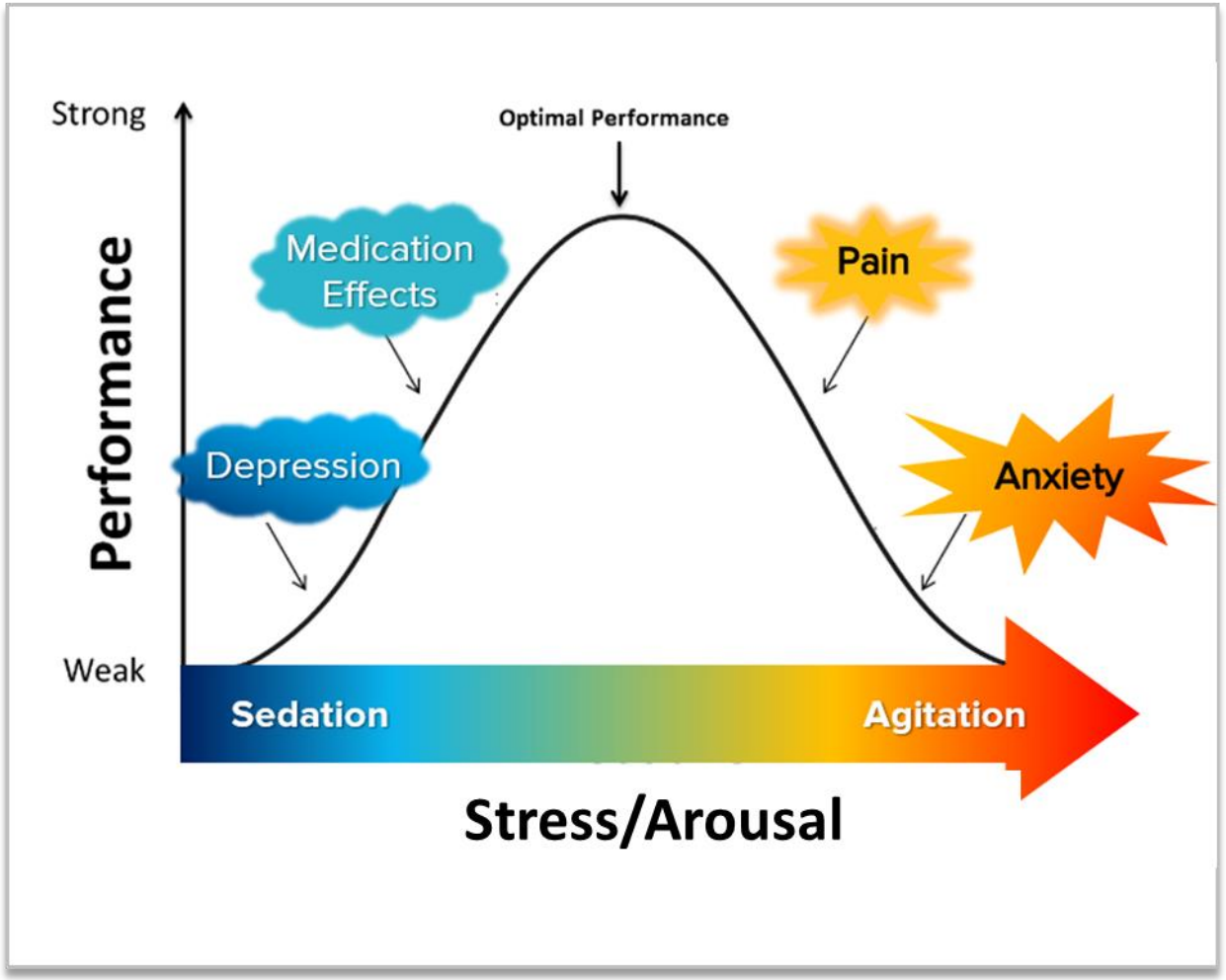
General medical conditions and cognition

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



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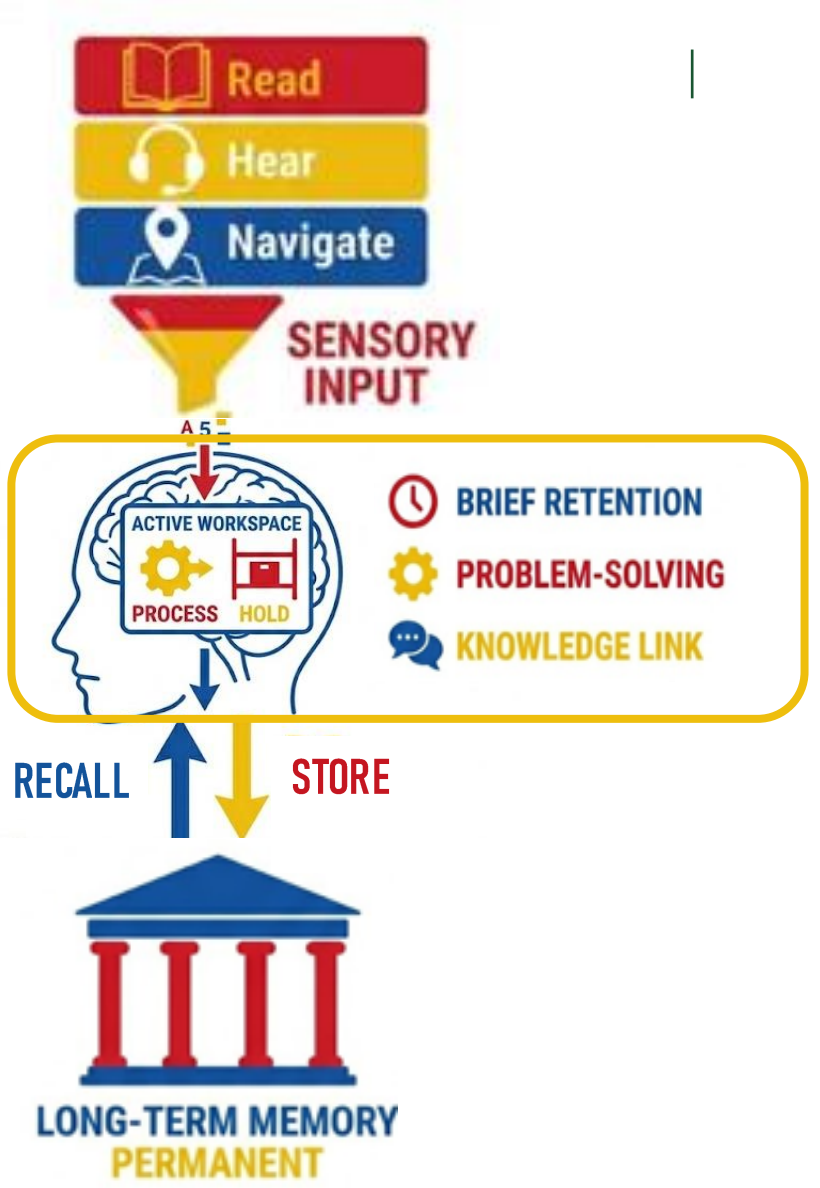
Working Memory
The brain's active workspace

