Memory Loss, Alzheimer's disease, & Dementia - Update 2023

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- Budson AE, O'Connor MK. *Seven Steps to Managing Your Memory: What's Normal, What's Not, and What to Do About It*, 2017 (Oxford University Press)
- Budson AE, O'Connor MK. *Six Steps to Managing Alzheimer's Disease and Dementia: A Guide for Families*, 2022 (Oxford University Press)
- Budson AE, Kensinger EA. *Why We Forget and How to Remember Better: The Science Behind Memory*, 2023 (Oxford University Press)

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Learning Objectives

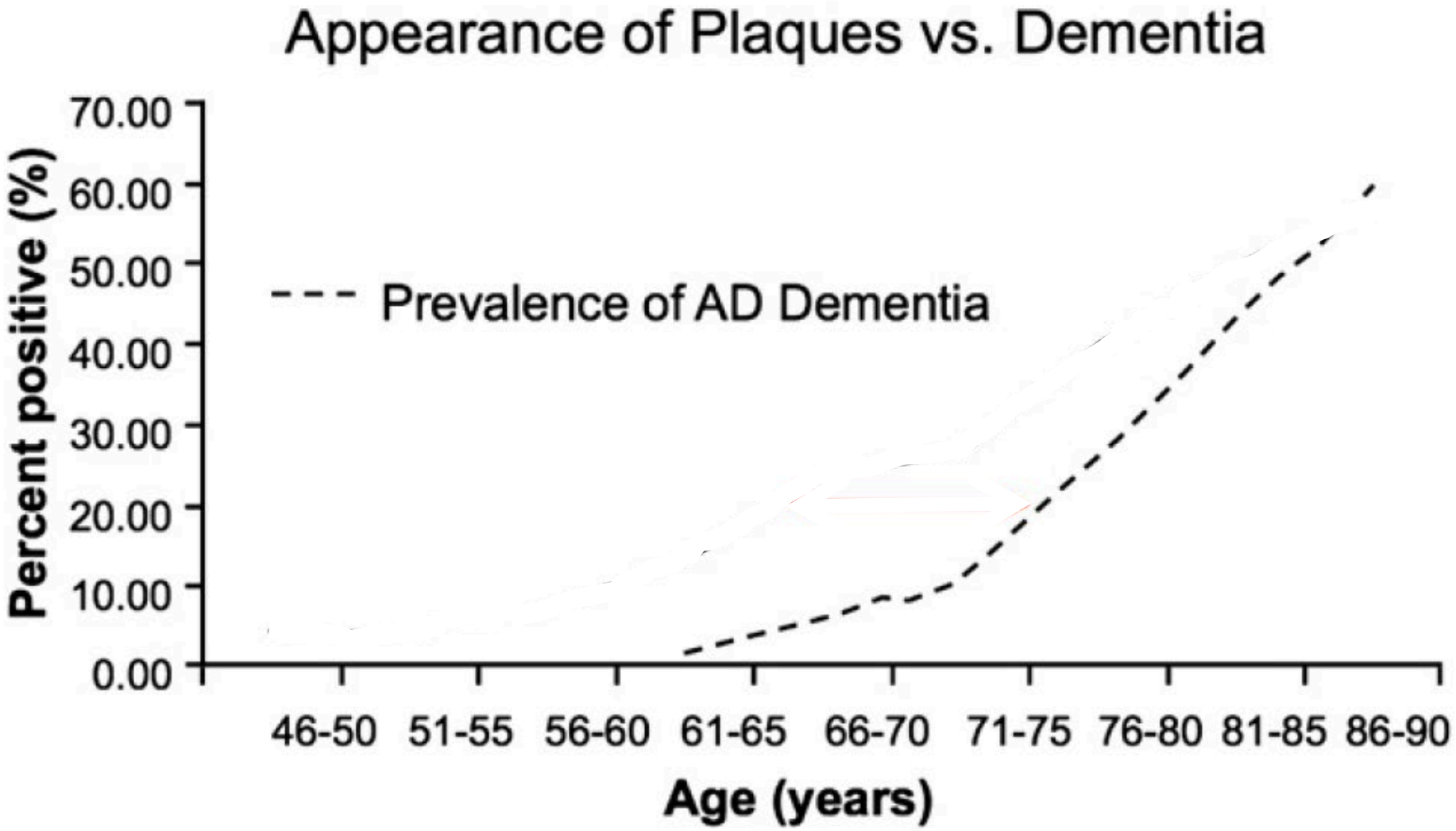
- Use the NIA-AA &/or DSM-5 Criteria for
  - Alzheimer's disease (AD) &
  - Mild Cognitive Impairment (MCI) due to AD
- Know when to obtain biomarkers
- Learn about LATE (Limbic-predominant, Age-related, TDP-43 Encephalopathy)
- Diagnose other common dementias including chronic traumatic encephalopathy
- Treat Alzheimer's disease & other common dementias
- Understand aducanumab (Aduhelm) & lecanemab
- Manage issues of driving, agitation, & pseudobulbar affect
- Know data on diet & exercise for memory

Patient 1

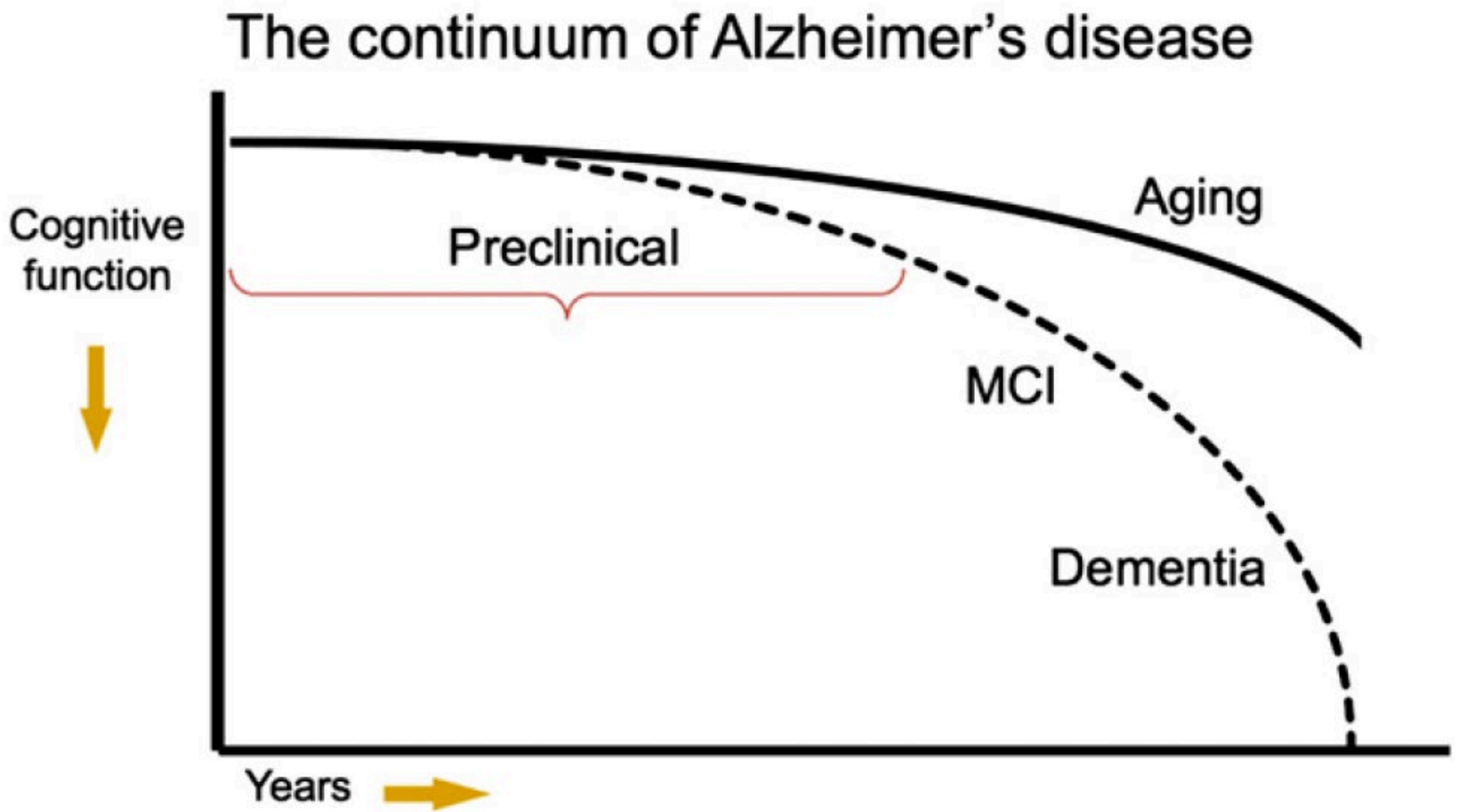
- 81 M with memory difficulties.
- 8 years ago got lost, asked the same questions repeatedly.
- Gradual worsening, last 6-12 mos unable to learn new information
- Prominent word finding difficulties
- Remembers everything about his days during WWII

Alzheimer's disease (probably)

Pathophysiology starts decades prior to clinical disease



Budson & Solomon, Practical Neurology 2012;12:88–96; After Sperling et al., AlzDement 2011;7:280



Budson & Solomon, 2016; After Sperling et al., AlzDement 2011;7:280

NIA-AA Criteria: All-Cause Dementia

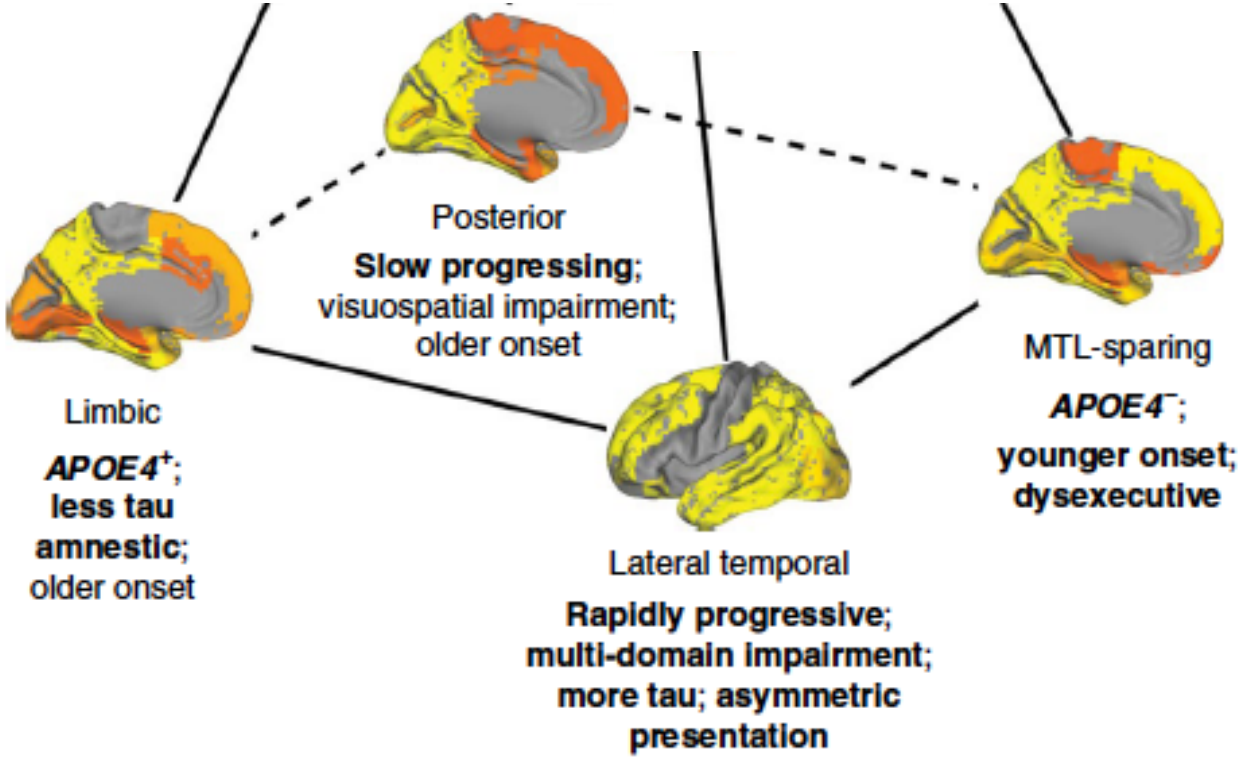
- Decline from prior level of function
  - function at work or usual activities impaired
- Cognitive impairment
  - History from patient & informant
  - Objective cognitive testing (office or formal)
- 2 or more cognitive domains impaired:
  - Memory
  - Reasoning & judgment
  - Visuospatial ability
  - Language
  - Personality, behavior, comportment

NIA-AA Criteria: Alzheimer's disease dementia

- Dementia present using All-Cause Dementia criteria
- Insidious onset months to years
- Progressive cognitive impairment

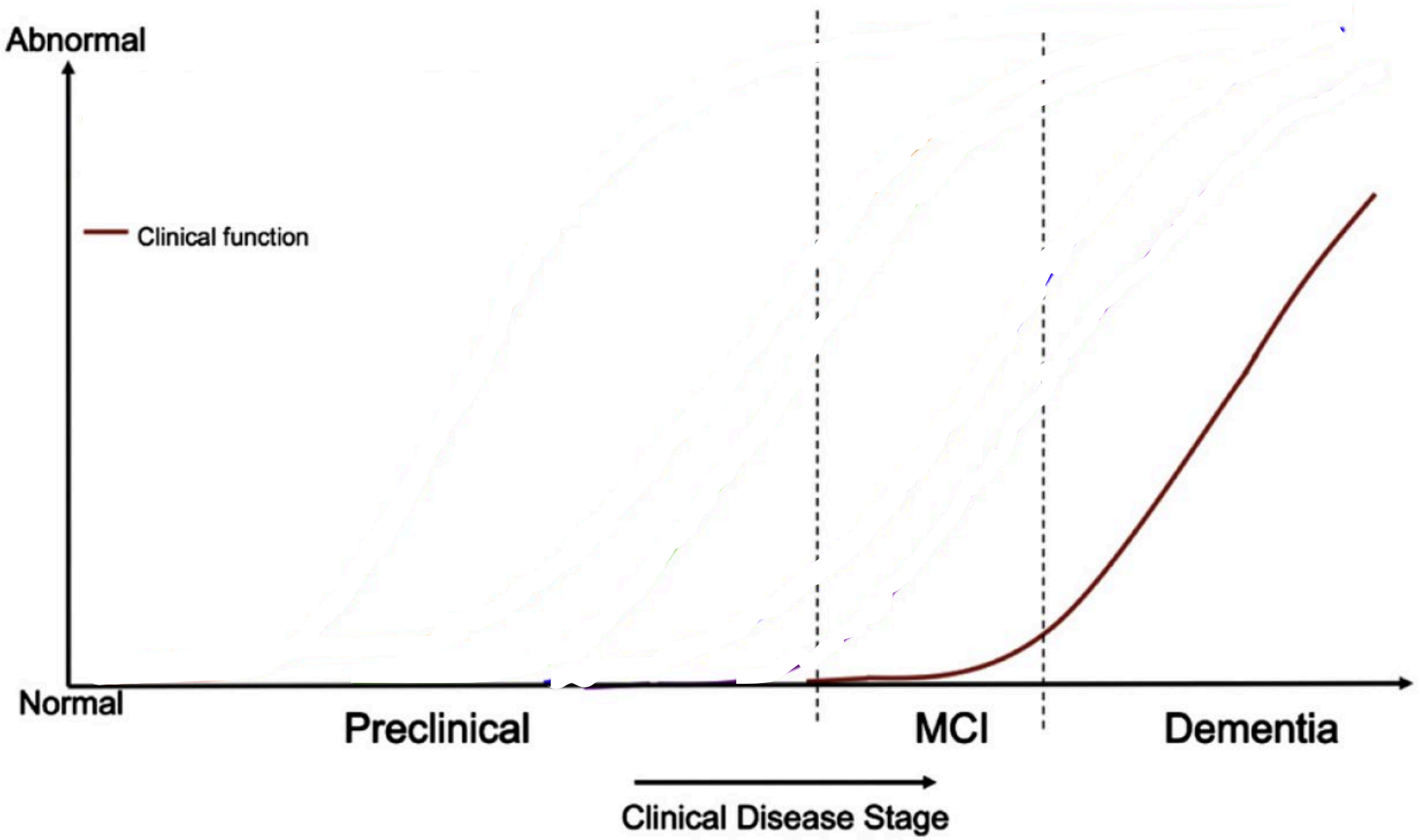
Four distinct trajectories of tau deposition identified in Alzheimer's disease

NATURE MEDICINE | VOL 27 | MAY 2021 | 871–881 |

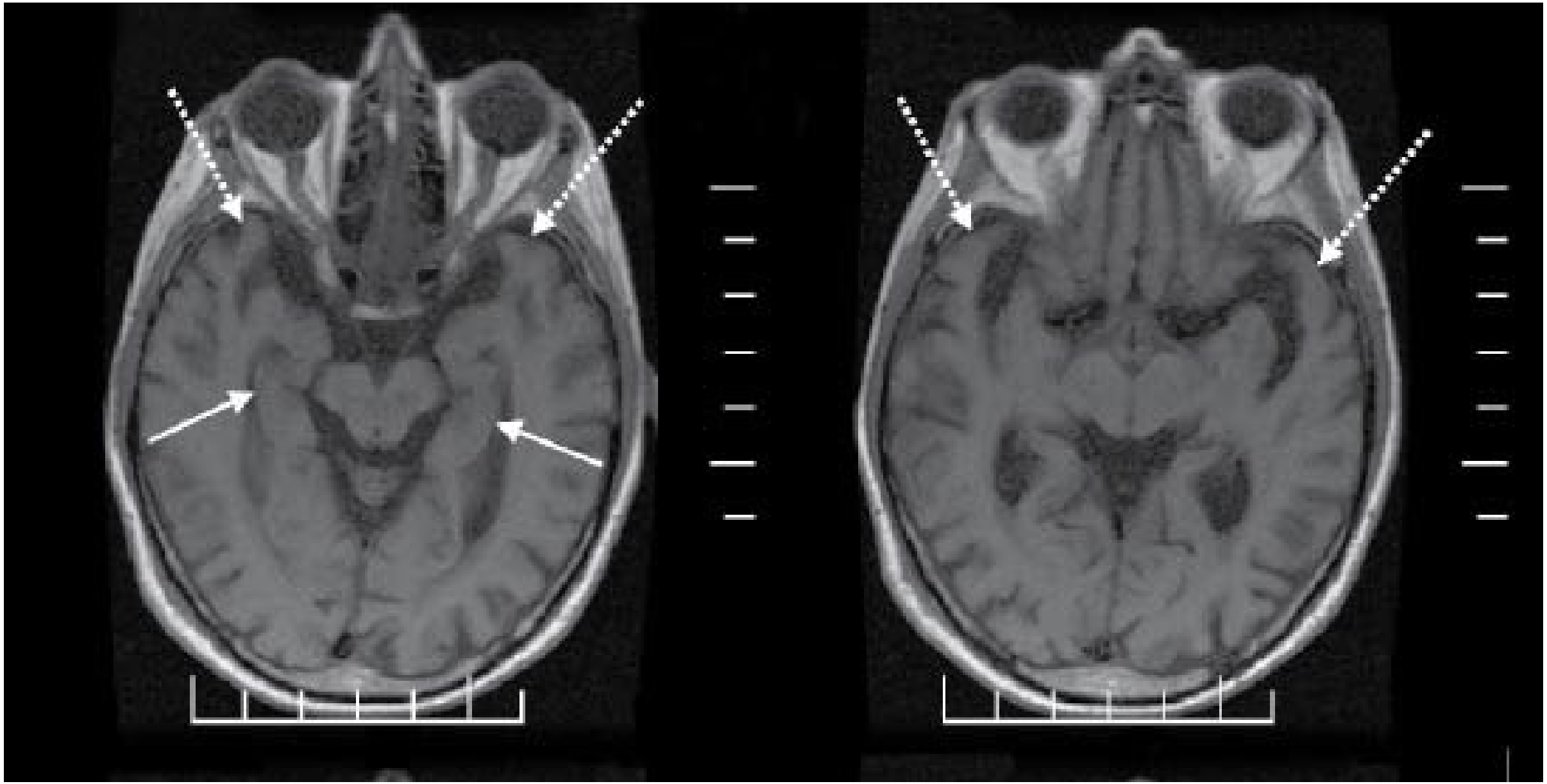


  - 33% Amnestic presentation
  - Non-amnestic presentation
    - 19% Language: word finding
    - 30% Visuospatial: getting lost, impaired face recognition
    - 18% Executive dysfunction: reasoning, judgment, problem solving