- 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



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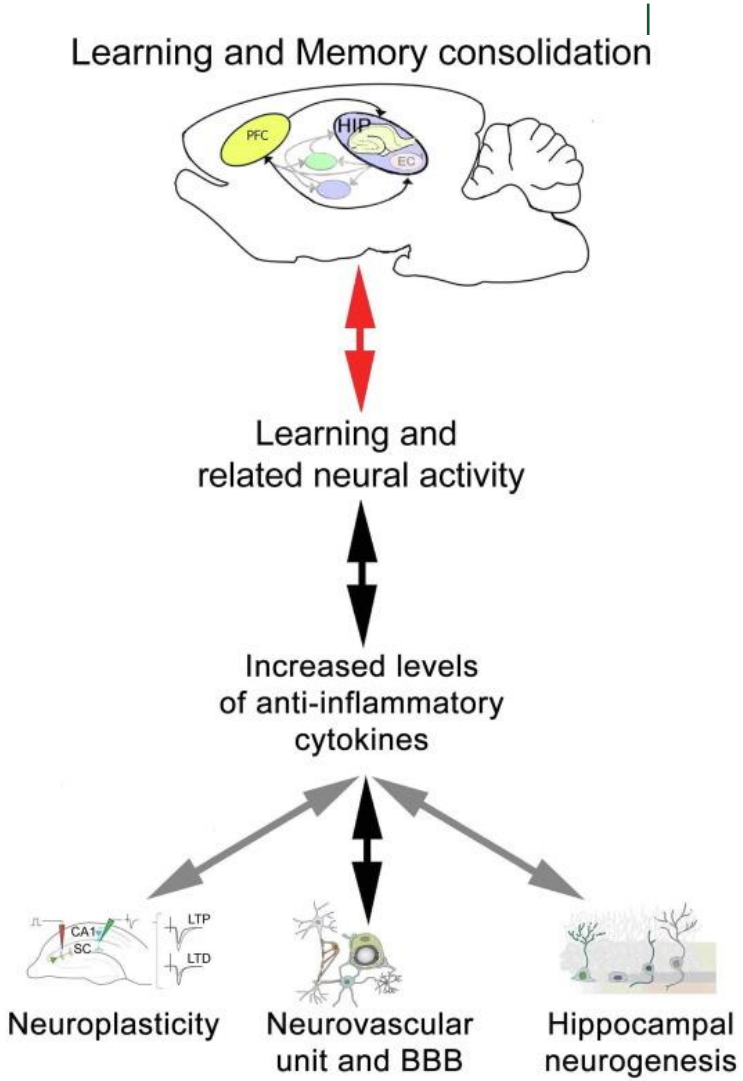
Inflammation and working memory

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.

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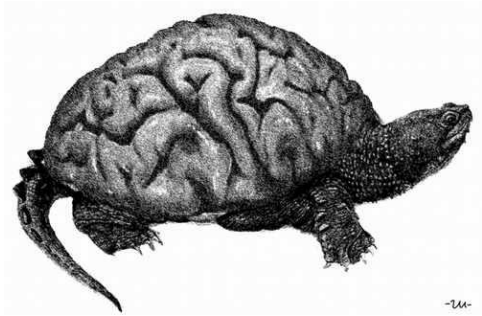
Specific “software” syndromes that affect working memory

Adverse medication effects on cognition

Reduced neuronal responsiveness

- Opiates:
  - Sedation and cognitive impairments are reported frequently[1]
  - Impairment in attention, working memory, and verbal memory for ~5 hours after dosing (Oxycodone)[2]
- GABA-ergic treatments
  - Sedative and cognitive effects of gabapentin appear to be more idiosyncratic than dose-related[3]
- Benzodiazepines
  - Attention, working memory, planning, mental flexibility impairments[4]
  - Anterograde amnesia with acute dosing
- Anticholinergics
  - Increased risk for cognitive decline and dementia in older adults[5]



https://www.toonpool.com/user/2141/files/turtle_285845.jpg

1. Chau DL et al. *Clin Interv Aging*. 2008; 3: 273-8
2. Cherrier MM et al., *J Pain*, 2009;10:1038-50
3. Parsons BL et al *Am J Geriatr Pharmacother*, 2004;2:157-62
4. Contreras-Gonzalez N et al. Neurol Res 2015;37:1047-53
5. Carriere I et al. Arch Intern Med 2009;169:1317-24

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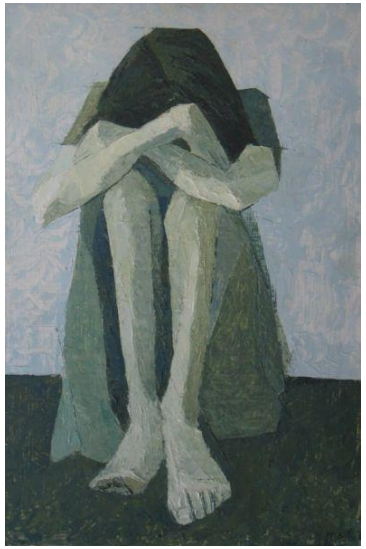
Depression

- Present in up to 50% of memory clinic referrals[1]
  - Anxiety is often concomitant
- 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
  - Impaired 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.

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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[1]
- Residual cognitive difficulties
  - Subjective feelings of reduced capability
  - Impaired decision-making
  - Adverse consequences on social function[2]
- 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

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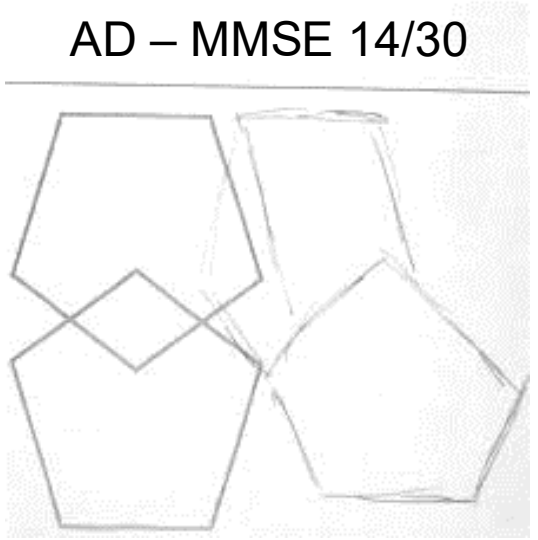
“Giving up” on cognitive tasks

Learned helplessness

Depression – MMSE 23/30

Early Quitting

AD – MMSE 14/30



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

Persistent/Perseverative

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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

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Sleep and cognition

- Older adults with poor sleep report problems with[1]
  - Memory
  - Motivation
  - Concentration
  - Decision-making
- Cognitive deficits with sleep apnea[2]
  - Attention
  - Working memory
  - Executive function
- Long term consequences of sleep apnea
  - 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

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Pharmacologic Approaches to Software Issues

UAB Memory Clinic preferences

- **Meds**
  - Subtract neuro-active agents when possible
  - Use Beers List for guidance: https://www.guidelinecentral.com/guideline/340784/
- **Mood/Anxiety**
  - SSRIs, buspirone
- **Pain**
  - Duloxetine, not gabapentin
- **Sleep**
  - Trazodone, Mirtazapine

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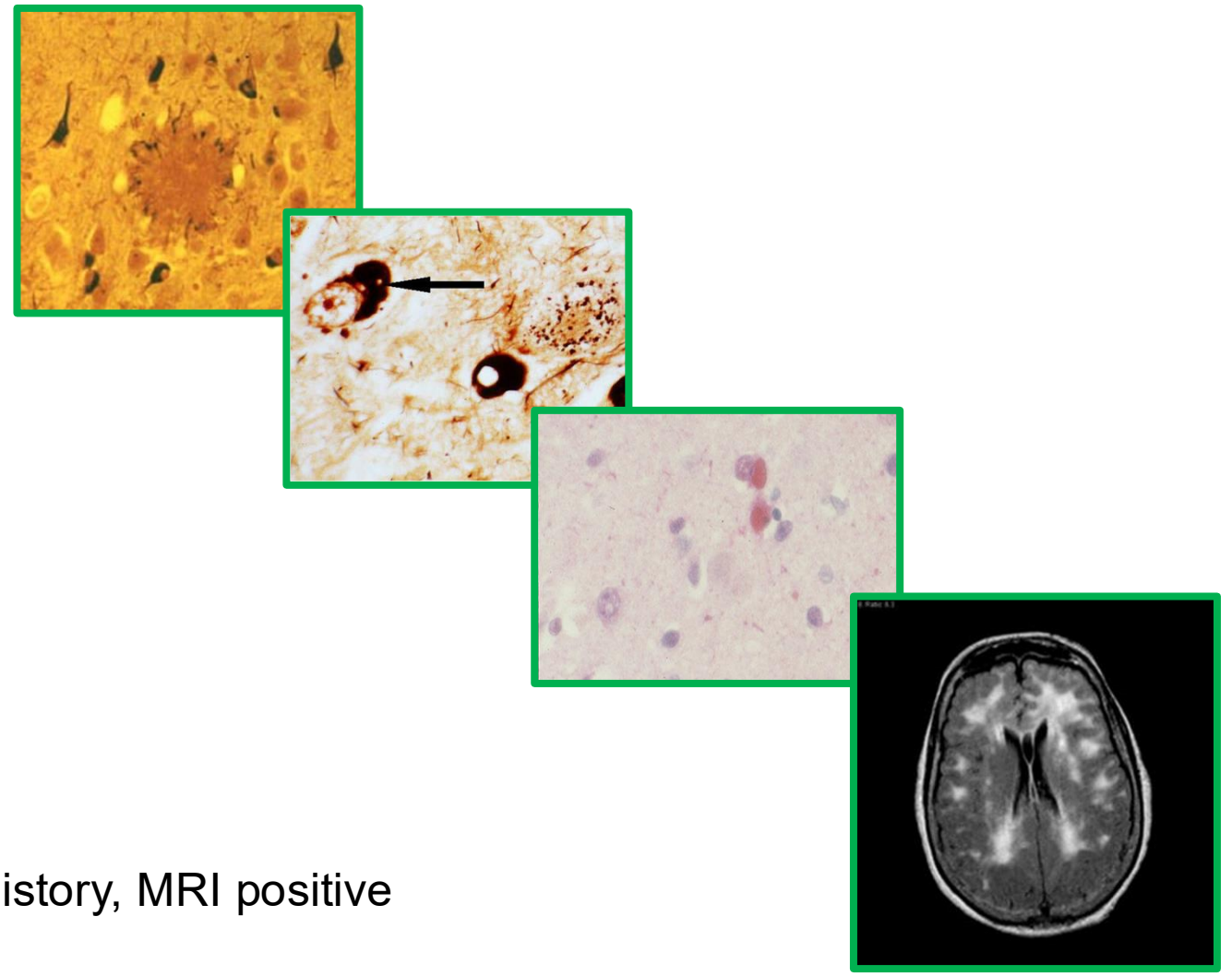
Structurally-mediated cognitive disorders

Structural diseases causing dementia

The big four of "Hardware" issues

- Alzheimer's disease
  - Proteinopathy: Amyloid, Tau
  - Clinical: Poor memory formation
- Frontotemporal lobar degeneration
  - Proteinopathy: Tau, TDP
  - Clinical: Behavior Change
- Dementia with Lewy Bodies/Parkinson's
  - Proteinopathy: Synuclein
  - Clinical: Early hallucinations
- Vascular Brain Injury
  - Vascular lesions
  - Clinical: Slowing, focal signs, Stroke/TIA history, MRI positive



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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

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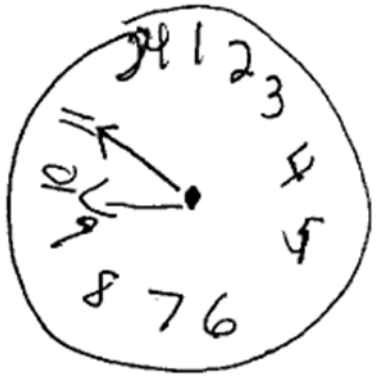
Practical Approach to Cognitive Assessment
Mini-Cog



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.