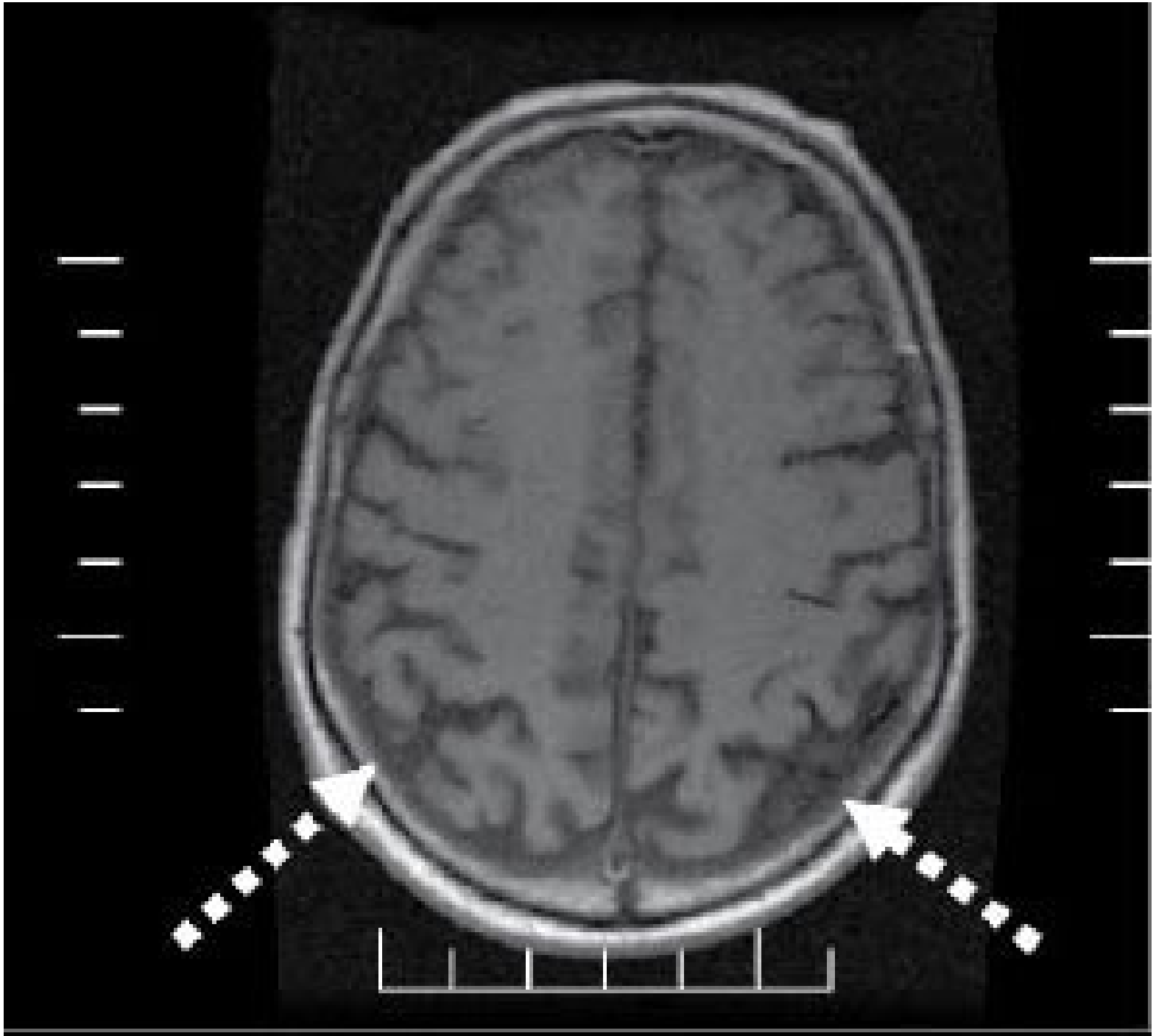
Biomarkers



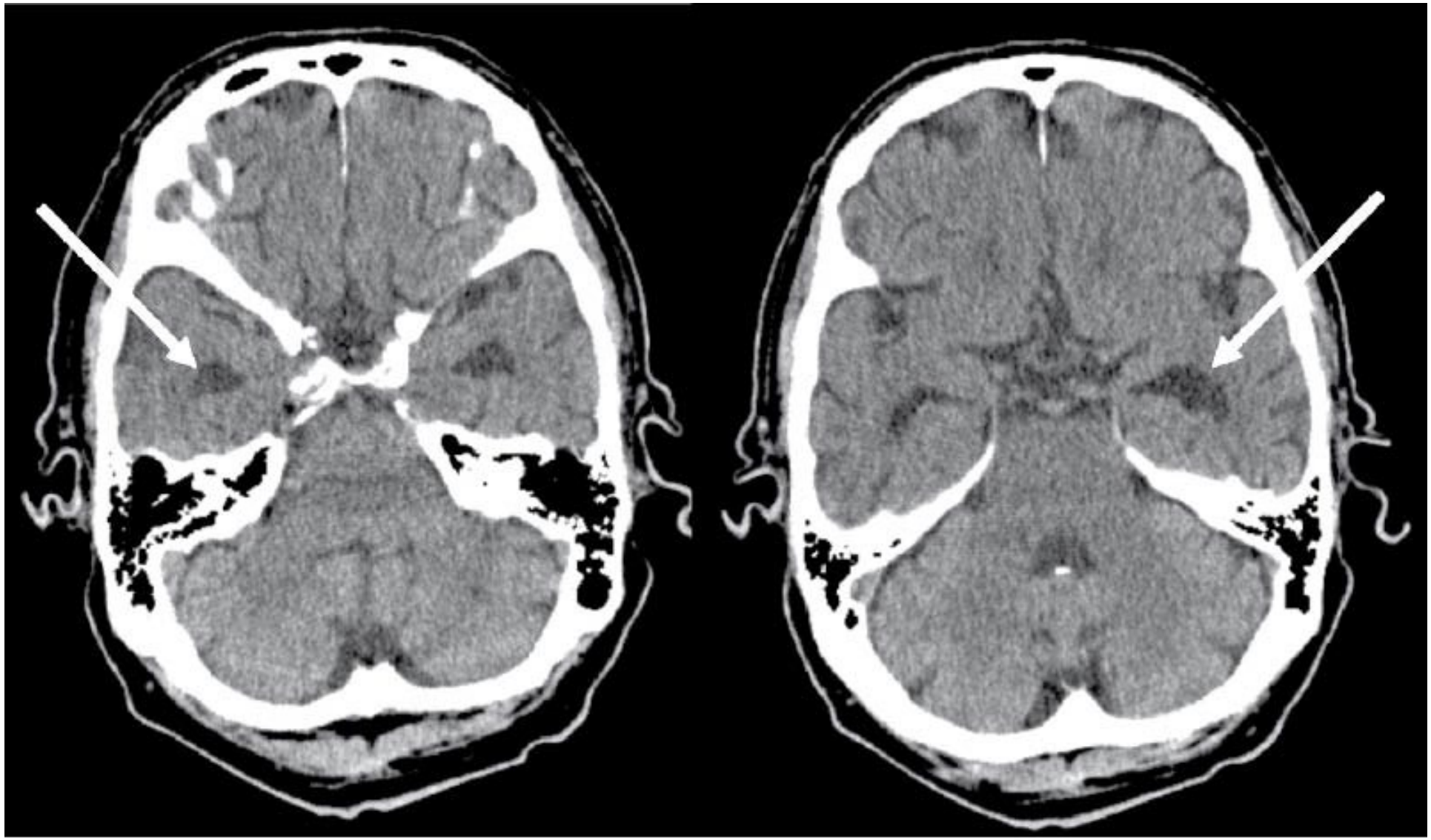
Budson & Solomon, Practical Neurology 2012;12:88–96



From Budson & Solomon, 2022



From
Budson
&
Solomon,
2022



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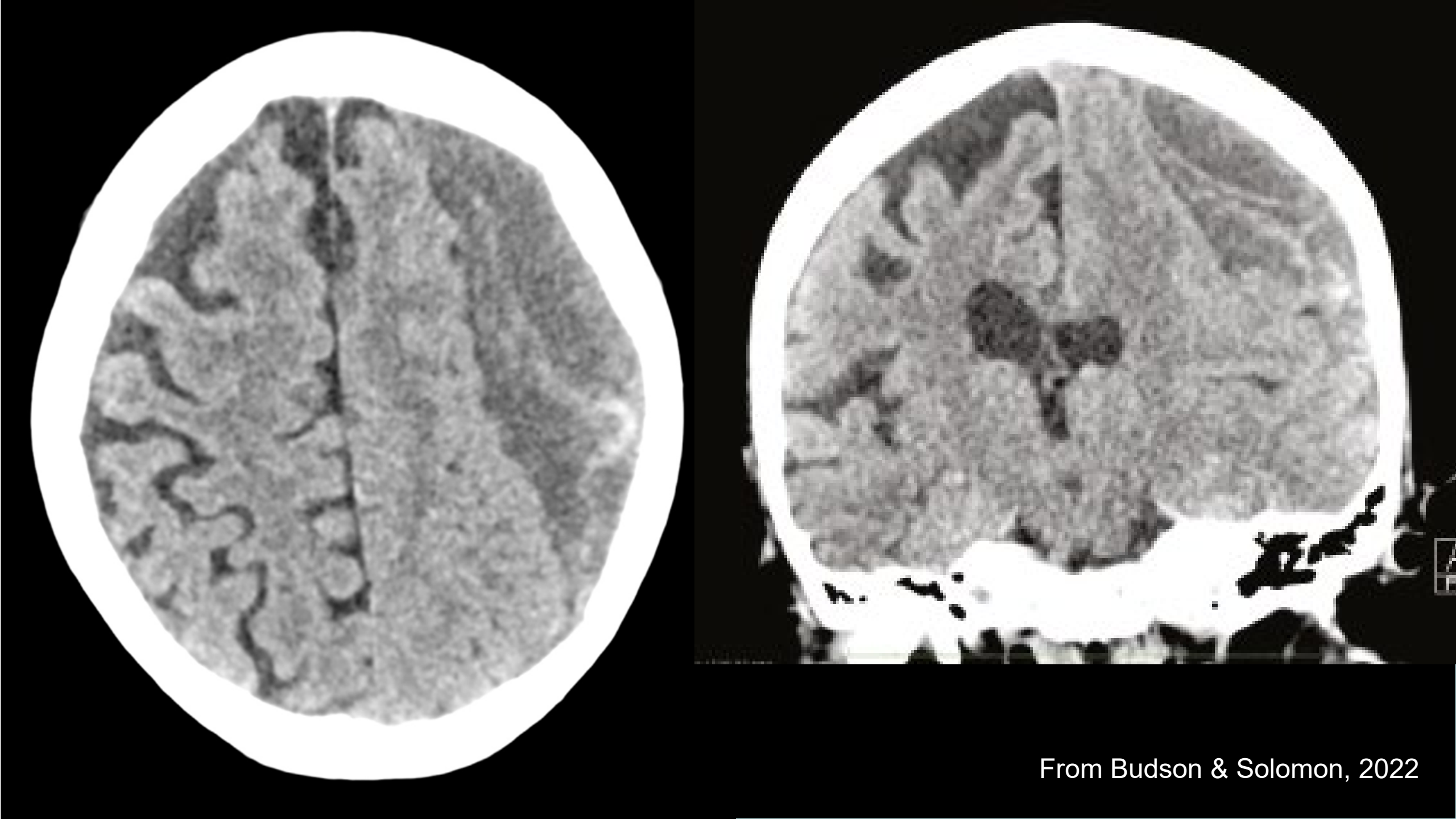
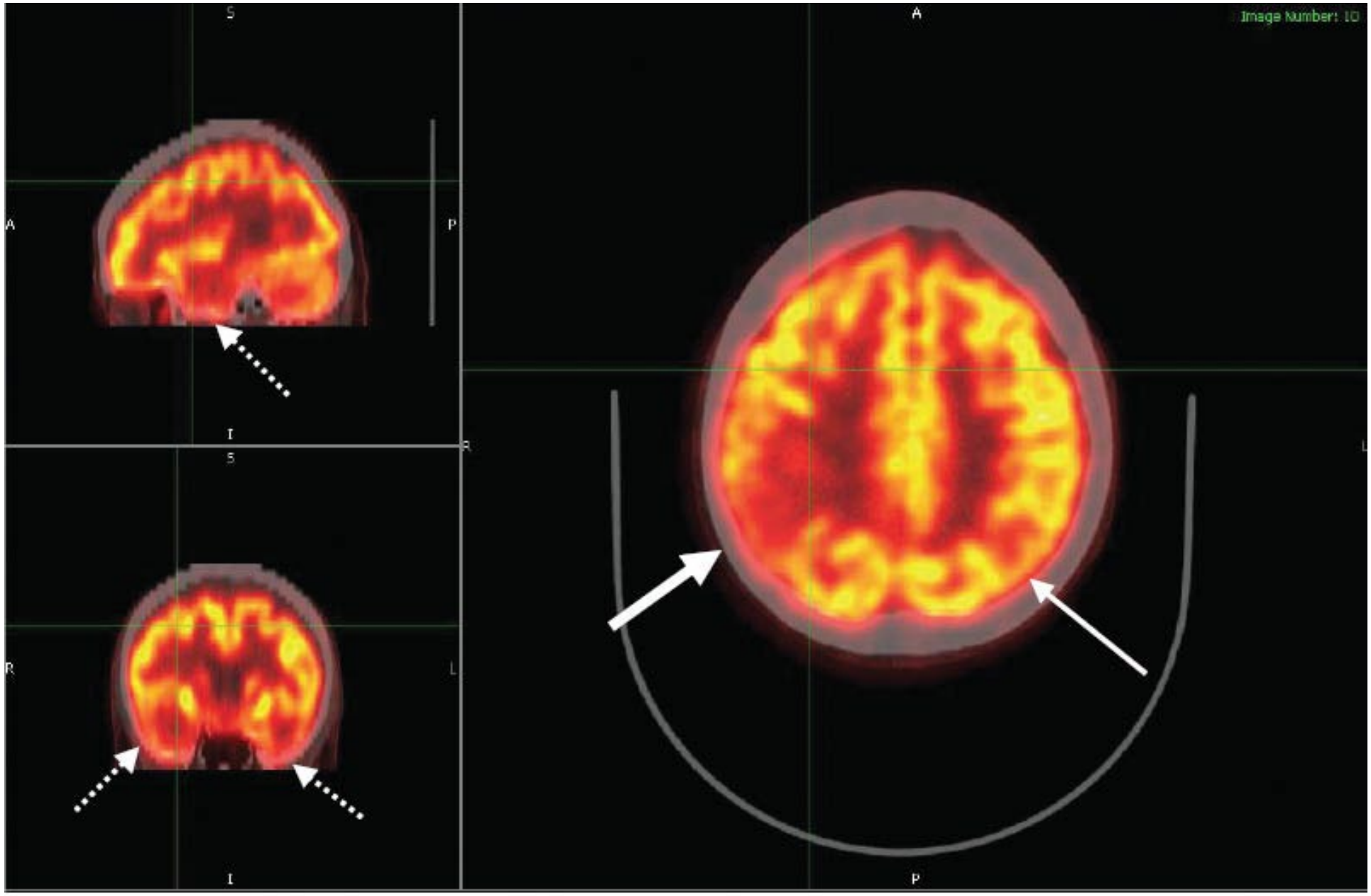


From Budson & Solomon, 2022

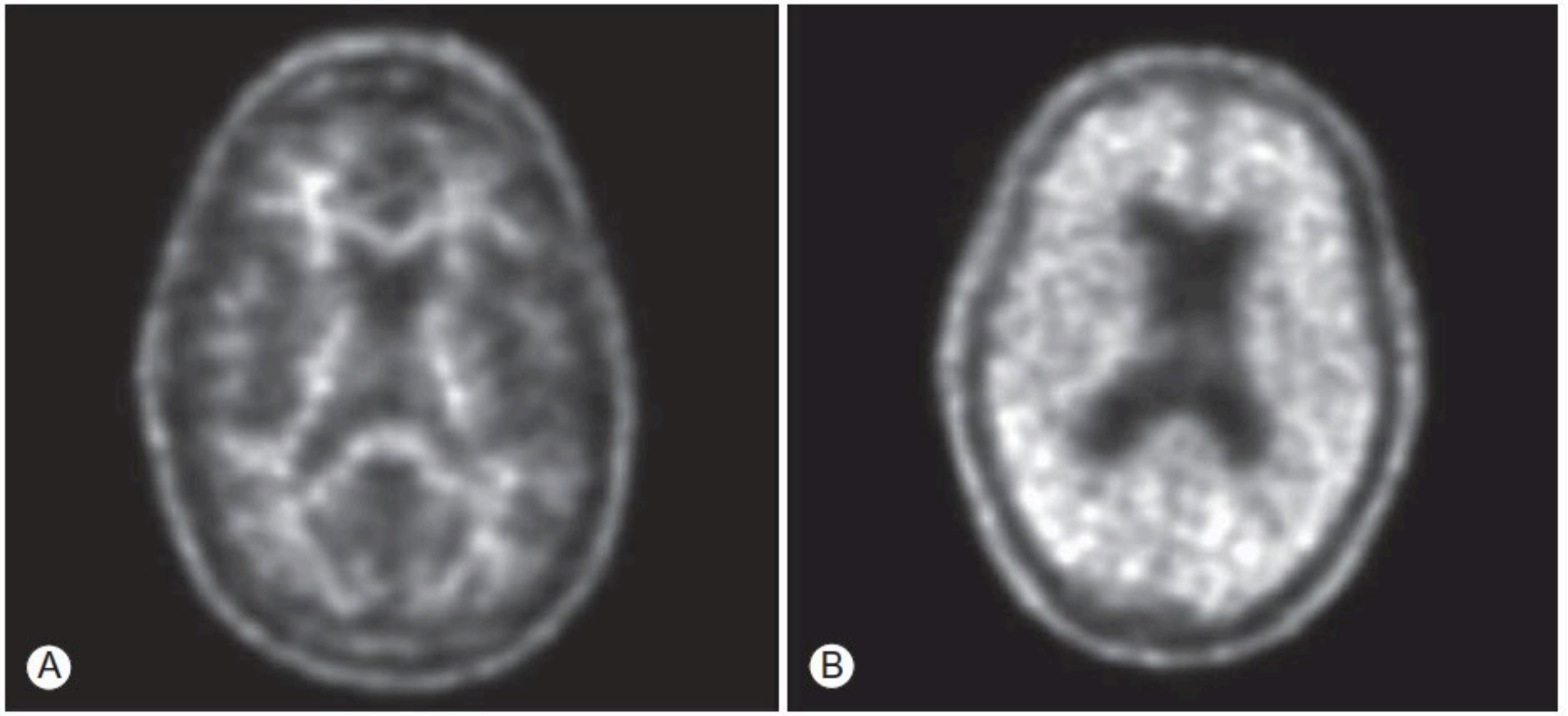
Biomarkers: what to look for / when to use them

- Structural MRI/CT
  - Qualitative atrophy of medial temporal, anterior temporal, & parietal cortex
  - Always look for on scan (cannot depend on radiology)
- CSF Aβ, phospho tau (p-tau), & total tau
  - ↓Aβ & ↑ p-tau, total tau (www.athenadiagnostics.com)
  - Pt clearly demented, unclear if AD, & knowing would change management or prognosis, e.g., young patient
- FDG-PET
  - ↓ metabolism in temporal and parietal cortex
  - Pt clearly demented, unclear if AD, Lewy body, FTD,CTE, & knowing would change management or prognosis



From Budson & Solomon, 2022

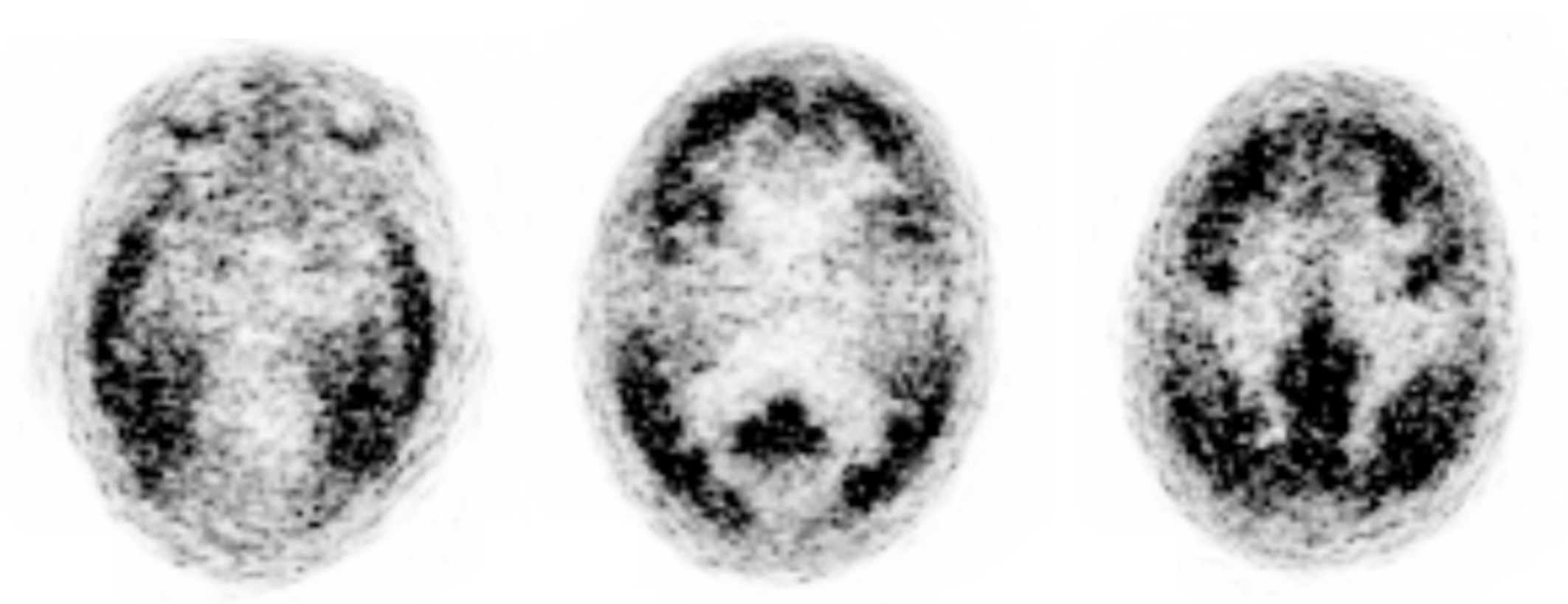
Amyloid Imaging : FDA approved April 2012



- Use when knowing that AD pathology is present in symptomatic patient would change management.
- May detect amyloid plaques in asymptomatic patients who may not develop disease for 10-15+ years
- Not paid for by Medicare or other insurance companies
- Can obtain through Veterans Affairs hospitals, clinical trials/research studies, and self-pay.
- Will have broader use when disease modifying therapies are available.