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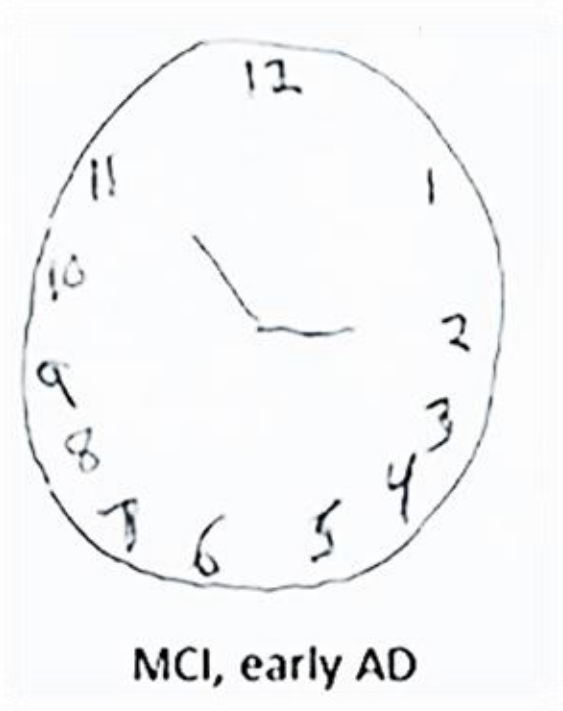
Using cognitive test *data*, not *scores*

- Overall MMSE score is not sensitive to early AD
- Errors on “Memory” tests 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 the 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.

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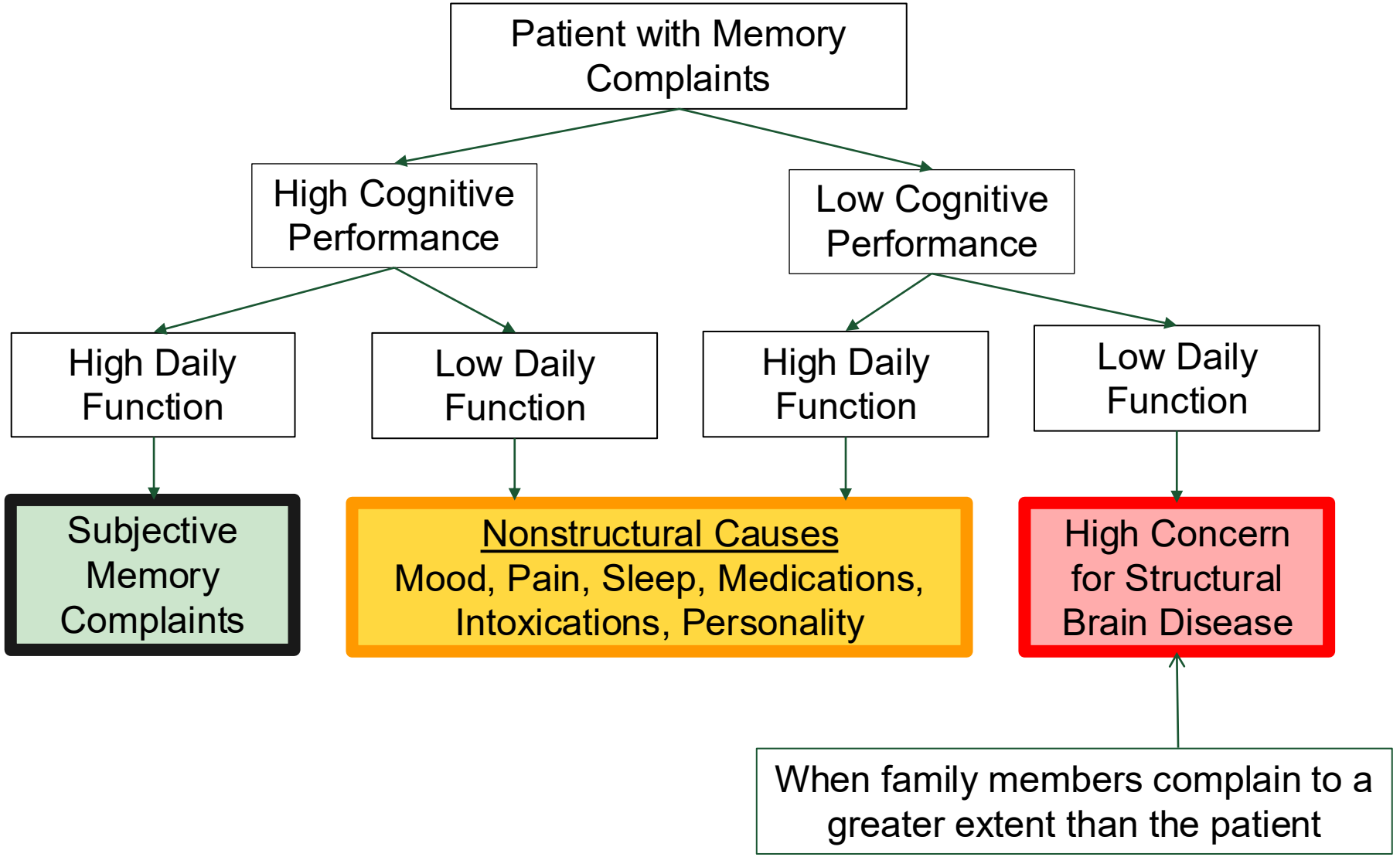
Using Daily Function in Differential Diagnoses



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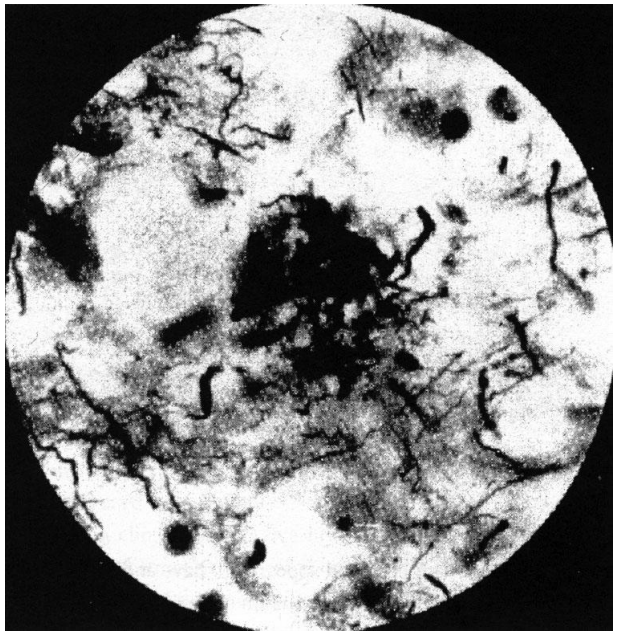
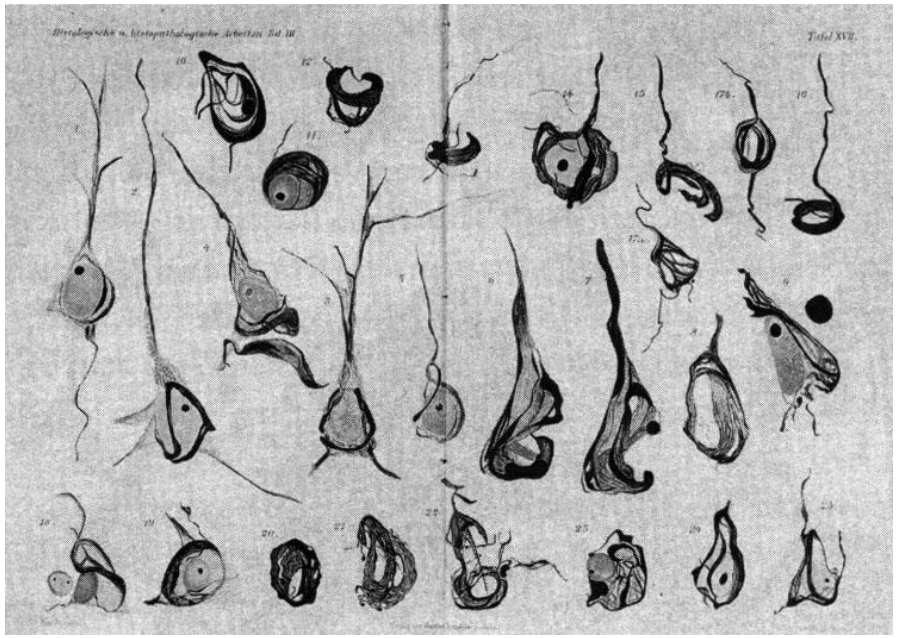
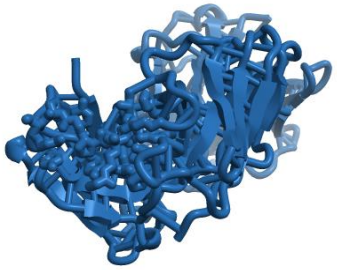
Alzheimer's disease
Evolving concepts; Emerging treatments