From Budson & Solomon, 2022

Tau Imaging: FDA approved May 2020



- Use when knowing that AD pathology is present in symptomatic patient would change management.
- Will detect AD tau tangles in symptomatic patients and should correlate with symptoms
- May detect other types of tau tangles in other dementias (not yet clear)
- Not paid for by Medicare or other insurance companies
- Can obtain through Veterans Affairs hospitals, clinical trials/research studies, and self-pay.
- Will have broader use when disease modifying therapies are available.

From Budson & Solomon, 2022

Alzheimer's disease-like disorder with negative amyloid and/or tau biomarkers?

- Some patients appear to have Alzheimer's disease clinically but do not have amyloid and/or tau biomarkers—the pathologic definition of Alzheimer's.
- How do we understand this?

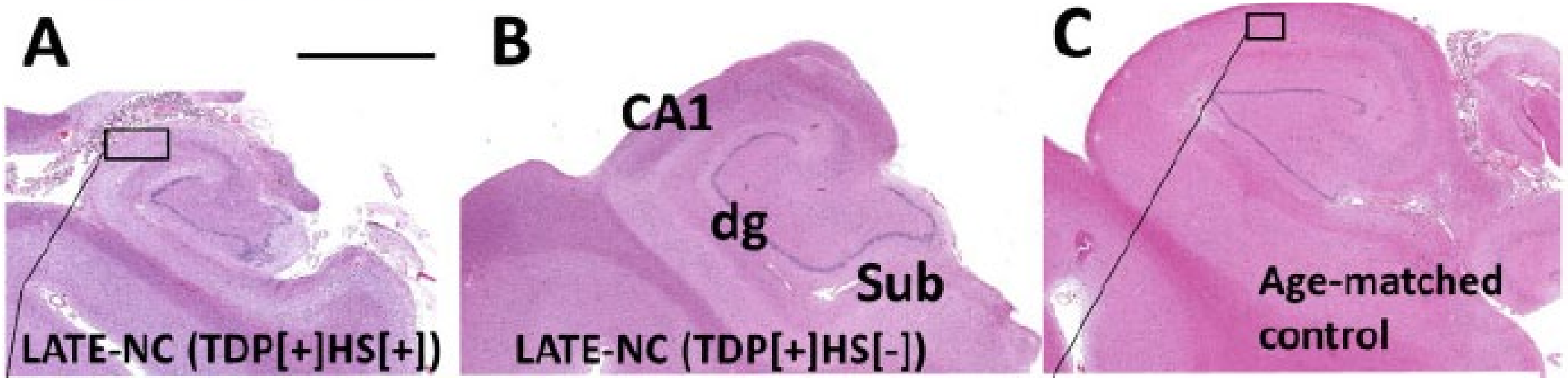
- Maybe these patients have another disorder…

doi:10.1093/brain/awz099 BRAIN 2019: 142; 1503–1527 | 1503

BRAIN
A JOURNAL OF NEUROLOGY

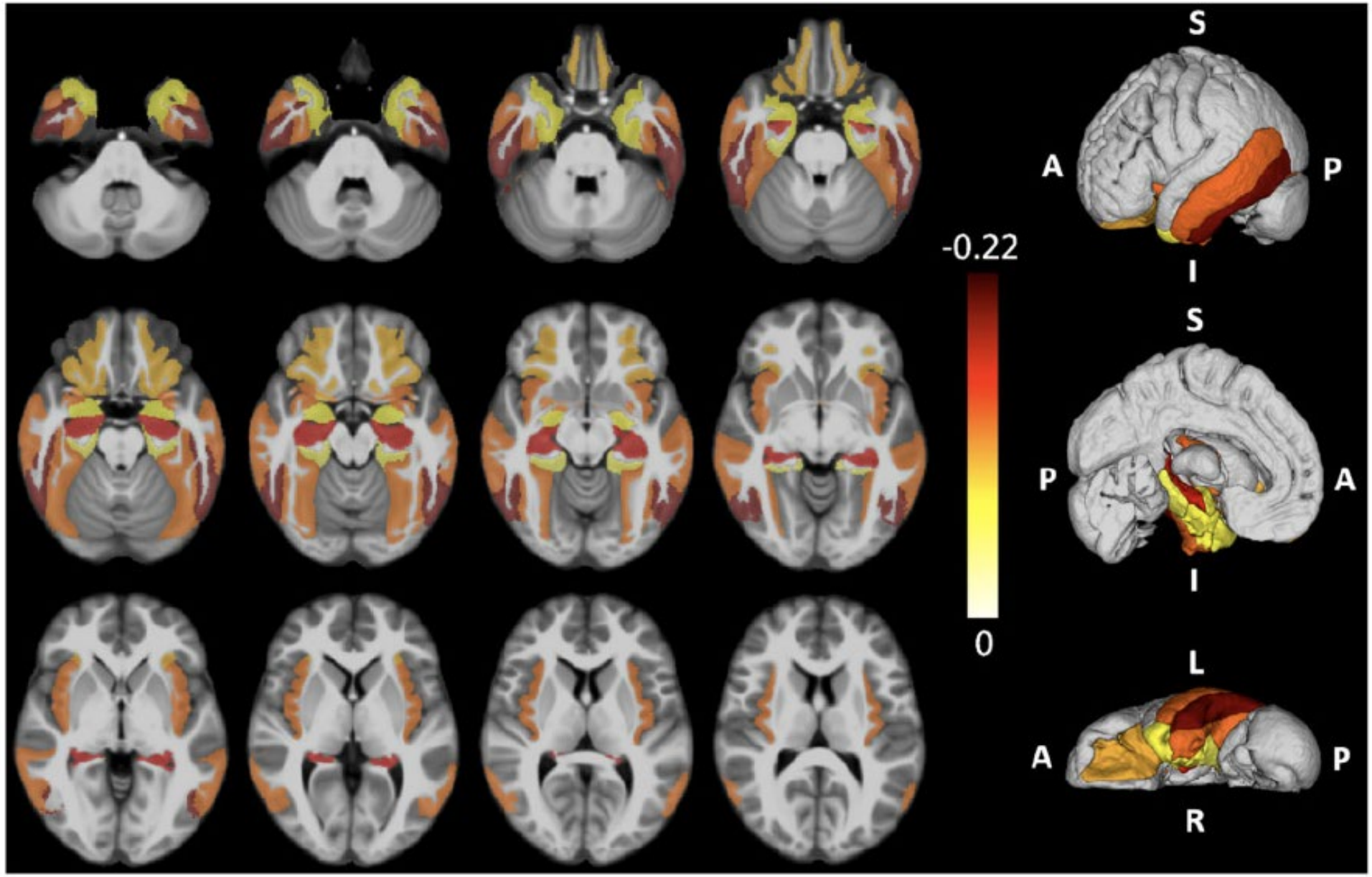
REVIEW

Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report



A

Brain atrophy associated with autopsy-confirmed LATE-NC:
Data from Rush University ROS-MAP community-based autopsy cohorts



Rush University community-based cohort data (*n* = 1376)

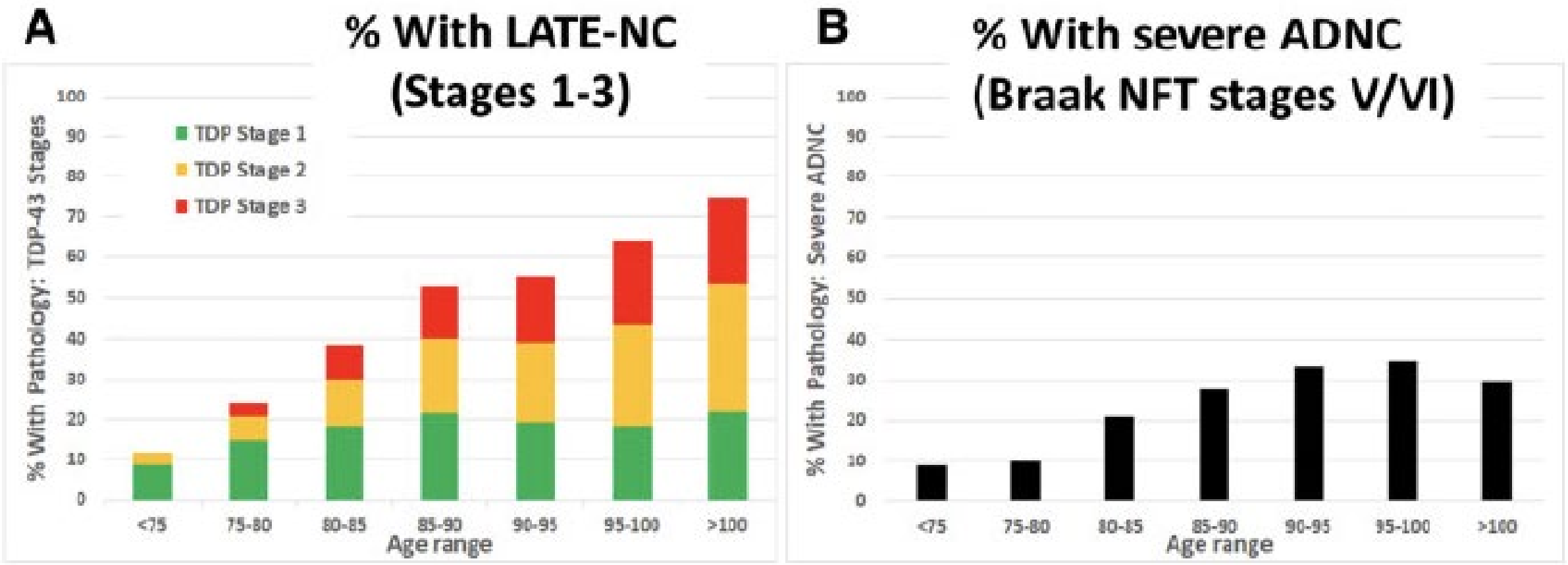


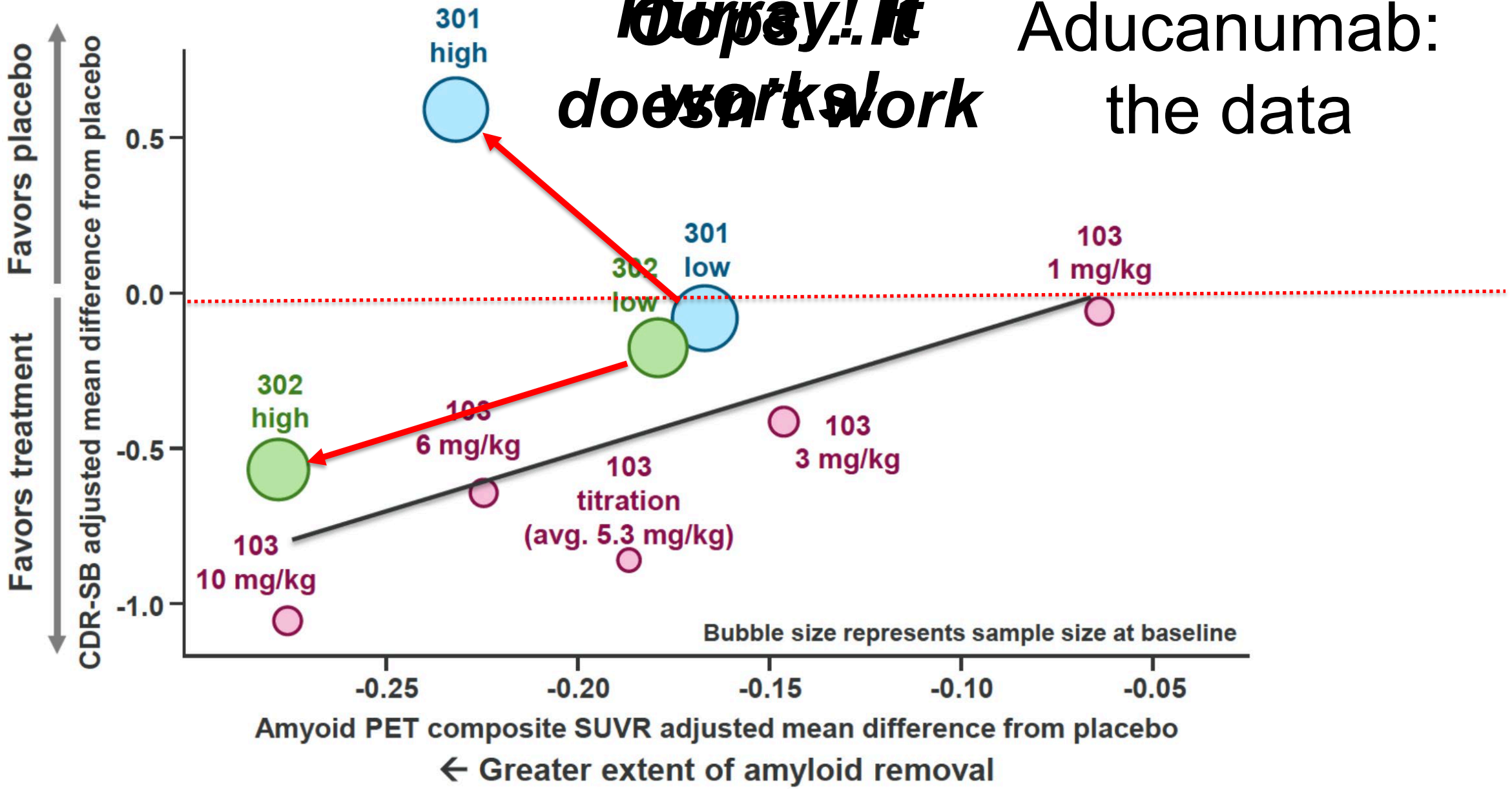
Table 2 **A statistical analysis of attributable risk from research volunteers in two clinical-pathological studies of ageing from Rush University**

Neuropathological indices	Fraction attributable % (95% CI)[a]
Alzheimer's disease (ADNC)	39.4 (31.5–47.4)
Vascular disease pathology[b]	24.8 (17.3–32.1)
LATE-NC	17.3 (13.1–22.0)
α-Synucleinopathy/Lewy body pathology	11.9 (8.4–15.6)

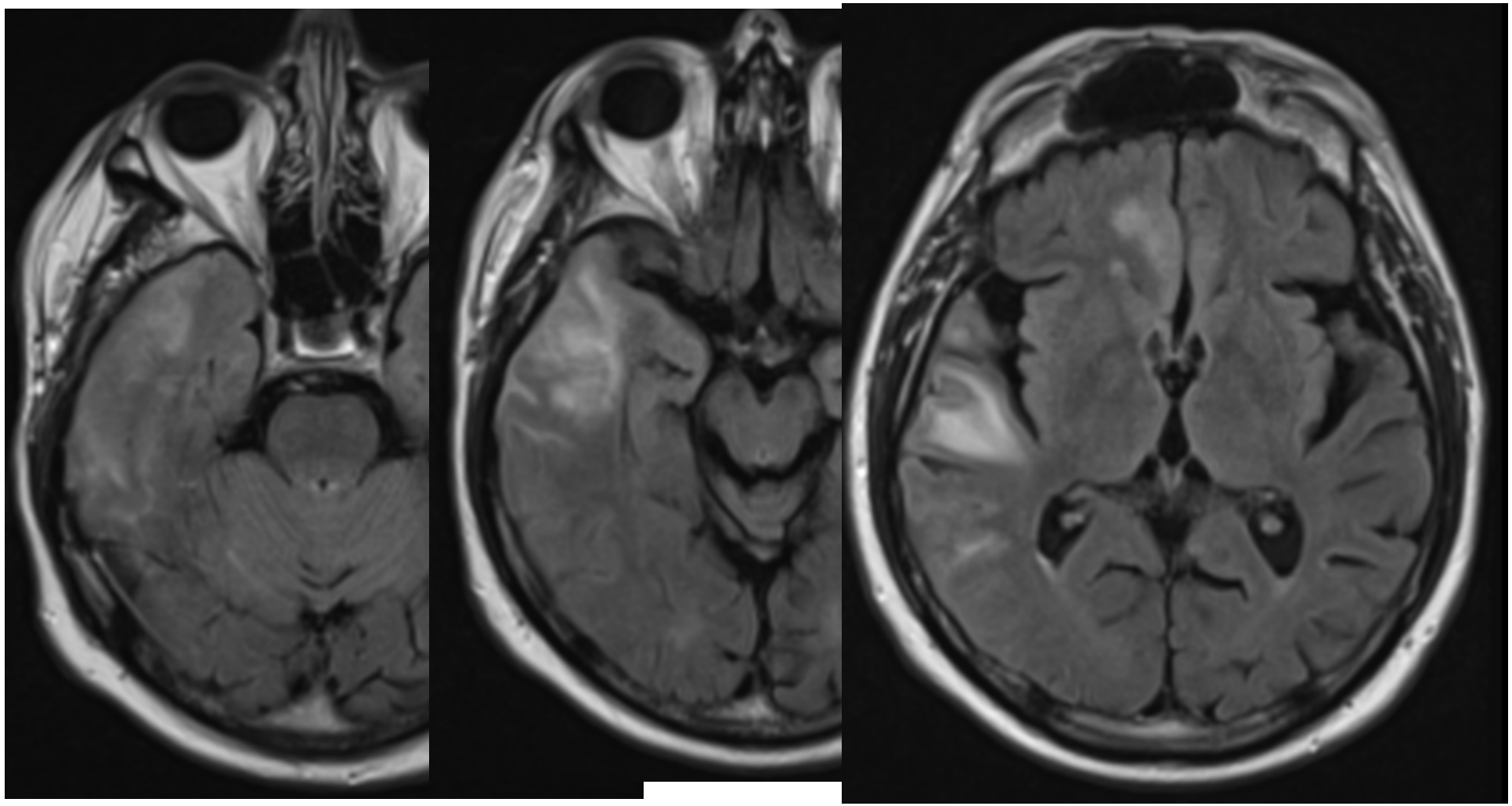
Treatment: What's new?

- New symptomatic medications being developed which modulate neurotransmitters to improve cognition and/or reduce agitation.
- New disease modifying therapies also being developed
  - Most use monoclonal antibodies directed against either β-amyloid plaques or tau tangles.
  - Some induce a special frequency of EEG waves in the brain.
  - Some try to reduce infectious brain pathogens theorized to cause Alzheimer's.