Defining Alzheimer’s disease - 1906





Defining Alzheimer’s disease - 2024



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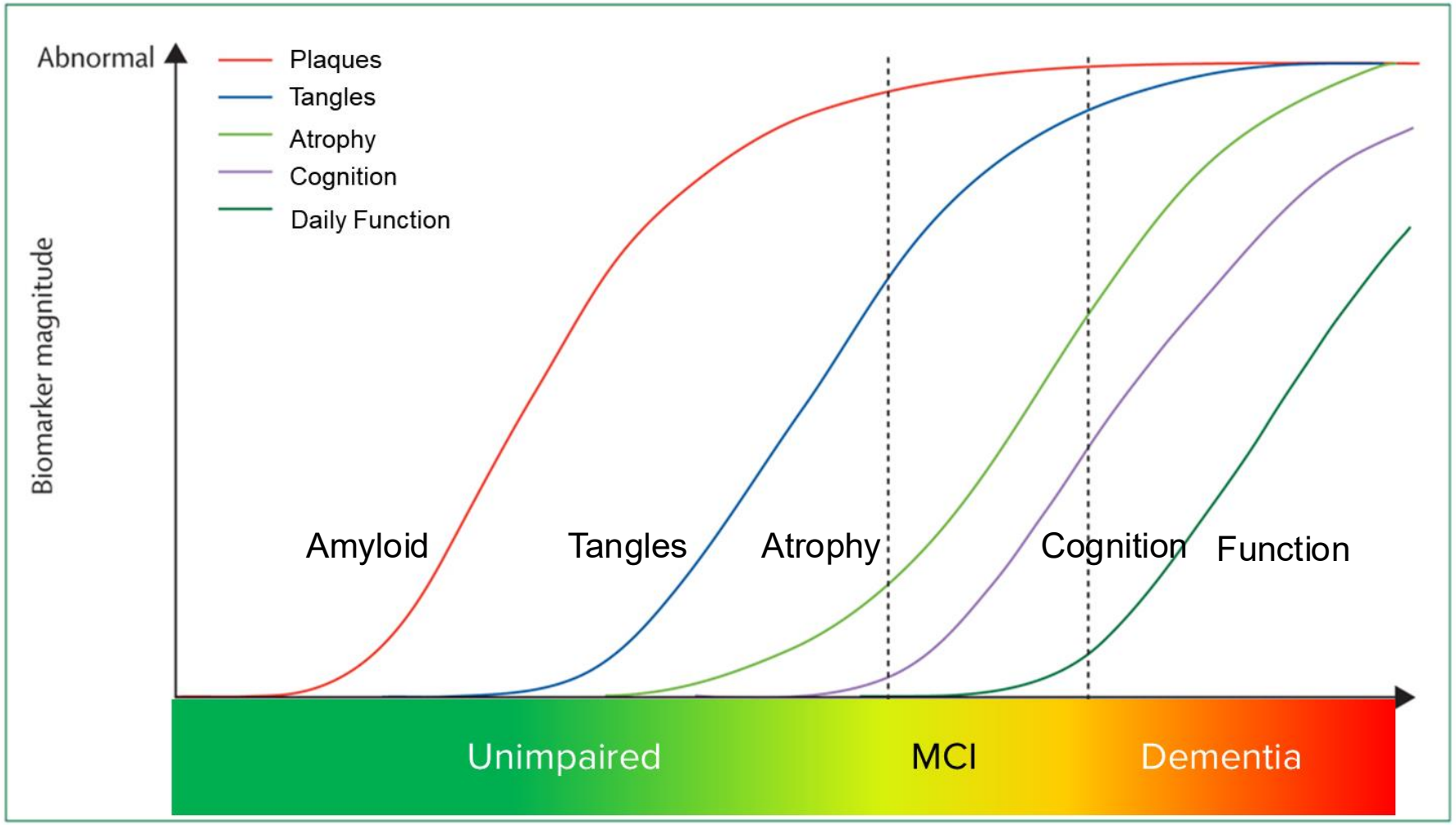
Alzheimer's re-envisioned in the 21st Century