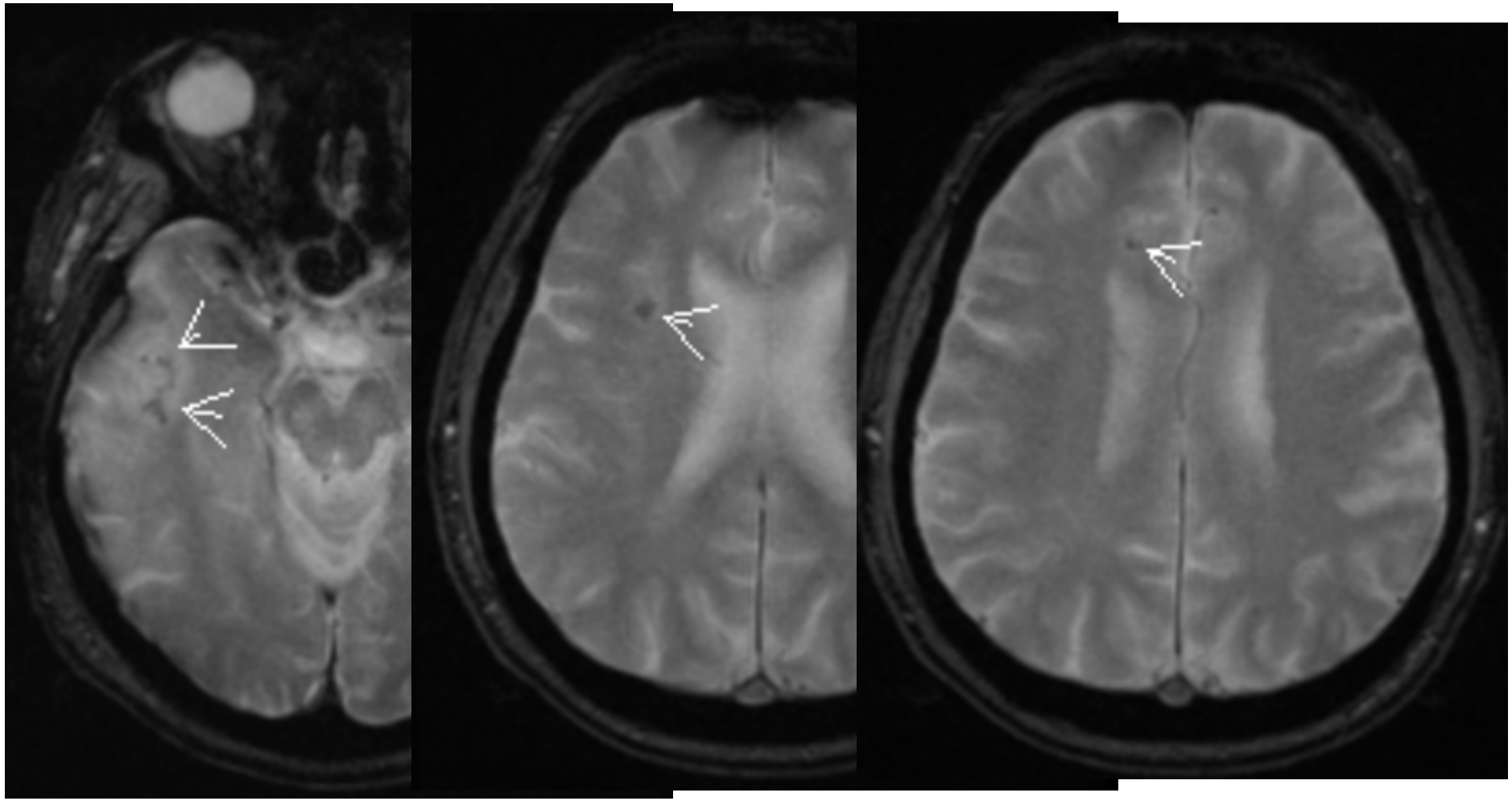
Aducanumab: the data



Aducanumab Amyloid-Related Imaging Abnormalities
ARIA-E vasogenic edema 30%



Aducanumab ARIA-H Hemorrhages 10%



The NEW ENGLAND JOURNAL of MEDICINE

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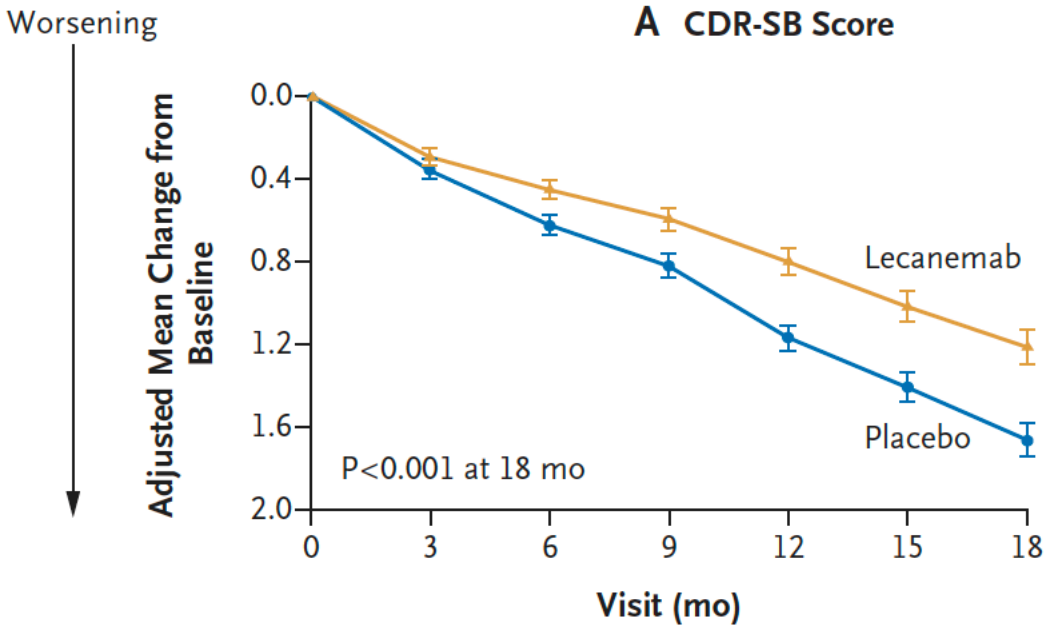
ORIGINAL ARTICLE

Lecanemab in Early Alzheimer's Disease

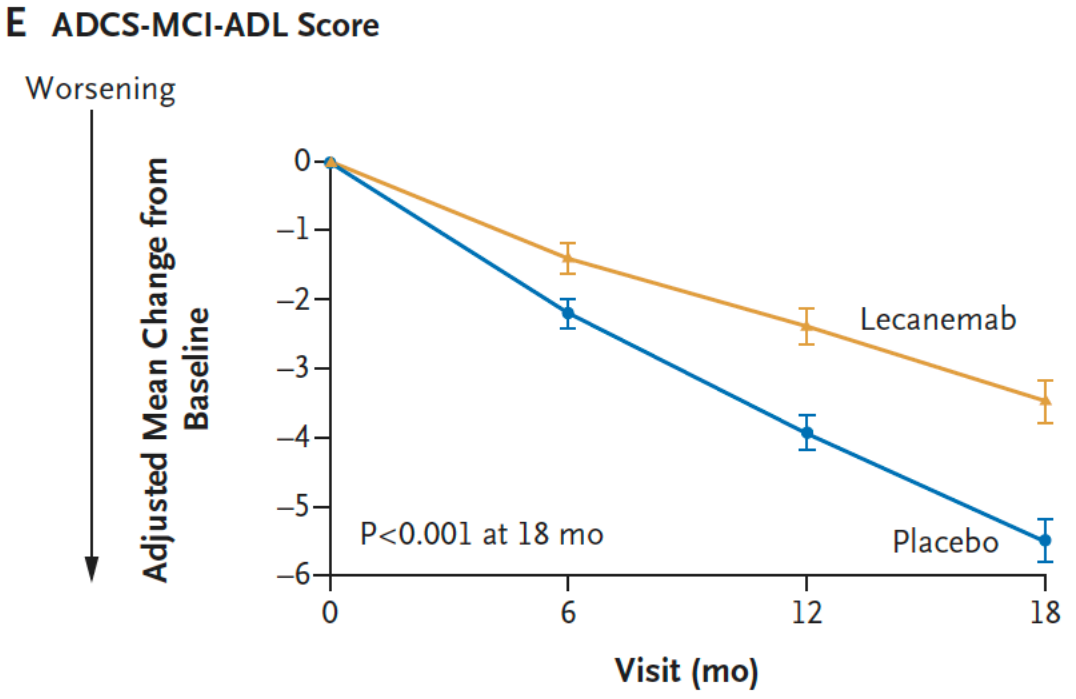
C.H. van Dyck, C.J. Swanson, P. Aisen, R.J. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L.D. Kramer, and T. Iwatsubo

1,795 PARTICIPANTS



No. of Participants

Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

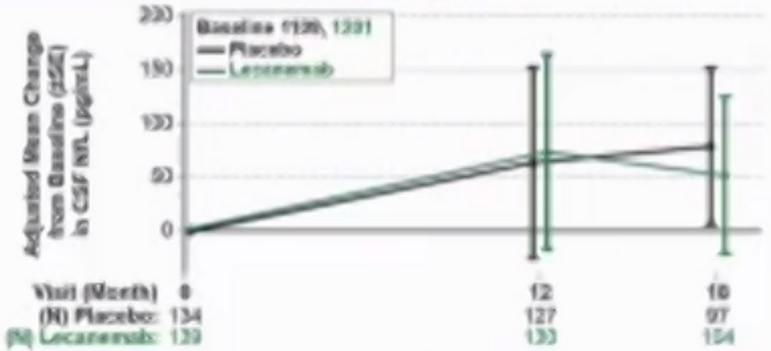


No. of Participants

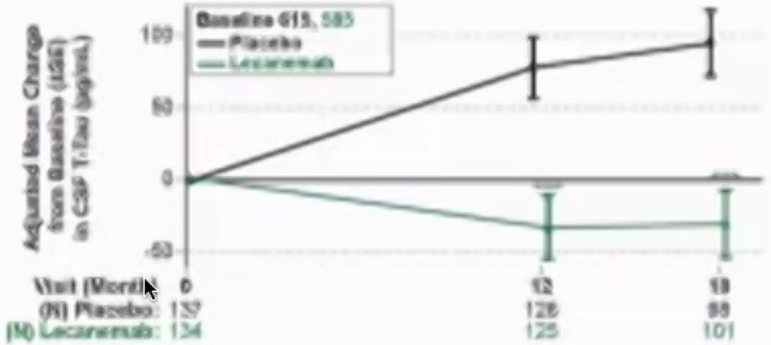
Lecanemab	783	756	716	676
Placebo	796	783	739	707

Neurodegeneration Biomarkers

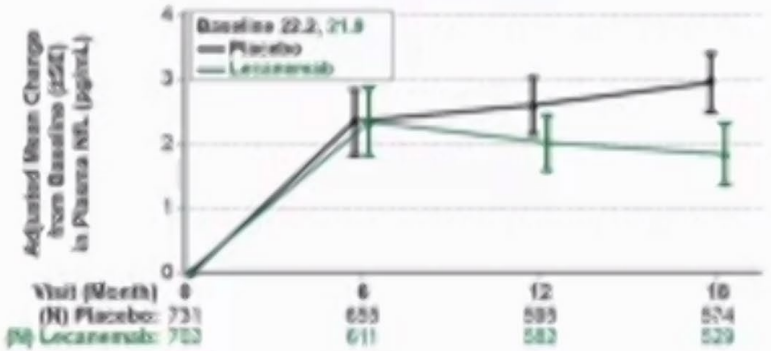
CSF NfL



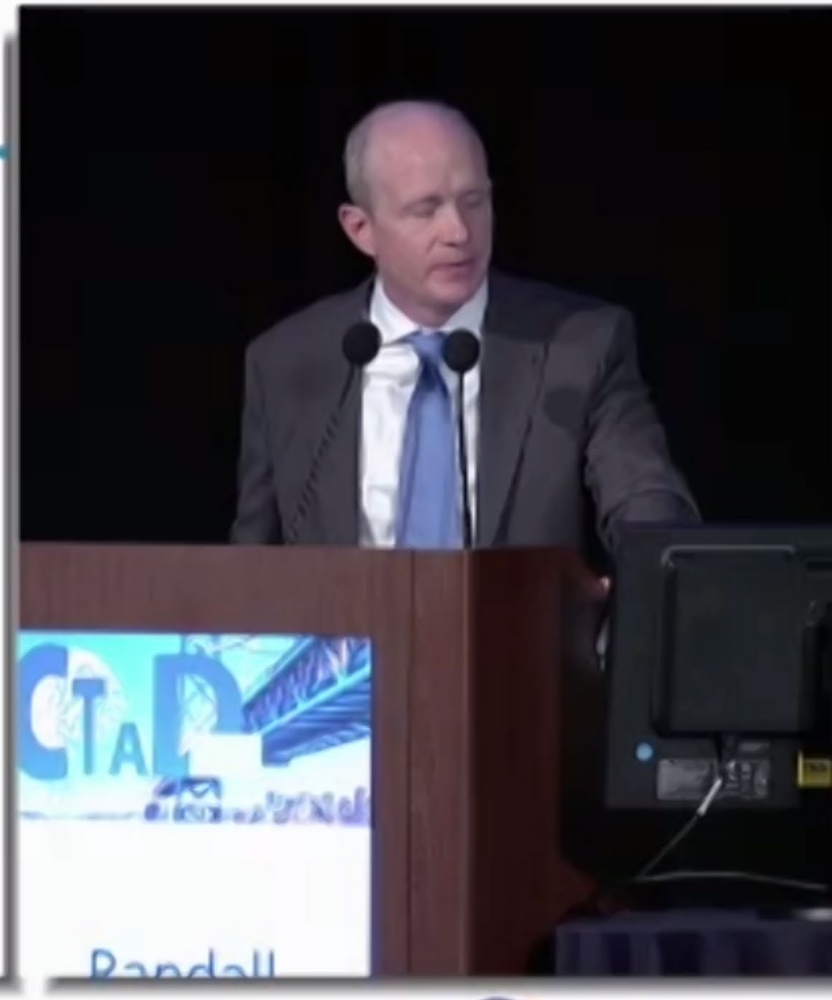
CSF T-Tau



Plasma NfL



- No difference in CSF NfL which had large variability
- Plasma NfL, with larger sample size, trends towards difference (P=0.06) at 18 months
- CSF-total tau increase in placebo and decreased in lecanemab treated group

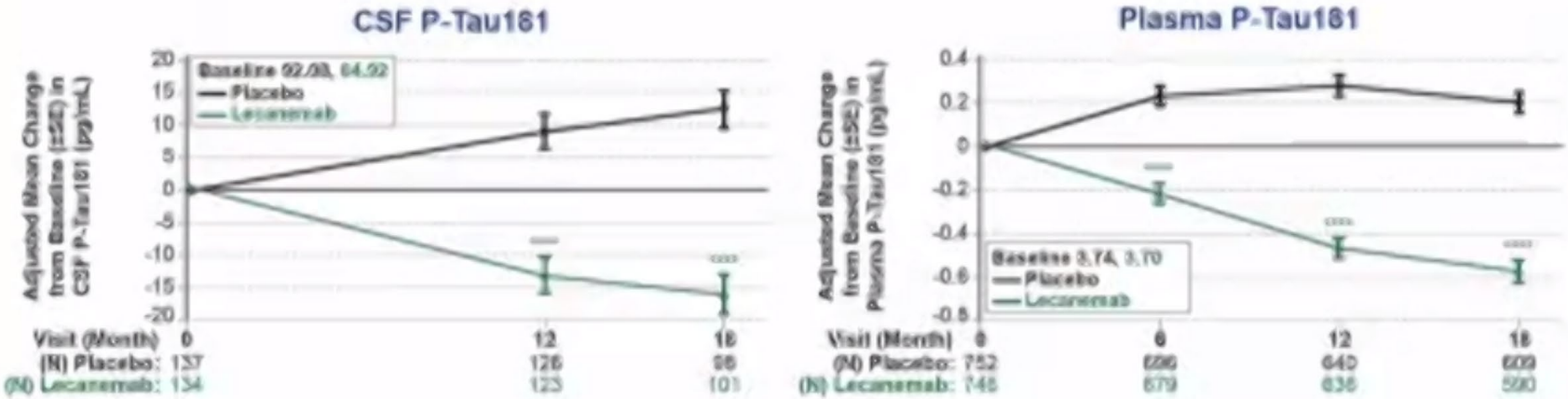


CTAD 2022

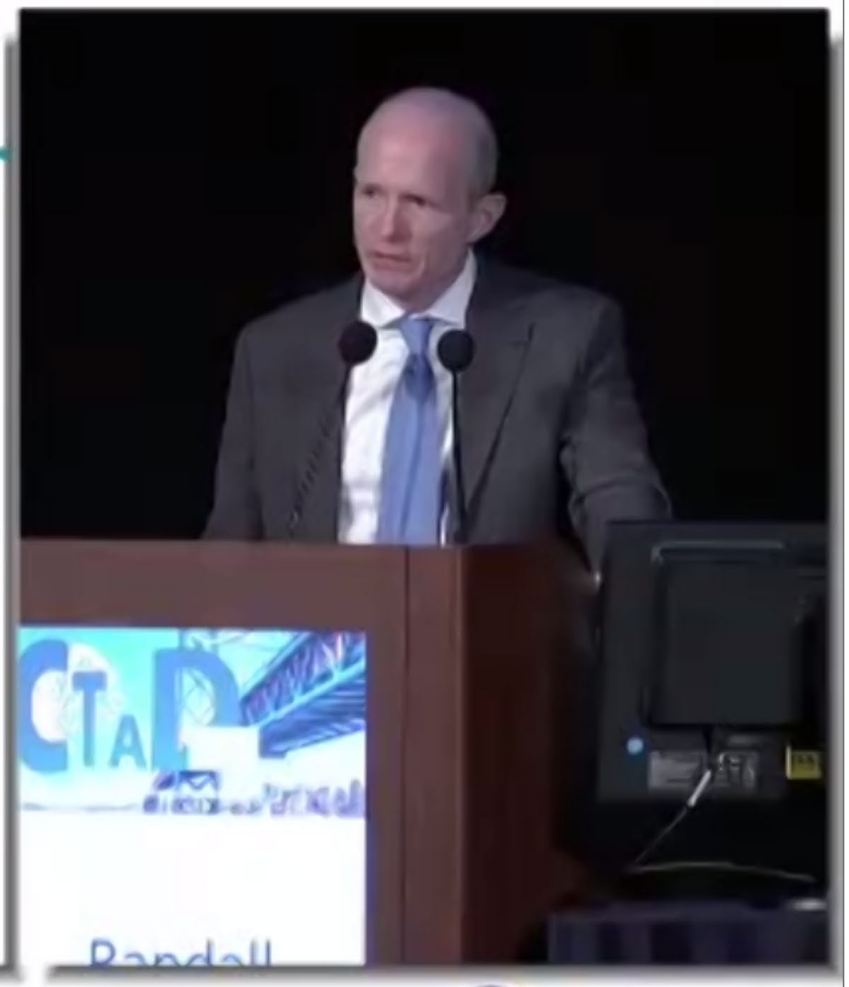
Recording

Tau Biomarkers

- CSF and plasma p-tau181 continued to increase in placebo group
- CSF and plasma p-tau181 decreased in lecanemab group towards normal at all times measured
- Indicates removing amyloid improves downstream tau phosphorylation at amyloid responsive 181 site



54 CSF, cerebrospinal fluid; p-tau, phosphorylated tau; SE, standard error.



CTAD 2022

Recording

Tau PET

*Lecanemab Slows Tau Pathology in Temporal Lobe (Early Braak Regions)**

	No. of Participants (placebo, lecanemab)	Adjusted Mean Difference	P Value
	Favors lecanemab		
Medial temporal	122, 135	-0.068	0.0024
Meta temporal	122, 135	-0.071	0.012
Temporal	132, 136	-0.065	0.016
Frontal	122, 135	-0.023	0.22
Cingulate	132, 135	-0.034	0.13
Parietal	122, 135	-0.029	0.25
Occipital	132, 135	-0.003	0.91
Whole cortical gray matter	122, 443	-0.035	0.10

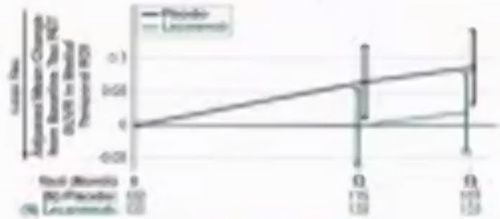
-0.12 -0.08 -0.04 0 0.04

Adjusted Mean Difference versus Placebo (95% CI)

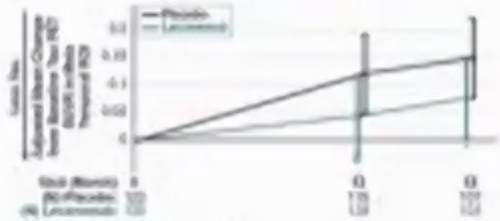
*Other regions favored lecanemab but were p > 0.05