Alzheimer pathology accumulates before cognitive decline



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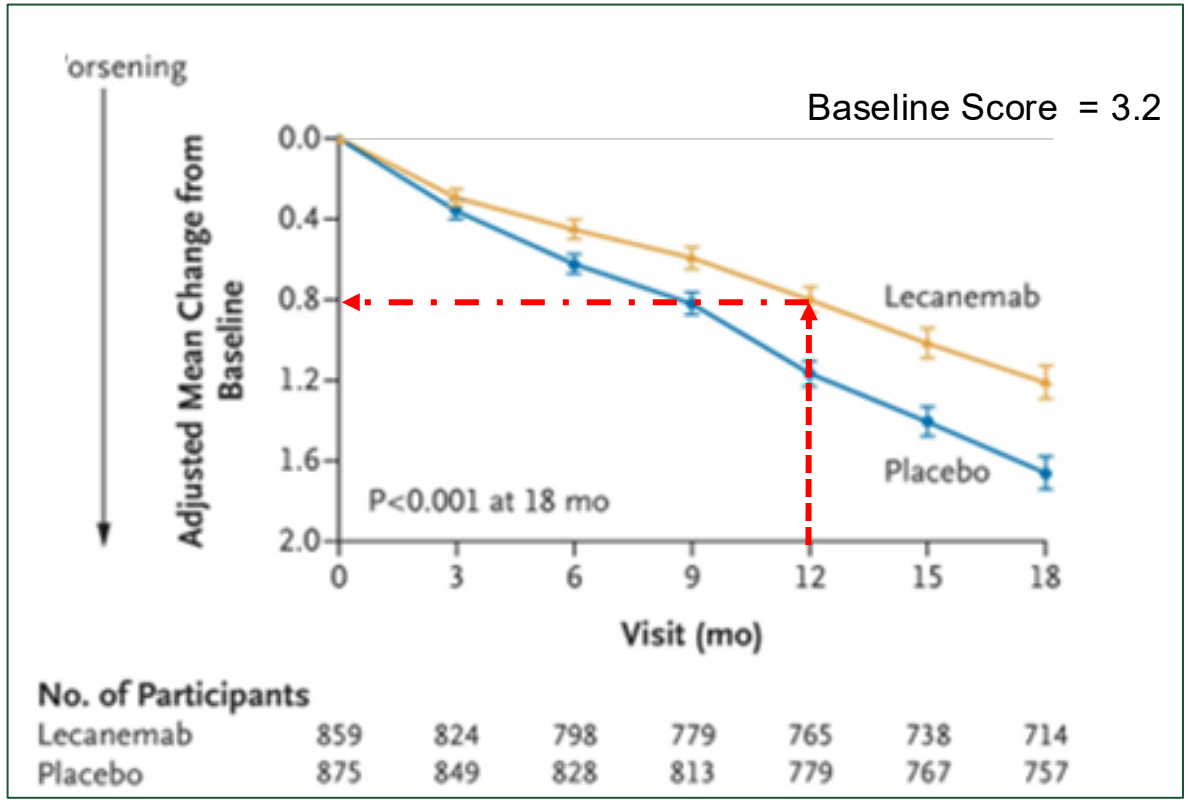
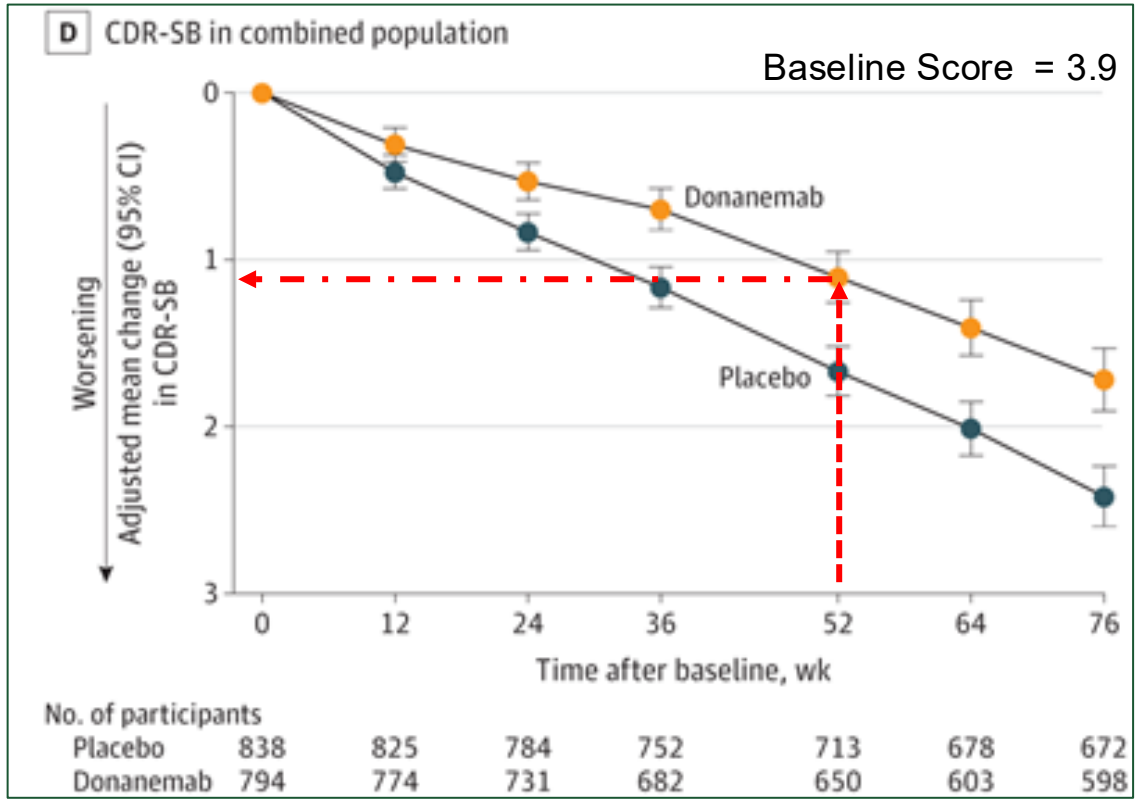
Clinical outcomes with Amyloid Targeting Therapies

CDR-SB side by side*

Lecanemab



Donanemab



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

*No statistical comparison should be inferred

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Why disease severity matters (donanemab)