CI, confidence interval; PET, positron emission tomography; SD, standard deviation

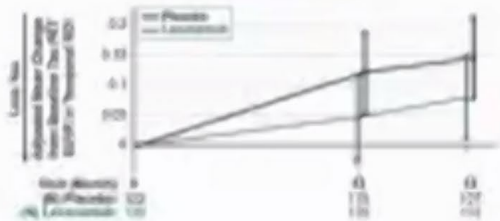
Medial Temporal

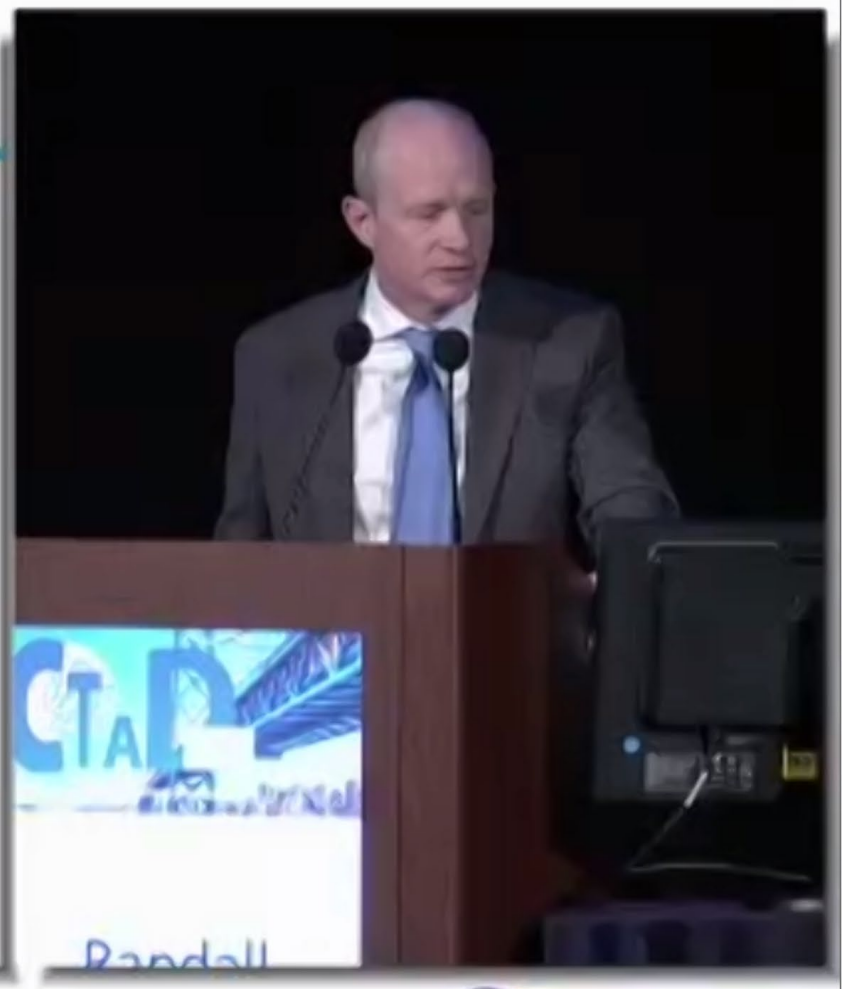


Meta Temporal



Temporal





CTAD 2022

CTAD-GS

Table 3. Adverse Events.*

Event	Lecanemab (N=898)	Placebo (N=897)
Overall — no. (%)		
Any adverse event	798 (88.9)	735 (81.9)
Adverse event related to lecanemab or placebo†	401 (44.7)	197 (22.0)
Serious adverse event	126 (14.0)	101 (11.3)
Death	6 (0.7)	7 (0.8)
Adverse event leading to discontinuation of the trial agent	62 (6.9)	26 (2.9)
Adverse event that occurred in ≥5% of participants in either group		
Infusion-related reaction	237 (26.4)	66 (7.4)
ARIA with microhemorrhages or hemosiderin deposits	126 (14.0)	69 (7.7)
ARIA-E	113 (12.6)	15 (1.7)
Headache	100 (11.1)	73 (8.1)
Fall	93 (10.4)	86 (9.6)
Urinary tract infection	78 (8.7)	82 (9.1)
Covid-19	64 (7.1)	60 (6.7)
Back pain	60 (6.7)	52 (5.8)
ARIA‡		
ARIA-E — no. (%)		113 (12.6)
Symptomatic ARIA-E — no. (%)§		25 (2.8)
ApoE ε4 noncarrier — no./total no. (%)		4/278 (1.4)
ApoE ε4 carrier — no./total no. (%)		21/620 (3.4)
ApoE ε4 heterozygote		8/479 (1.7)
ApoE ε4 homozygote		13/141 (9.2)
ARIA-E according to ApoE ε4 genotype — no./total no. (%)		
ApoE ε4 noncarrier		15/278 (5.4)
ApoE ε4 carrier		98/620 (15.8)
ApoE ε4 heterozygote		52/479 (10.9)
ApoE ε4 homozygote		46/141 (32.6)
ARIA-H — no. (%)		155 (17.3)
Microhemorrhage		126 (14.0)
Superficial siderosis		50 (5.6)
Macrohemorrhage		5 (0.6)
Symptomatic ARIA-H§		6 (0.7)
Isolated ARIA-H: no concurrent ARIA-E		80 (8.9)

SCIENCEINSIDER | HEALTH

Scientists tie third clinical trial death to experimental Alzheimer's drug

Amid lobbying for lecanemab's approval, a newly revealed death adds to doubts about safety of antiamyloid antibody

21 DEC 2022 · 5:40 PM · BY CHARLES PILLER

?

Recommend discussing with MCI/mild AD patients & their families when lecanemab is available

Treatment: currently available for AD (& LATE)

- Why will they likely work for LATE? Because participants with LATE were included in *all* the AD clinical trials!
  - Maybe they won't work for LATE—or maybe they will work better! New studies are needed.
- D/c or change anticholinergic agents, sedatives, etc.
- Other drugs/supplements to discontinue:
  - Prevagen (aka, snake oil)
  - Coconut Oil (no efficacy)
- Drugs that are not a problem:
  - Proton Pump Inhibitors (PPIs)
  - Statins

Treatment: currently available for AD (& LATE)

- To enhance cognition:
  - Cholinesterase Inhibitors:
    - donepezil (Aricept, *available oral dissolving tablet, now generic*)
    - rivastigmine (Exelon*, available QD patch)*
    - galantamine (formerly Razadyne, *now generic*)
    - huperzine A (Cerebra). Nutritional product.
  - Memantine:
    - Namenda

Current treatments for AD: Big picture

- Do we need better medications?
  - Yes
- Are the current medications just symptomatic?
  - Yes
- Do they actually work? Do they actually help patients in any meaningful way?
  - Yes
- Here is the data

Cholinesterase inhibitors

- Improved cognition, participation in activities of daily living, & global function in mild to moderate patients.
  - Neurology 1998;50:136
  - BMJ: 1999;318:633
  - Neurology 2000;54:2261
- Improves cognition & behavior in mild to moderate and moderate to severe disease
  - Neurology 2000;54:2269
  - Neurology 2001;57:613
- Reduces emergent behavioral disturbances in mild to moderate patients.
  - Am J Psychiatry 2004;161:532

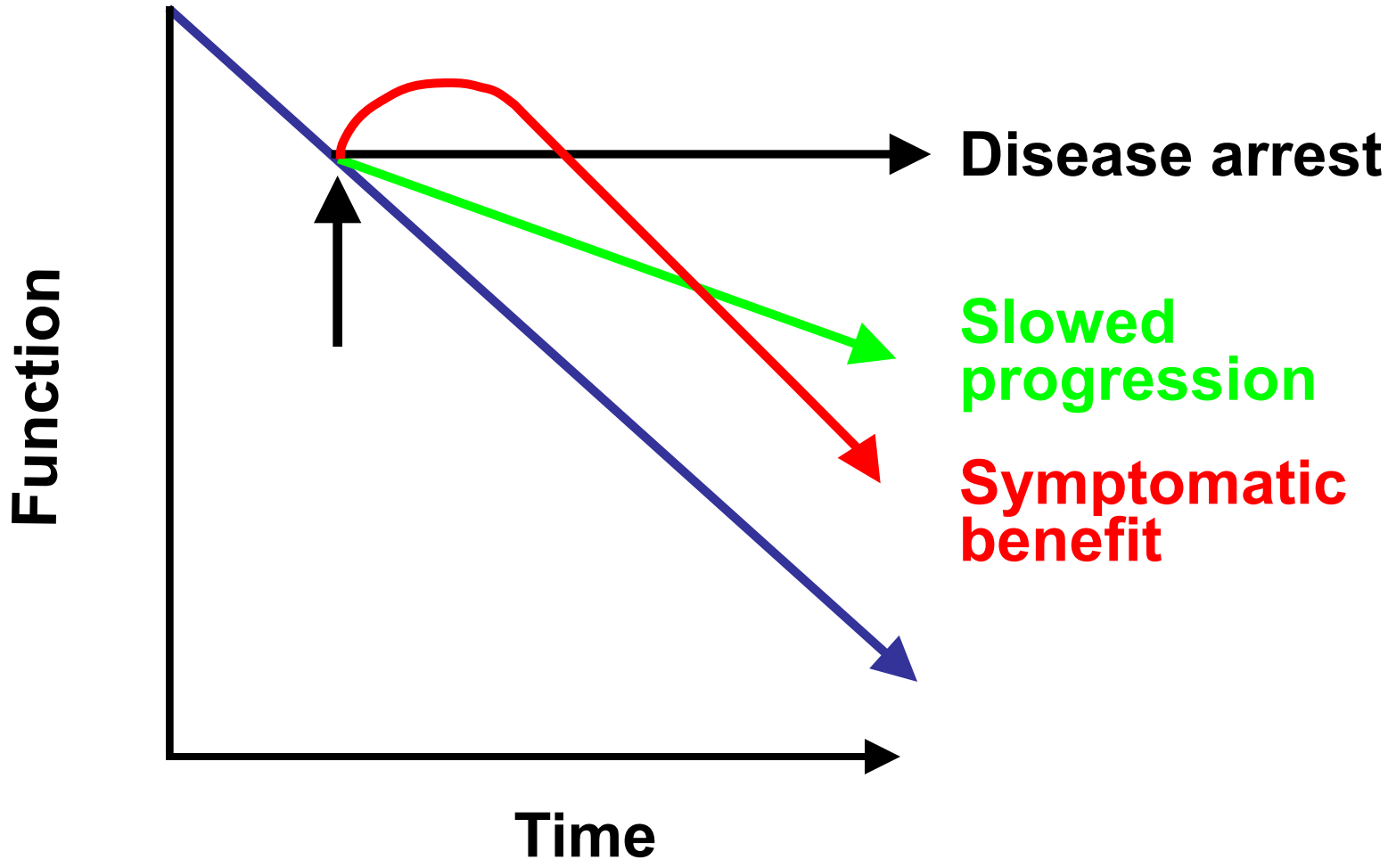
Treatment expectations

- Small but noticeable improvements:
  - Less time spent looking for keys, glasses, etc.
  - Repeats self less often
  - Dwells in past less
  - Easier time keeping track of conversation
  - More engaged, outgoing

Cholinesterase inhibitor side-effects

- Gastrointestinal effects
  - anorexia
  - nausea/vomiting
  - diarrhea
- Vivid dreams
  - take in AM or earlier PM dose
- Other cholinergic symptoms
  - Increased salivation
  - Increased rhinorrhea
  - Muscle cramps
  - rarely slows heart rate

Treatment Outcomes



From Budson & Solomon, 2022

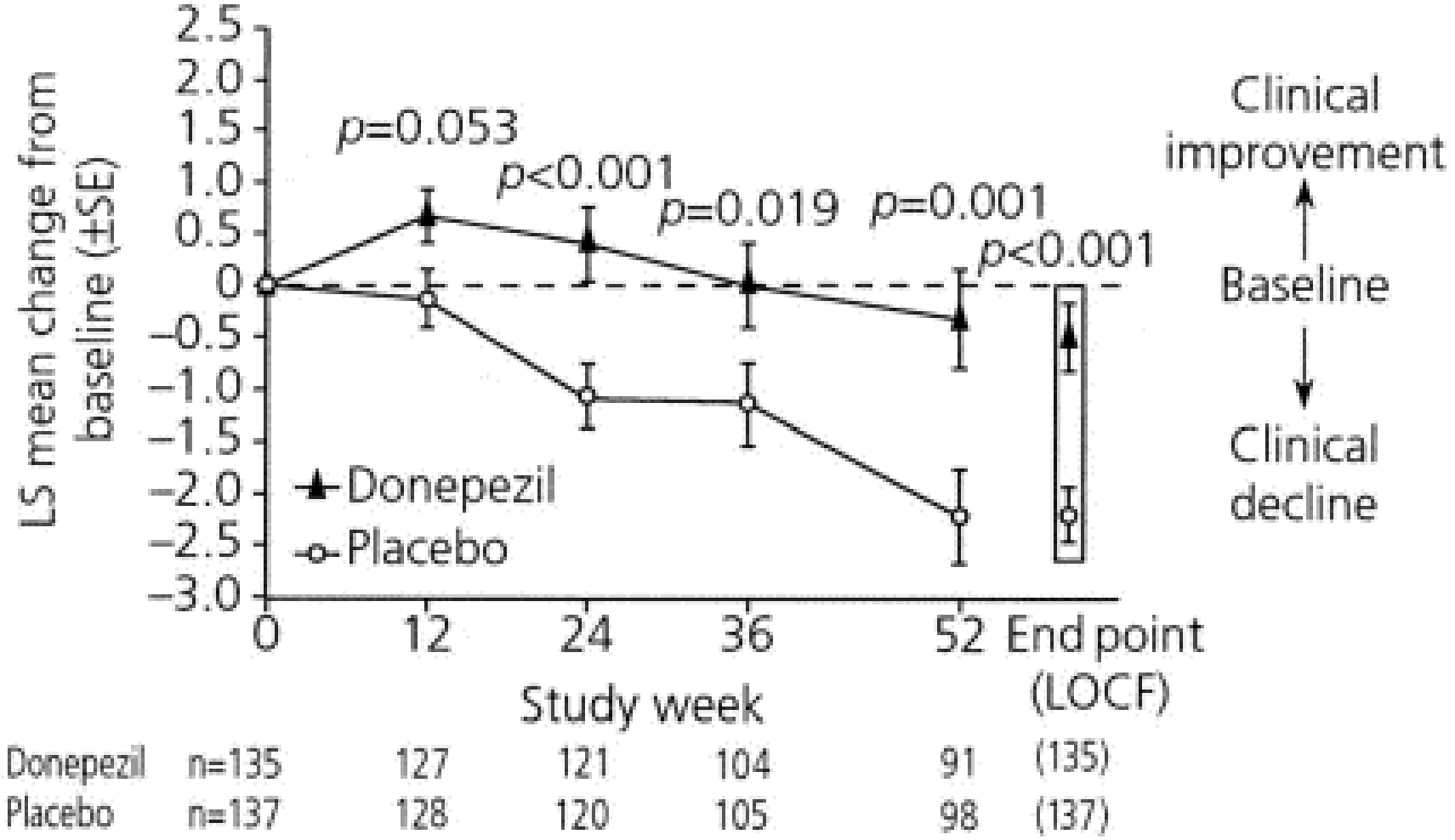
Turning back the clock

- About 25-30% show an improvement equivalent to a 1-year reversal of symptoms
- About 50-60% show an improvement equivalent to a 6-month reversal
- About 10-15% show either an improvement equivalent to less than a 6-month reversal or no improvement

NEJM 2004 351:56-67

- My recommendation: Give a trial, measure response
  - ask patient, ask caregiver, test patient

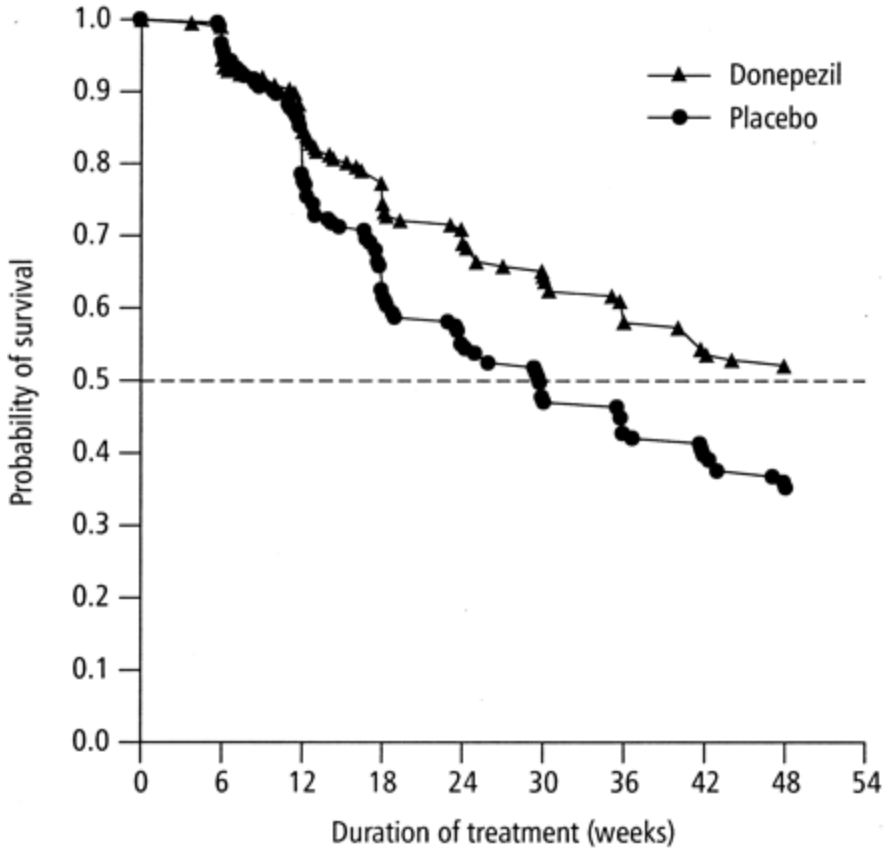
Change in MMSE in mild to moderate Alzheimer's disease



Neurology 2001 57:489-95

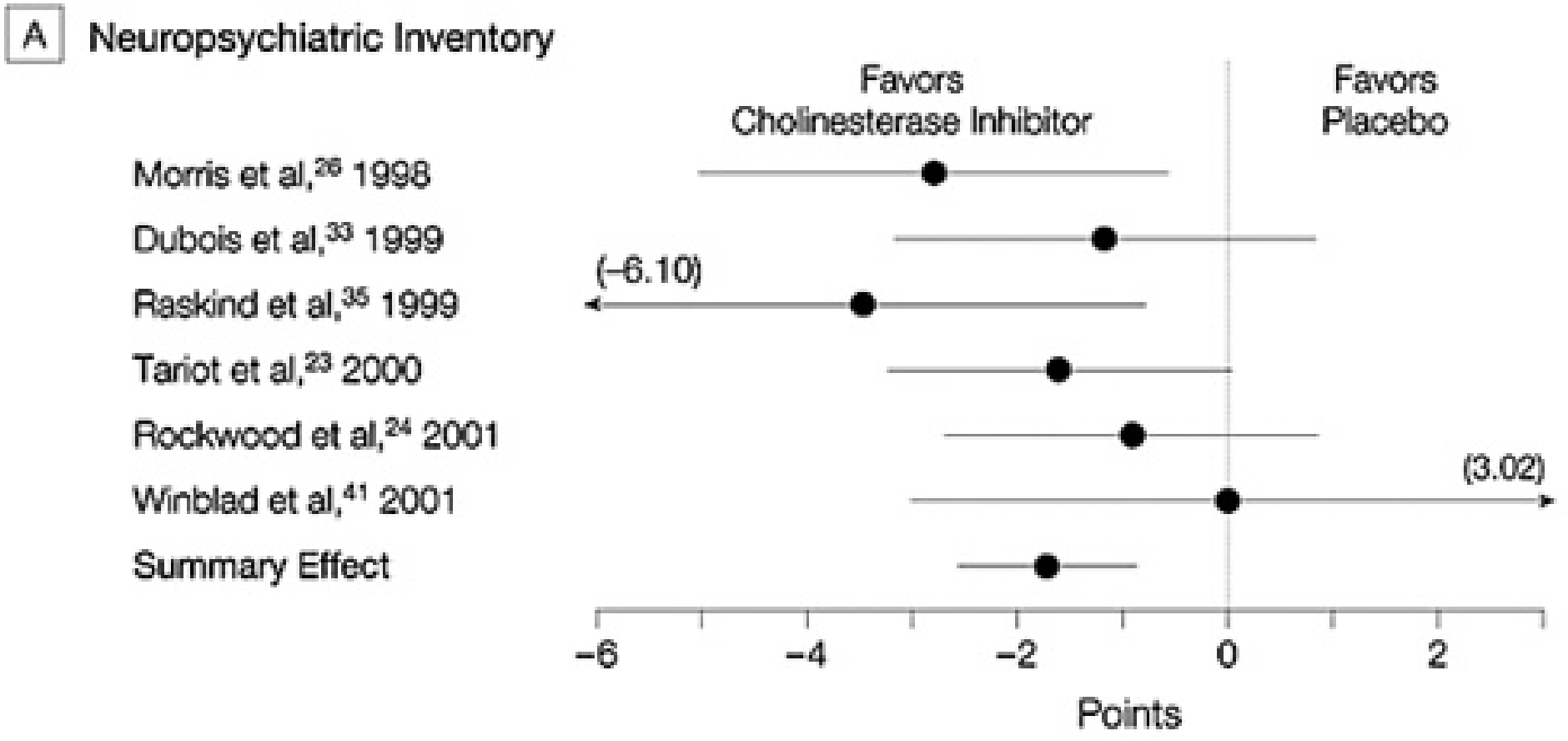
Time to clinically evident functional decline

- 431 patients
- mild to moderate AD
- double-blind placebo-controlled trial



Neurology 2001 57:481-8

Meta analysis: neuropsychiatric symptoms in AD

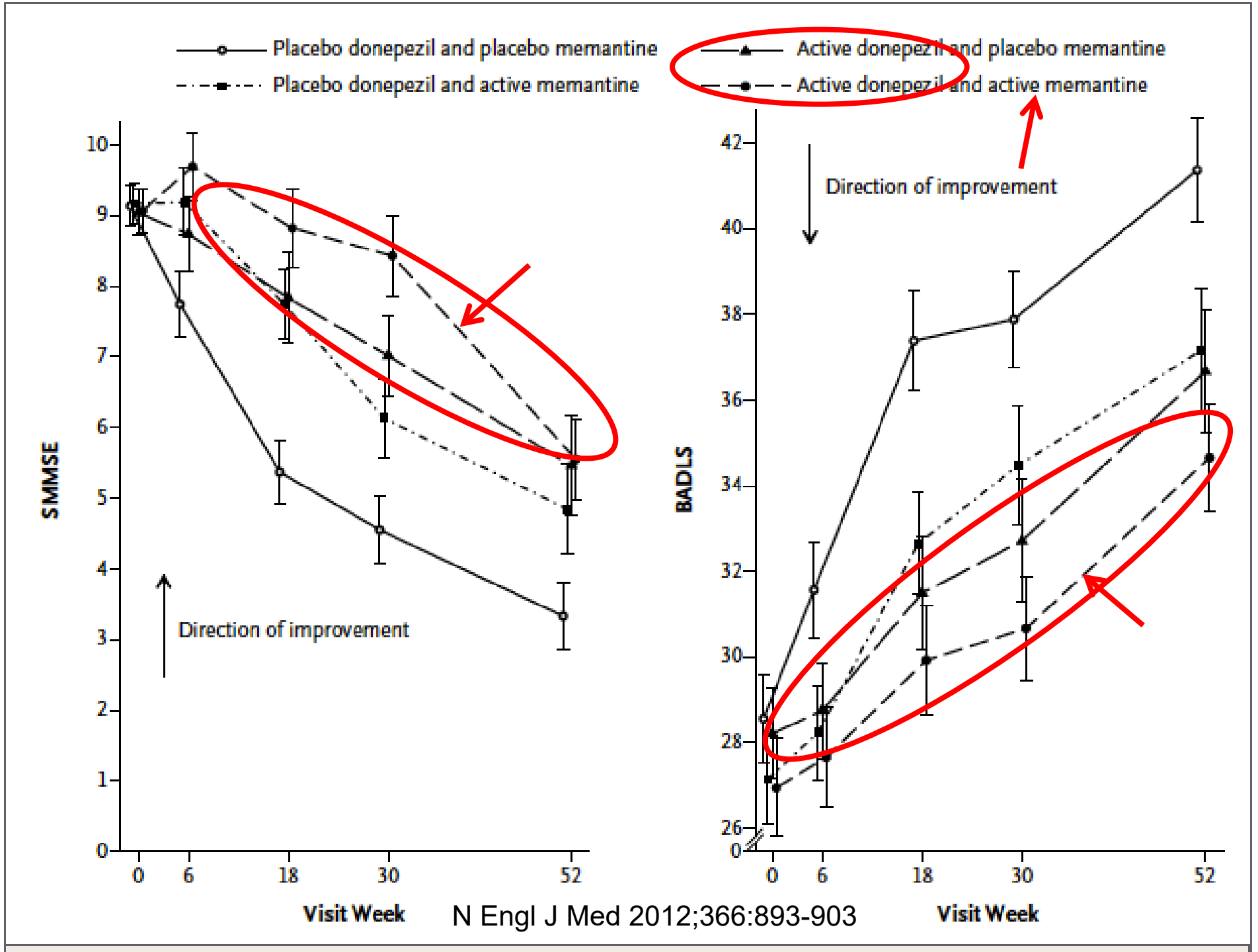


JAMA 2003 289: 210-16

Cholinesterase inhibitors: How long to use them?

- A double-blind placebo-controlled study found continued efficacy for 4 years.
- Retrospective & prospective studies suggest beneficial effects last for at least 5 years.
  - CNS Drugs 2004 18:757-68.

- Should we stop treatment in moderate or severe disease?



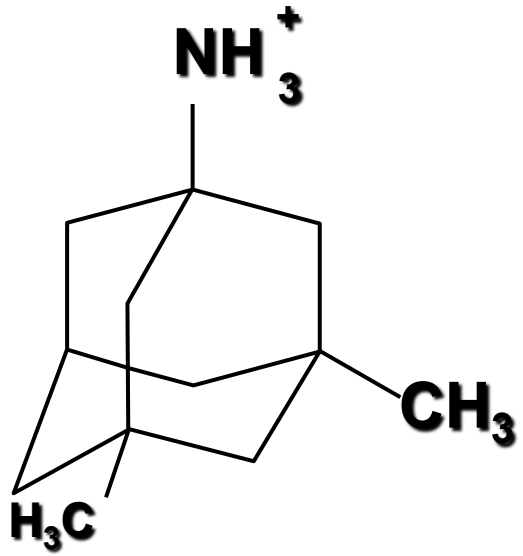
N Engl J Med 2012;366:893-903

- “In patients with moderate or severe Alzheimer’s disease, continued treatment with donepezil was associated with cognitive benefits that exceeded the minimum clinically important difference and with significant functional benefits over the course of 12 months.” (NEJM 2012; 366: 893-903)

- My recommendation: continue cholinesterase inhibitors as long as there is quality of life to preserve

Memantine (Namenda)

- Approved for use in patients with moderate to severe Alzheimer's disease, with or without cholinesterase inhibitors
- Uncompetitive NMDA-receptor antagonist
- Enhances dopamine activity
- Does not alter AChE activity in the presence or absence of AChEIs



Amantadine Derivative
1-amino-3,5-dimethyladamantane

Memantine in patients with moderate to severe AD

- Improvement or less decline in cognition, activities of daily living, and global change, as well as reduced care dependence
  - N Engl J Med 2003;348:1333
  - Int J Geriatr Psychiatry 1999;14:135
- Cognitive, functional, global, and behavioral outcome measures are better with memantine + donepezil versus donepezil alone
  - JAMA 2004;291:317

Treatment expectations

- Small but noticeable improvements:
  - More alert
  - More talkative
  - More engaged
  - More outgoing
  - Brighter overall
  - Less agitated

  - *Note: Memory not improved*

Memantine Side-effects

- None statistically more than placebo
- Agitation less than in placebo group
- “Dizziness”
- Drowsiness and confusion, dose related, sometimes transient, worse in milder patients
- FDA: moderate to severe AD (MMSE <16)
- Try in patients with AD or vascular dementia at the moderate to severe stage
- Try Patients with Lewy Body Dementia
- Try in patients with Frontotemporal Dementia

- **BUT discontinue if there is not clear improvement!!**

Patient 2

- 72M with mild memory complaints. CEO of a large company.
- Trouble remembering his schedule—secretary has to remind him.
- Trouble remembering the content of meetings; needs to take more notes.
- Gradual worsening over the last 2 years.
- Never forgot anything critically important
- No trouble with words or other things.
- Isolated problems with memory on testing

Mild cognitive impairment

NIA-AA Criteria: MCI due to AD

- Establish clinical & cognitive criteria
  - Concern of change in cognition by patient, informant, or clinician
  - Testing shows impairment in one or more cognitive domains, typically including memory
  - Preservation of independence in functional abilities
  - Not demented
- Examine etiology: MCI due to AD
  - R/o vascular, traumatic, medical causes
  - Provide evidence of longitudinal decline in cognition
  - Report history consistent with AD genetic factors

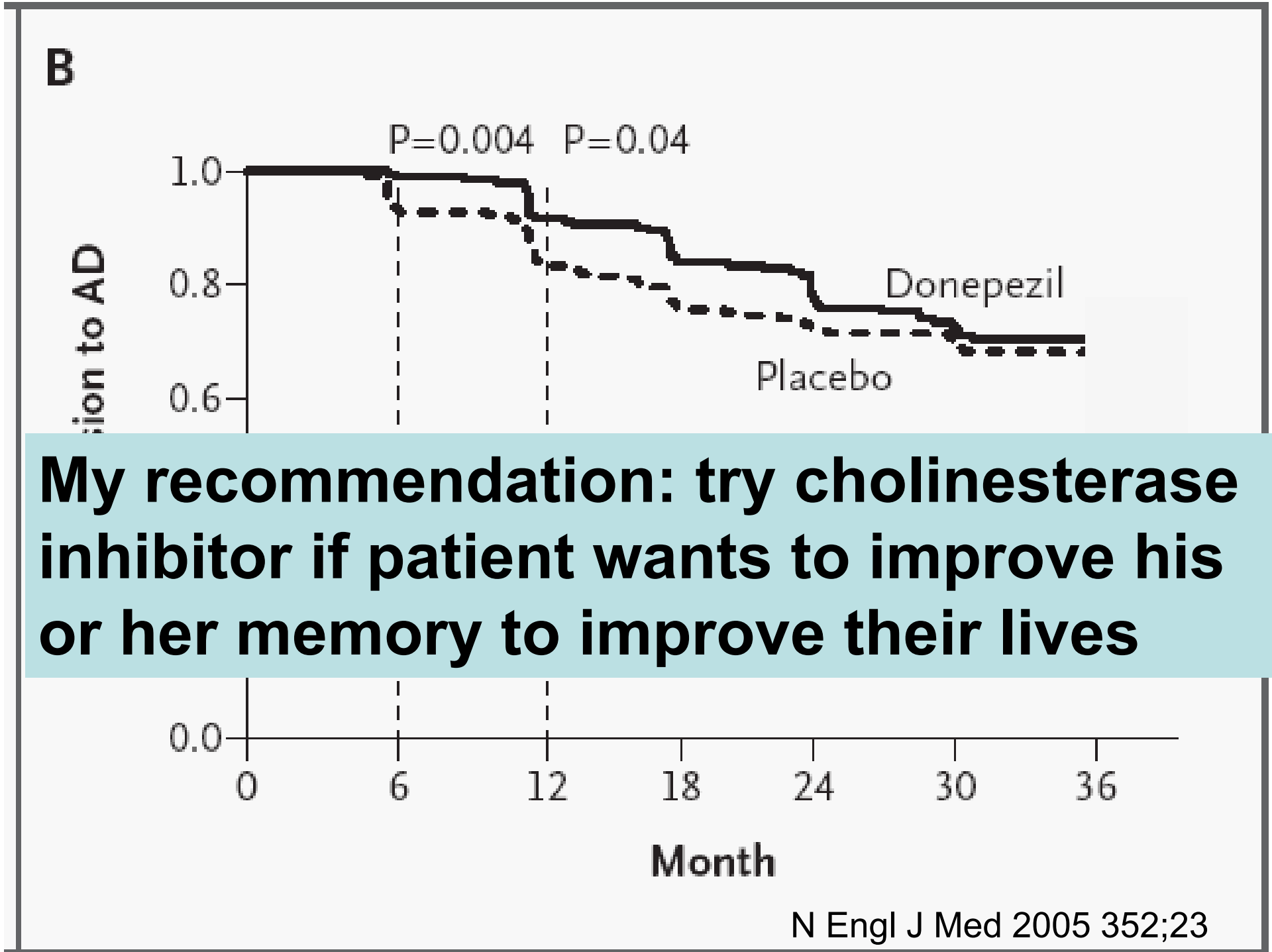
MCI: Prognosis & Treatment

- 50-70% progress to AD dementia or another dementia at a rate of 15% per year
  - 50% door-to-door community sample
  - 70% presenting to a memory center
- 30-50% stable or improve
- No FDA approved medications

- Should we use cholinesterase inhibitors?

- 769 patients with MCI studied for 3 years
- Vit E 2000 IU, donepezil 10 mg, or placebo
- Conclusion : no differences in the probability of progression to AD dementia over the three years for either treatment
- Donepezil treatment associated with a lower rate of progression to AD over one year
- Vit E showed no effect

N Engl J Med 2005 352;23



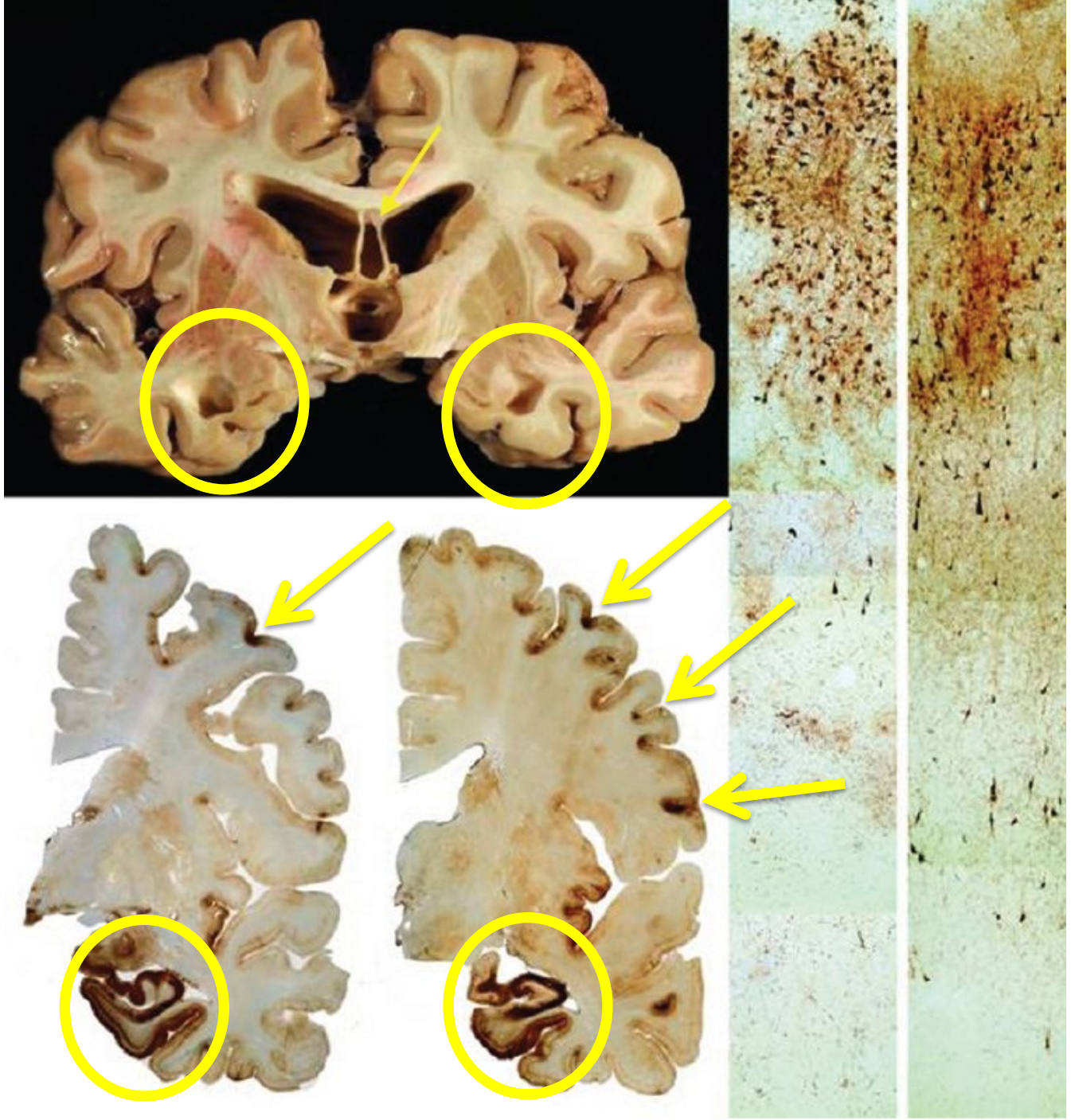
My recommendation: try cholinesterase inhibitor if patient wants to improve his or her memory to improve their lives

N Engl J Med 2005 352;23

Patient 3

- 59 F w/ forgetfulness
- Long history of domestic abuse with frequent blows to the head and “occasional” concussions
- Tearfulness & emotional blunting
- Language deficits including anomia, frequent paraphasic, phonemic, & neologistic errors
- Put plastic Tupperware into the oven, was cooking with incorrect ingredients.
- Exam: masked facial expression, bilateral resting tremor, glabellar tap sign, brisk reflexes
- Over time, became more aphasic, apraxic, and frontal