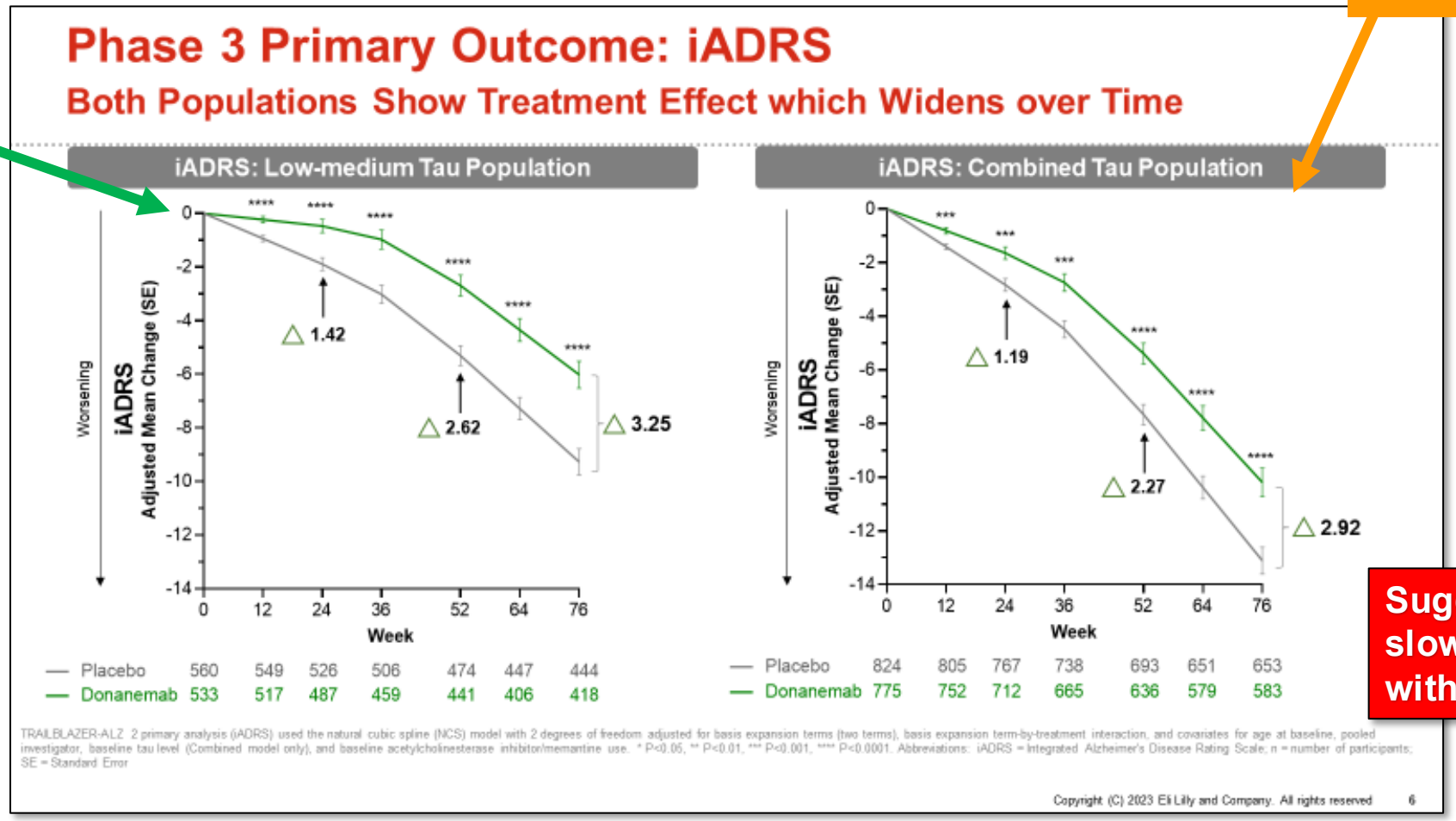
More tau = less effect

High tau excluded

35% slowing

High tau included

22% slowing

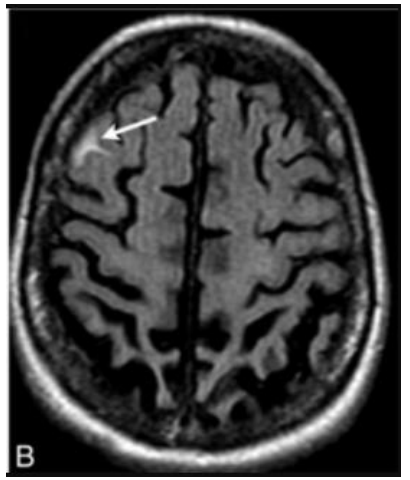


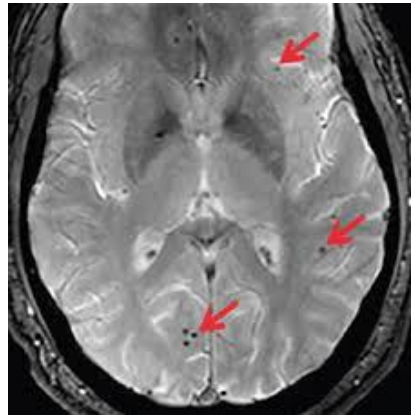
Suggests about 9% slowing for those with high tau burden

Adapted from Eli Lilly slide: presented under fair use doctrine

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





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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

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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

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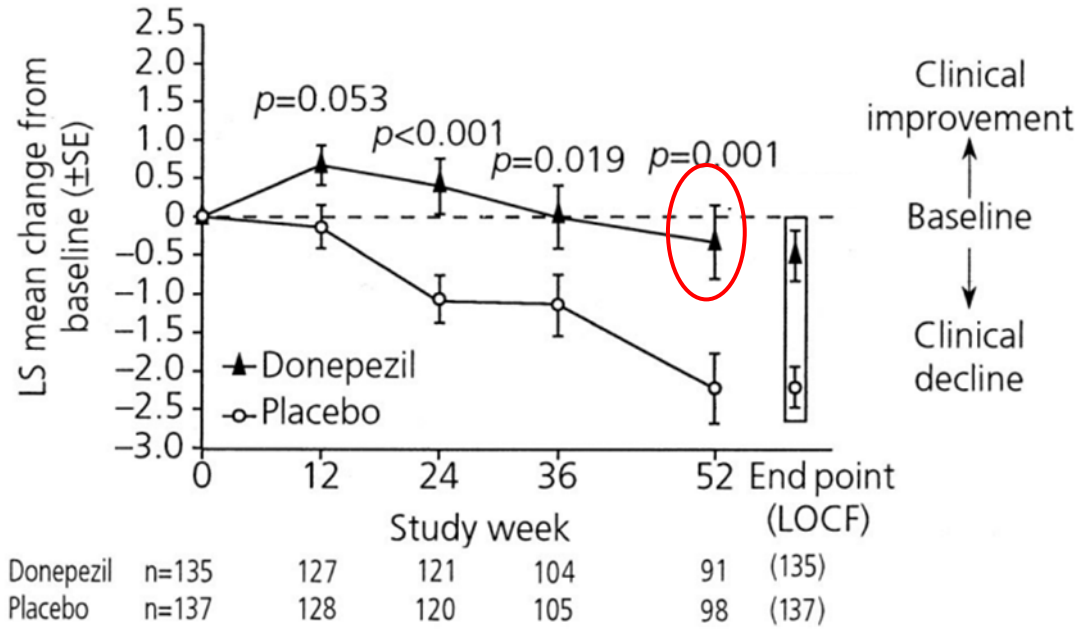
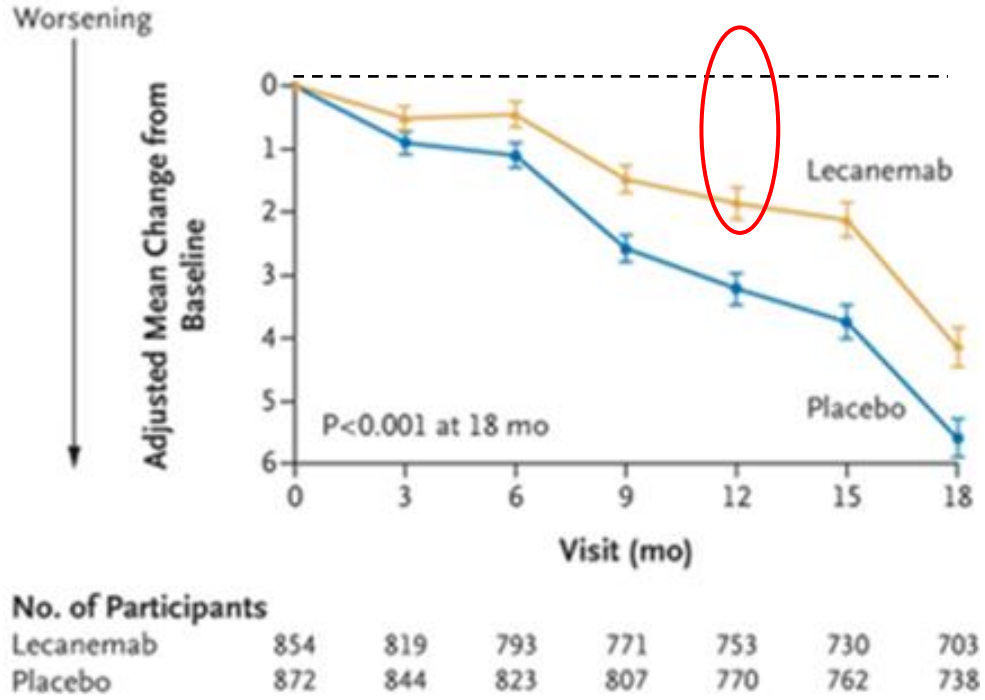
Comparison: donepezil and lecanemab 1 year data