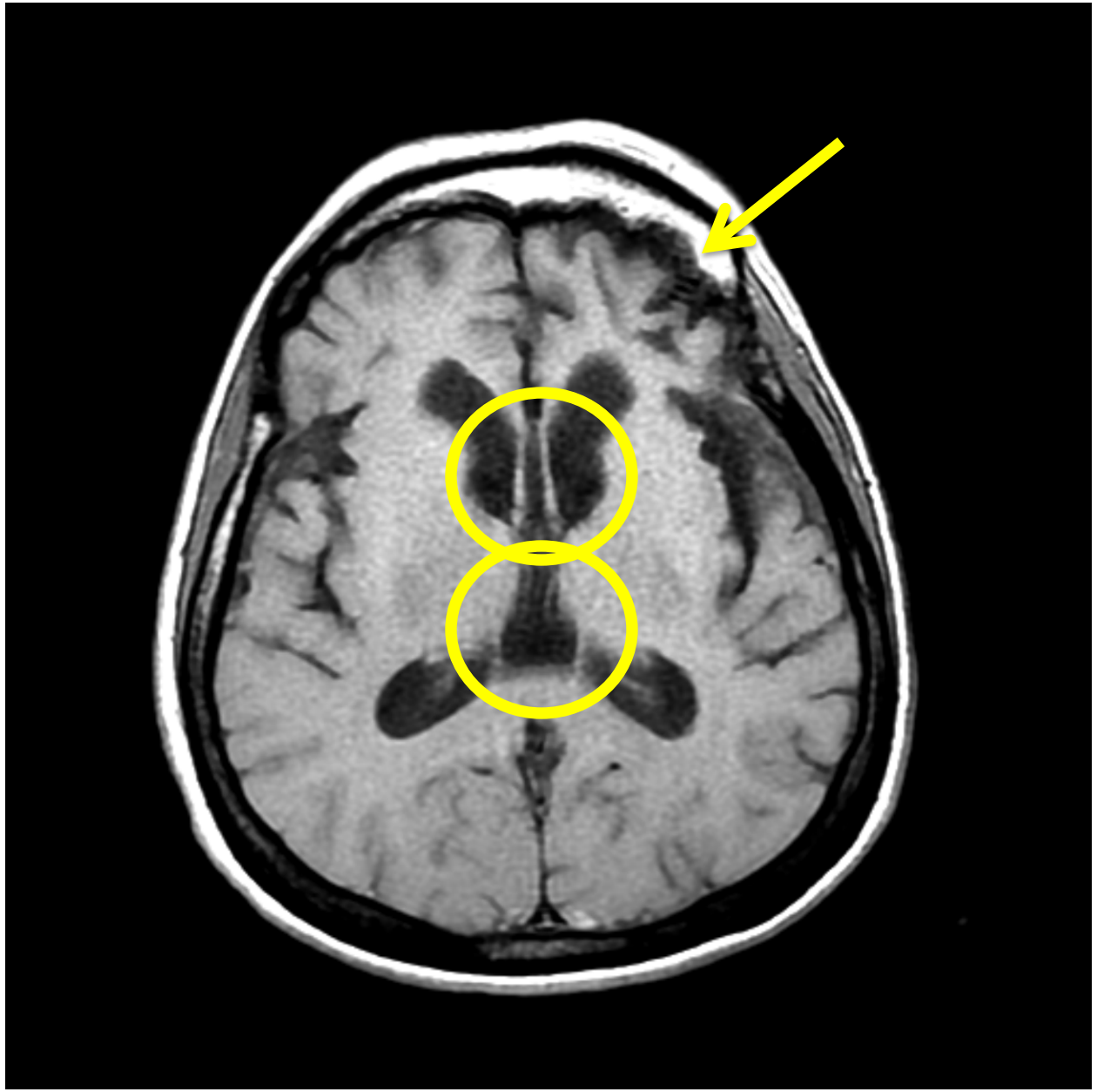
Chronic Traumatic Encephalopathy

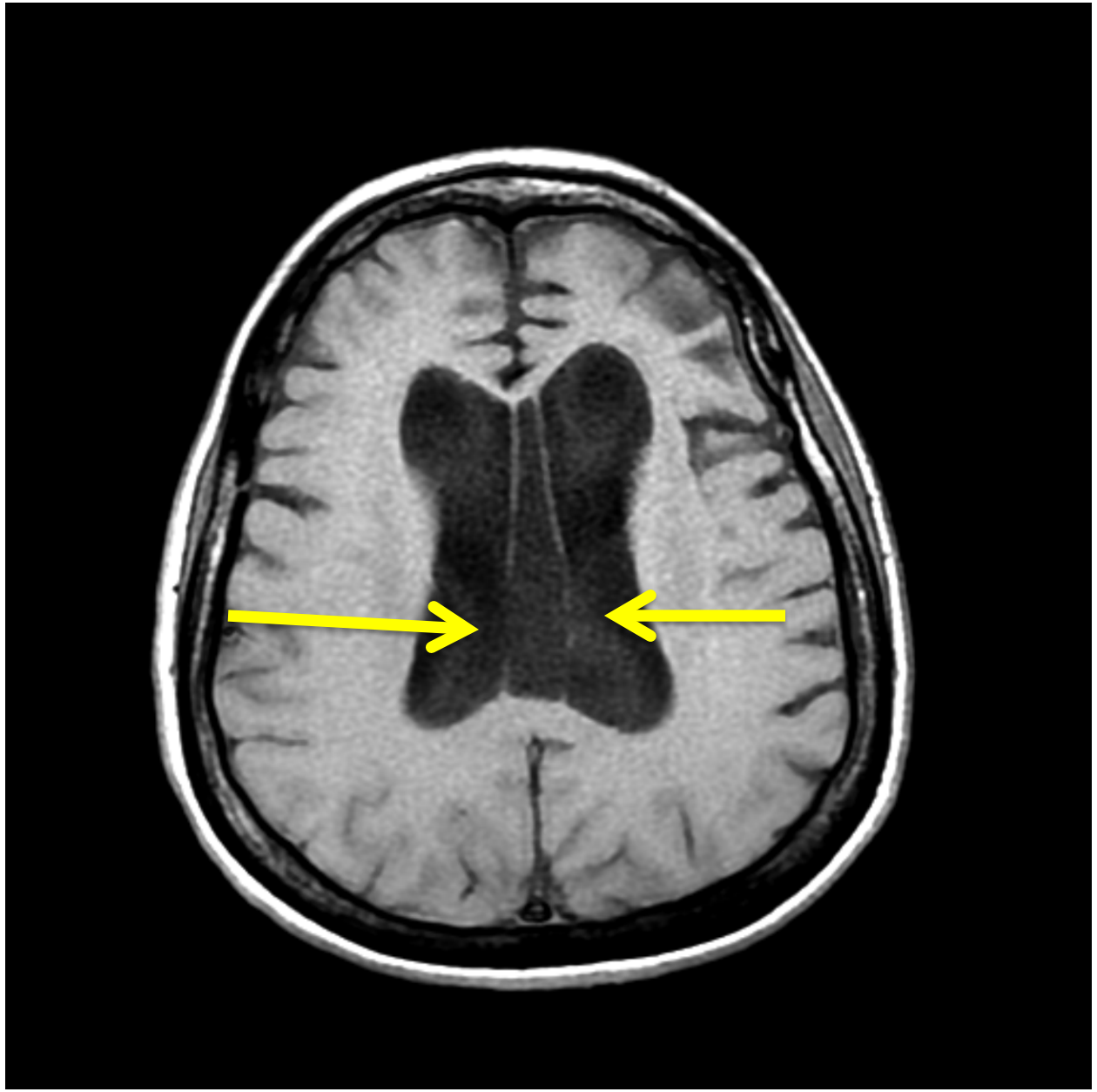


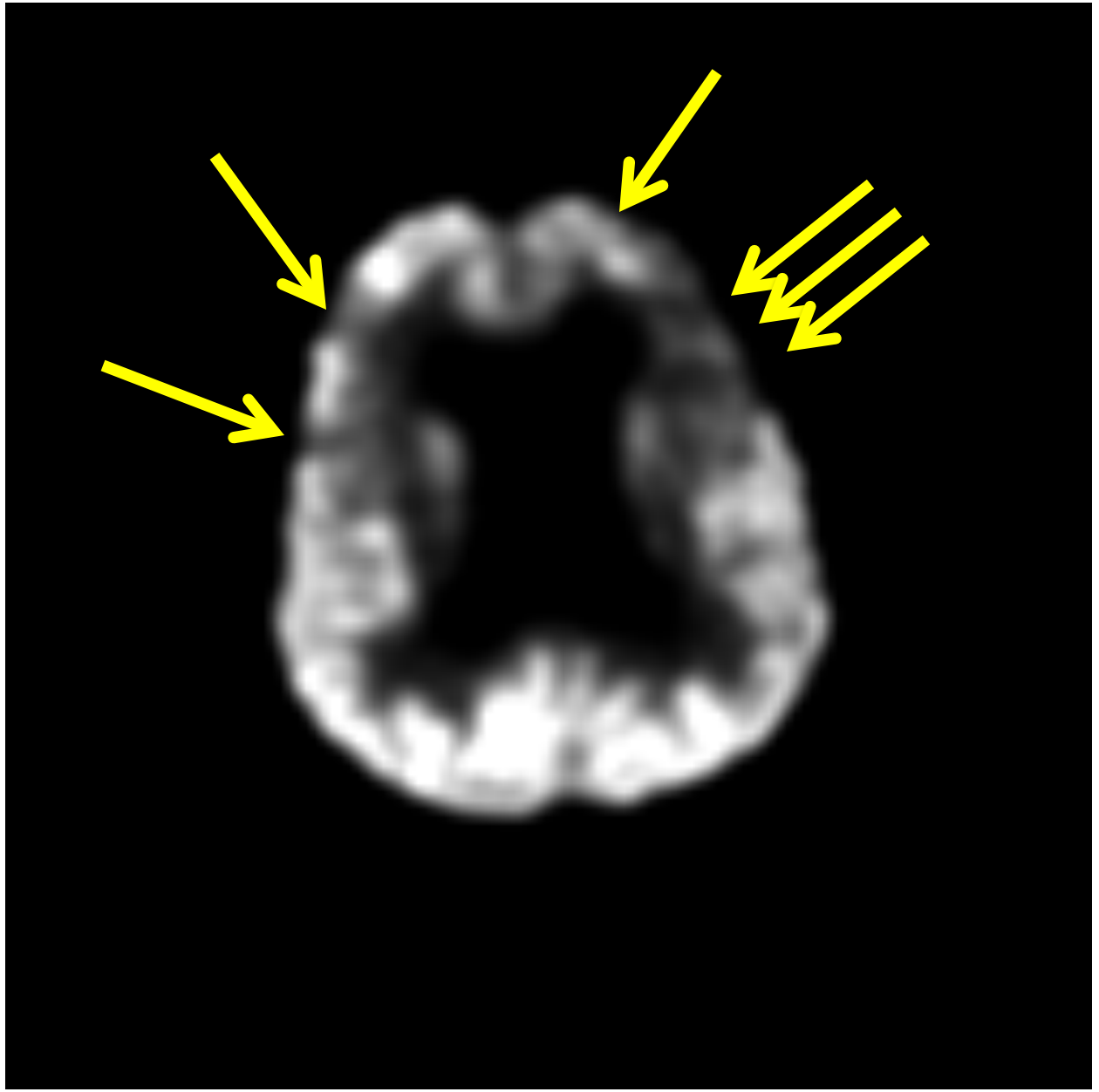
From Budson & Solomon, 2016

CTE Brief Summary

- Caused by multiple impacts to the head
- Characterized by perivascular accumulation of tau irregularly in the depths of cortical sulci
- Two main syndromes (also mixed & dementia):
  - Behavioral/Mood Variant (younger, m=35 yrs)
  - Cognitive Variant (older, m=59 yrs)
- Commonly initial features include:
  - Impairment in memory, executive function, attention, visuospatial, & language.
  - Depression, hopelessness, explosivity, out of control, violent





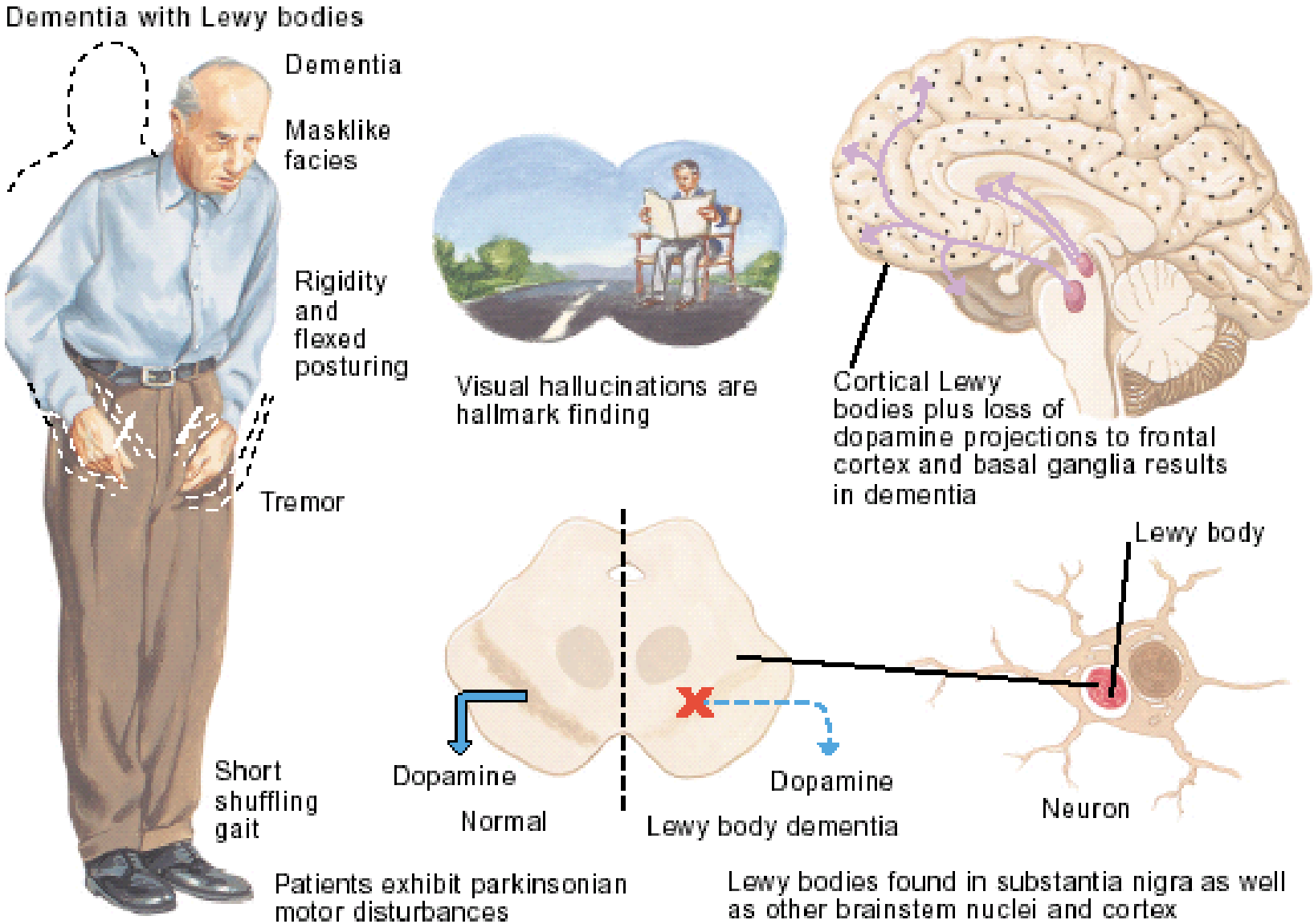


Patient 4

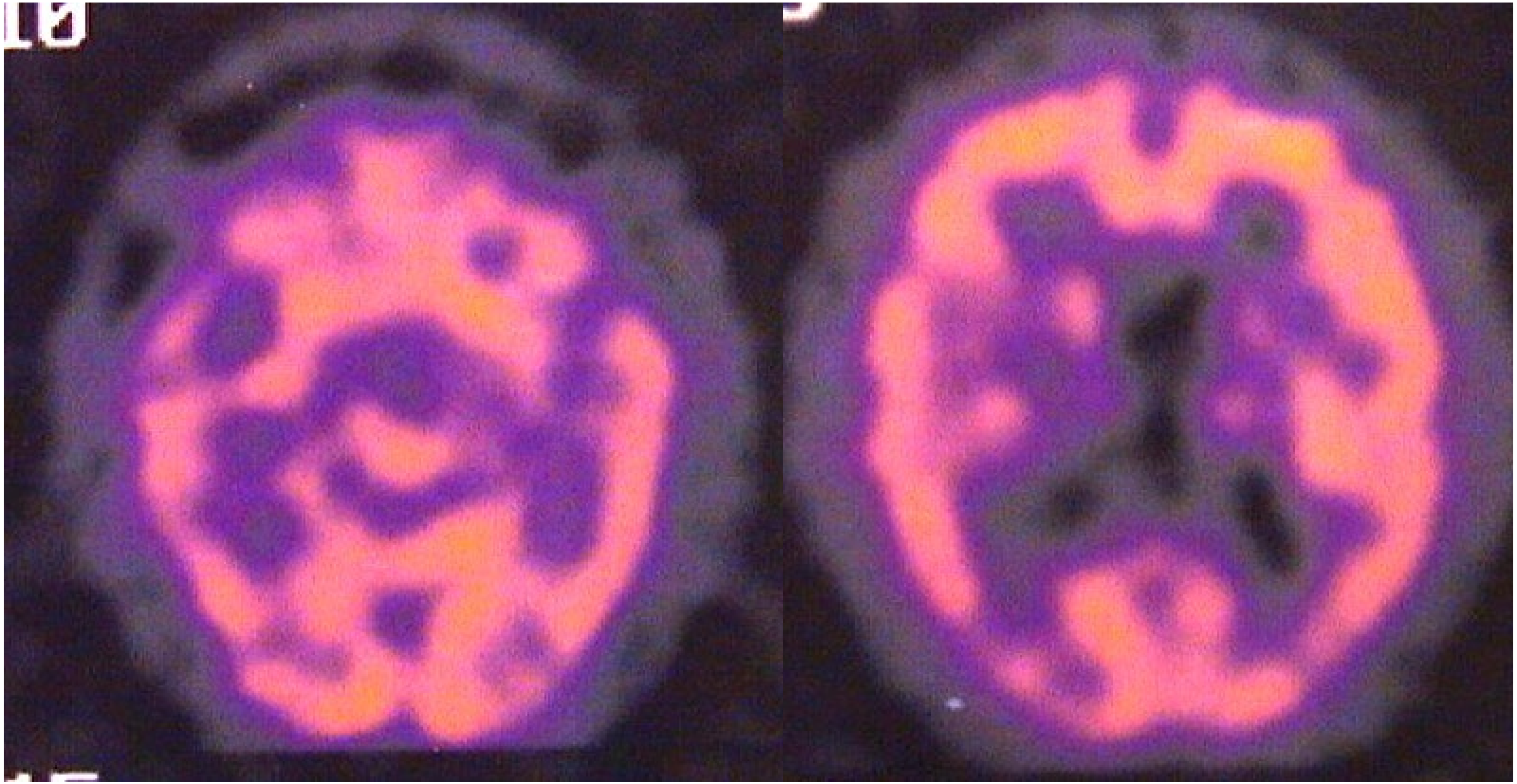
- 65M with memory problems.
- Also Parkinsonism
  - Masked faces, shuffling gait, cogwheeling
- Visual hallucinations of people and animals
- Visual perceptual defects
- Wife complains he is waking her up running, wrestling, and fighting in his sleep