MMSE Score



Donepezil

ADAS-cog13 Score



Lecanemab

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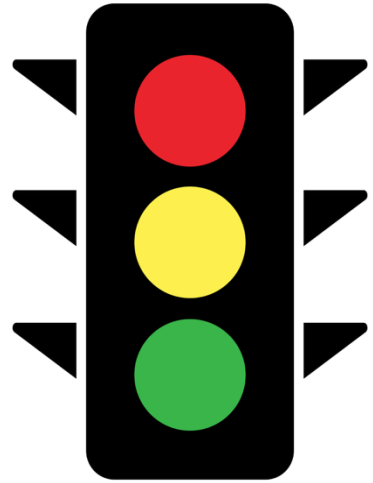
Lecanemab and Donanemab
Practical limitations



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

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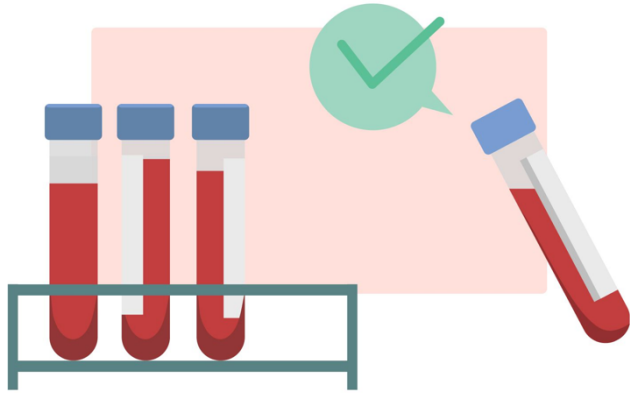
Biomarker diagnosis of AD

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 tangles
  - High tangle burden predicts reduced efficacy of ATT mAbs
  - Plasma tangle assay (MTBR-243) may become available soon

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

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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
  - Test results should always be interpreted within the clinical context.
- 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

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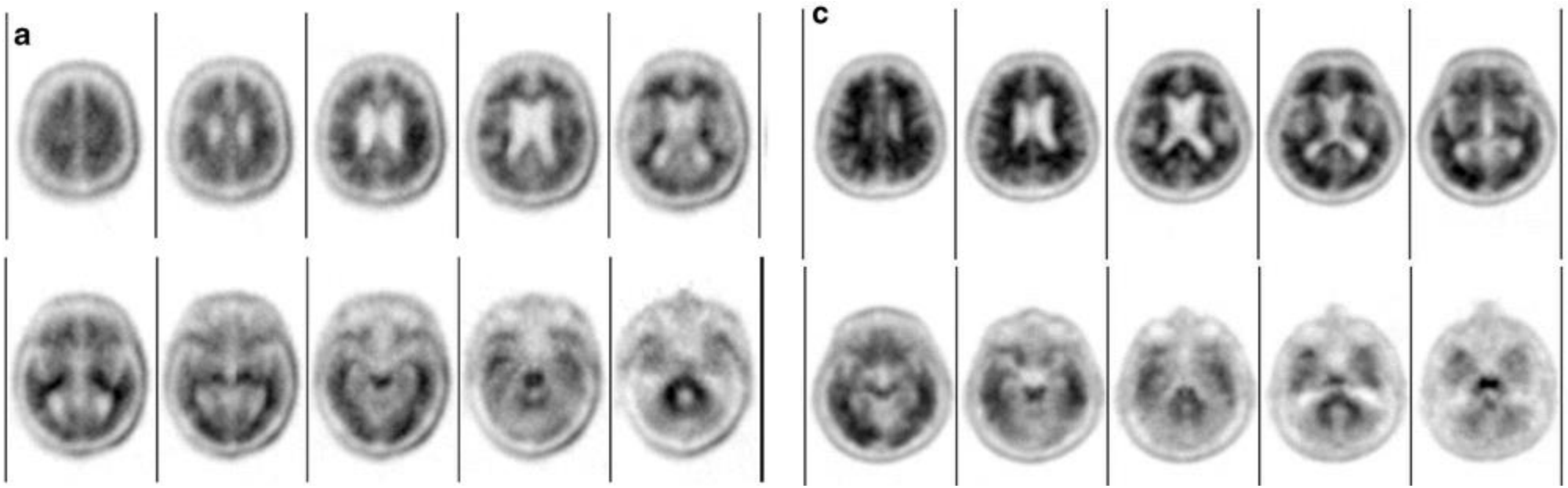
Amyvid PET
Visualizes AD plaque



- **Determining positive vs. negative by visual analysis is challenging!**
- **Semi-quantitative interpretation (centiloids) help standardize readings**

Pontecorvo M et al, 2017. European Journal of Nuclear Medicine and Molecular Imaging 44(5)DOI:10.1007/s00259-016-3601-4

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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
- Alzheimer’s disease is highly prevalent among structural causes (“hardware”)
  - Biological diagnosis is available, but nuanced
  - Pathology-modifying treatments are in clinical use

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Questions?