Dementia with Lewy Bodies / Parkinson's Disease Dementia

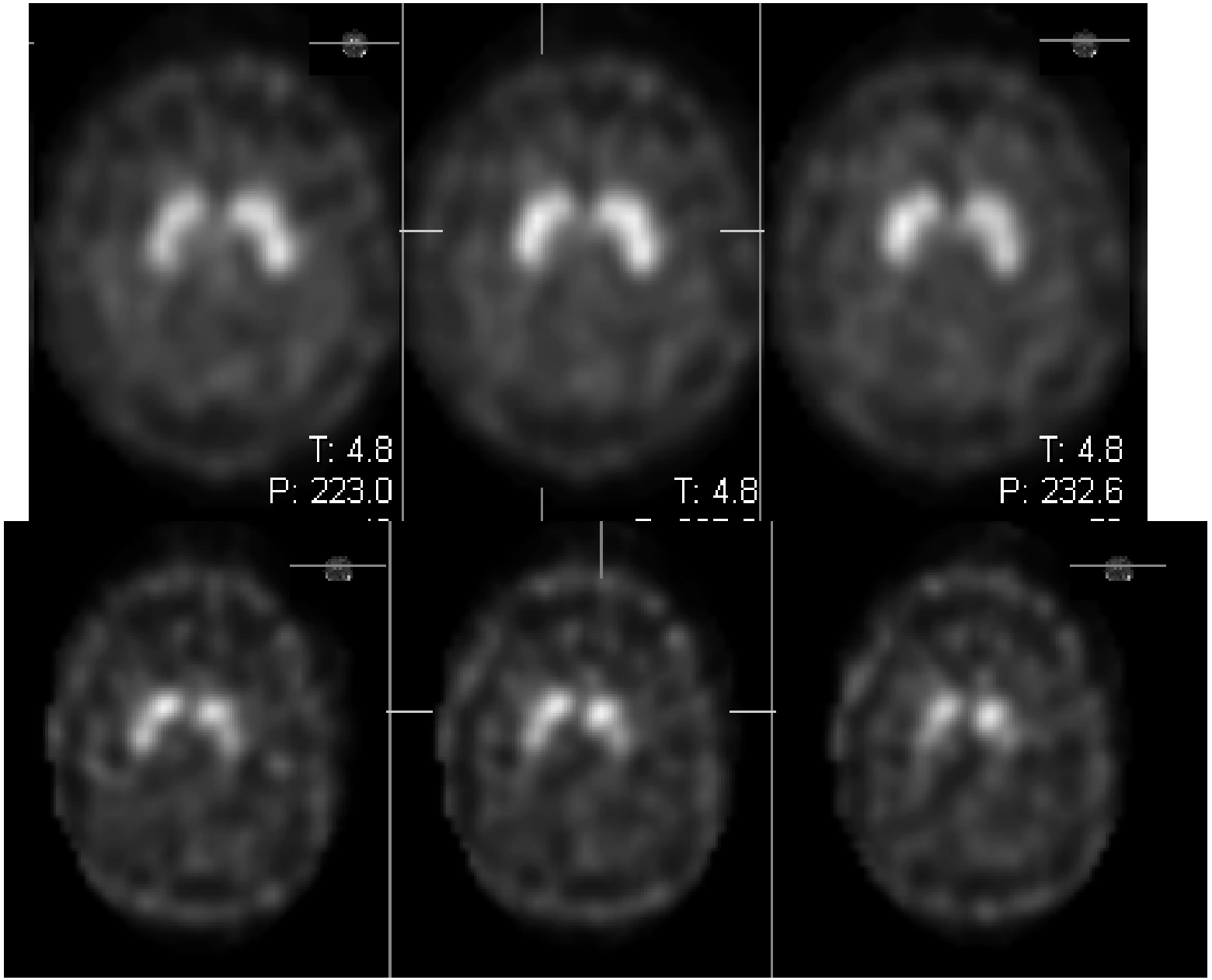
Dementia with Lewy Bodies



From Budson & Solomon, 2016



From Budson & Solomon, 2022

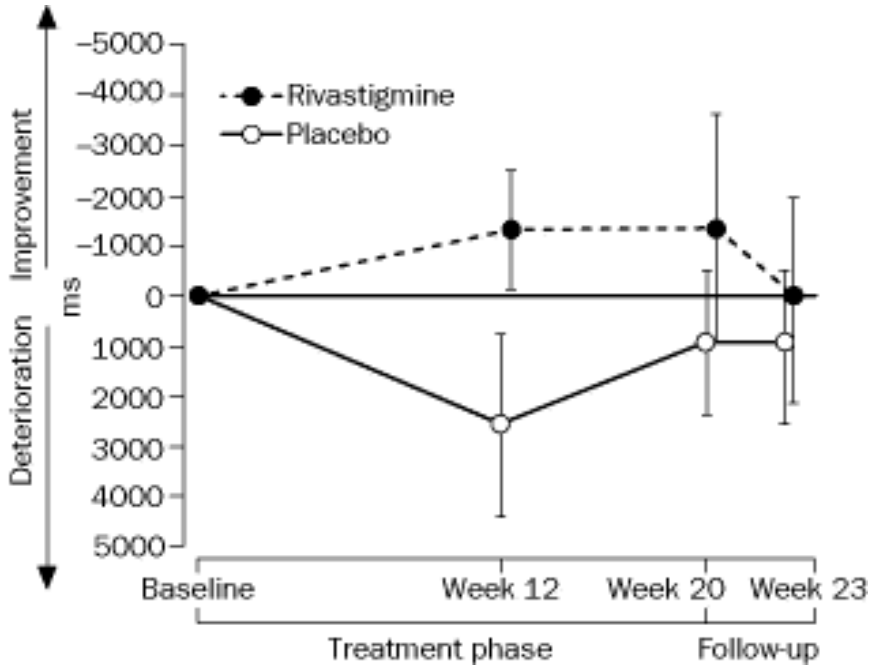


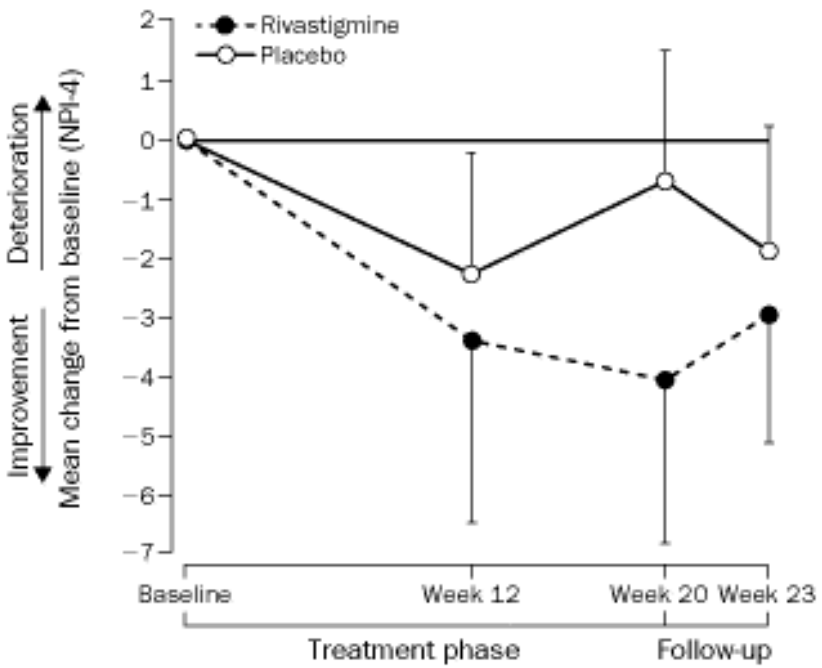
"Comma sign"
Normal Dopamine Transporter (DaT) Scan

"Period sign"
Abnormal DaT Scan

From Budson & Solomon, 2022

Rivastigmine in Dementia with Lewy Bodies





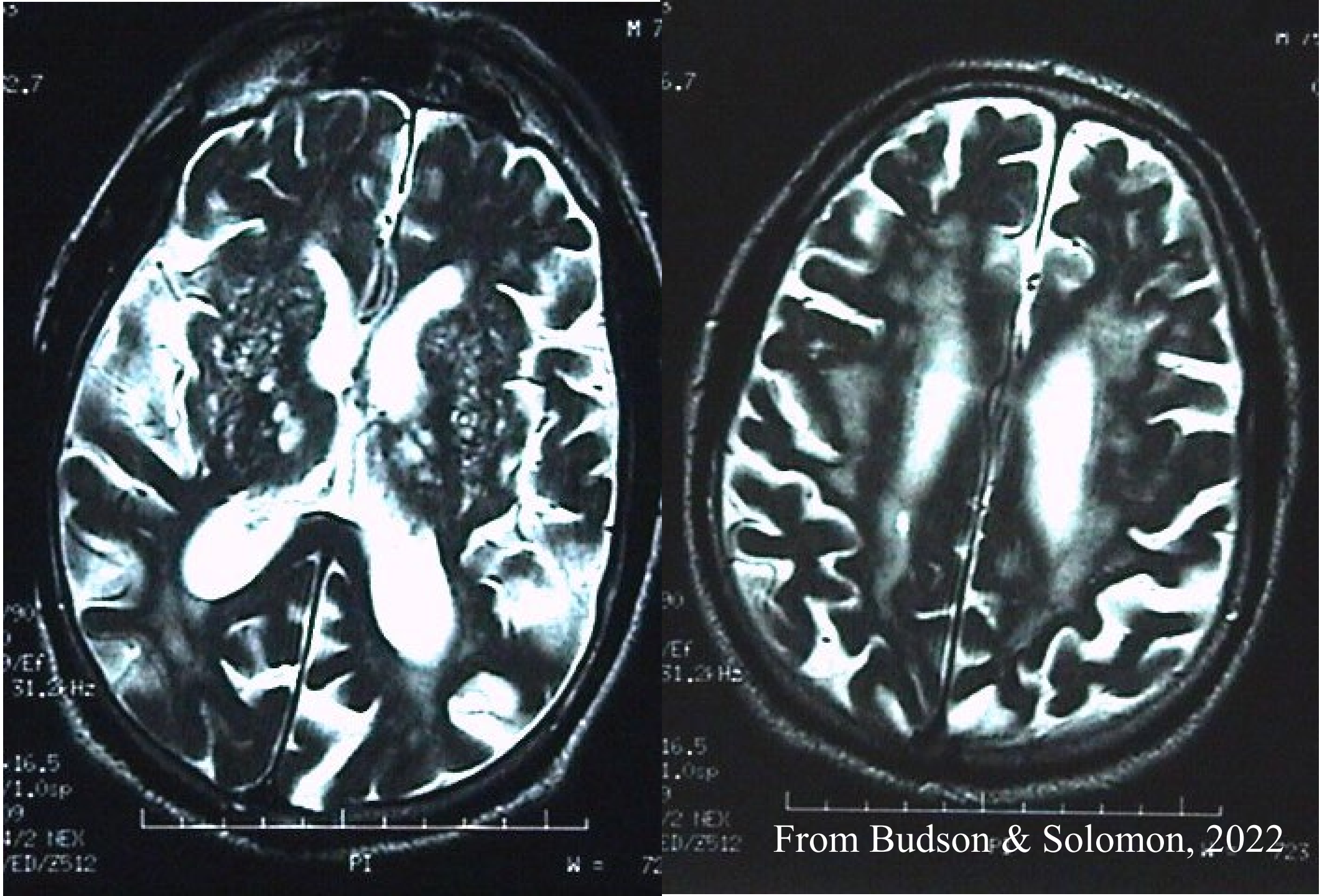
Rivastigmine patch is FDA approved for Parkinson's Disease Dementia

Lancet 2000 356:2031-6

Patient 5

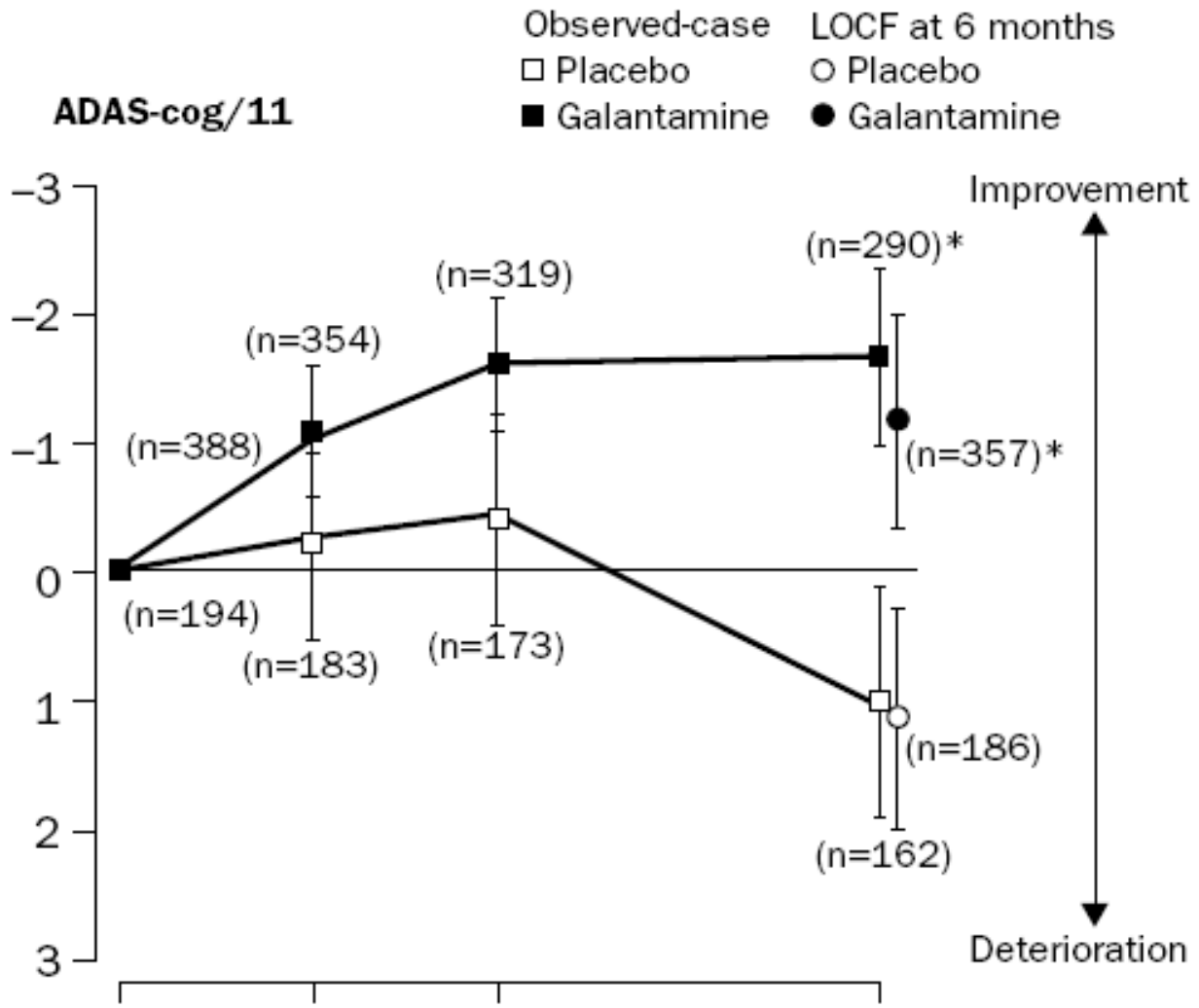
- 74M 6 yr history of “Small TIAs.”
- Family complains of memory problems, but patient remembered the last Red Sox game well
- Has trouble recalling specific things, but is generally oriented to time, place & what is going on
- Poor walking
- Early incontinence

Vascular Dementia



From Budson & Solomon, 2022

Galantamine in vascular dementia



Lancet 2002 359:1283-90

Managing agitation

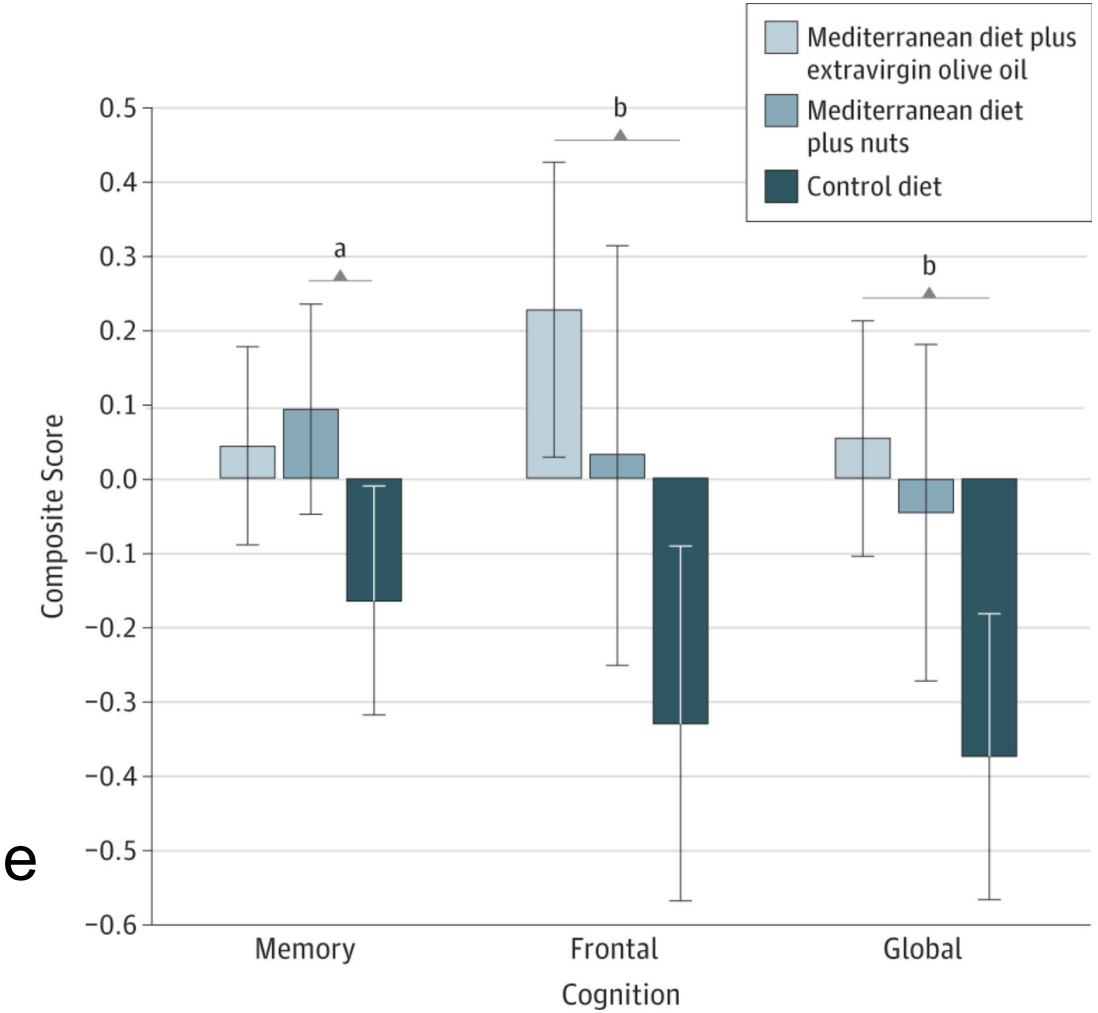
- Try to determine the underlying cause of agitation
- 4 R's: Reassure, Reconsider, Redirect, Relax
- Start with small steps
- Agitation is often due to anxiety
  - Start with sertraline/Zoloft 50 to 100 mg (or escitalopram/Lexapro; others not as good)
- Manage sleep cycle disturbances
  - Limit naps, no more than 8 hours in bed.
  - Melatonin, acetaminophen
- Daytime agitation
  - risperidone/Risperdal: start 0.25 mg QD
- Nighttime agitation
  - quetiapine/Seroquel: start 25 mg QHS
- Prazosin: start 1 mg, increase 1 mg/wk. Watch BP.
- Pimavanserin (Nuplazid) 40 mg QD for PDD
- 20 mg Dextromethorphan HBr/10 mg Quinidine sulfate (Nuedexta)

Driving

- Patients with very mild AD have accident rates similar to 16-19 year old drivers.
  - (Neurology 2010 74:1316)
- Family member to ride as passenger monthly.
  - If family members are comfortable riding with patient driving, then patient may be OK to drive.
  - Adult children are best. (Am J OT 2015 69: 6903270030)
- Driving evaluation at local registry of motor vehicles or rehabilitation hospital if controversy.

Mediterranean diet improves cognitive function vs. control diet

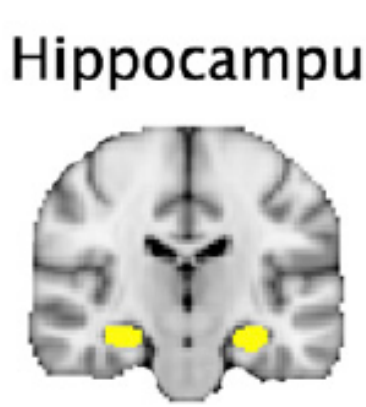
- 334 cognitively healthy adults
- Mean age 67 years
- Randomly assigned
  - Med diet + olive oil
  - Med diet + nuts
  - Control
- Fish, olive oil, avocado, fruit, vegetables, beans, nuts, whole grains, red wine

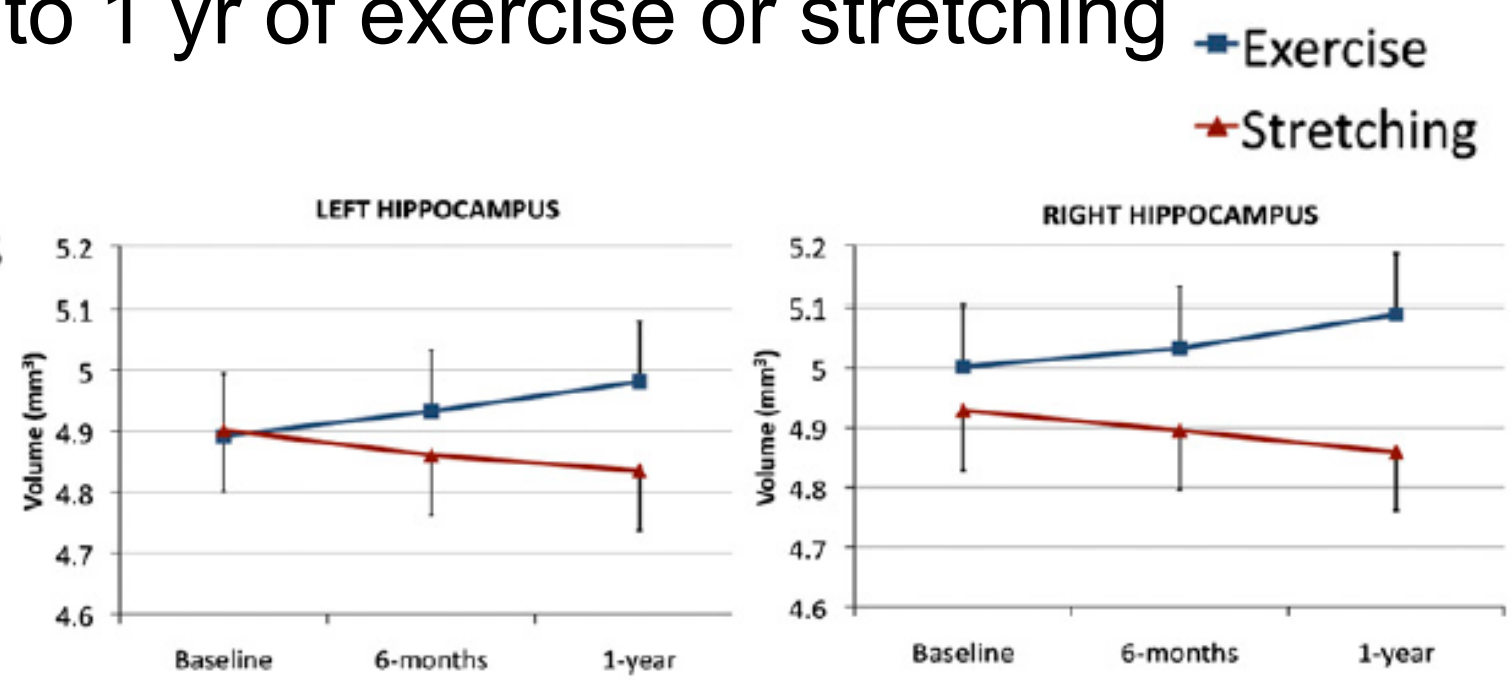


From: **Mediterranean Diet and Age-Related Cognitive Decline: A Randomized Clinical Trial**
JAMA Intern Med. 2015;175(7):1094-1103. doi:10.1001/jamainternmed.2015.1668

Exercise increases hippocampal volume in older adults

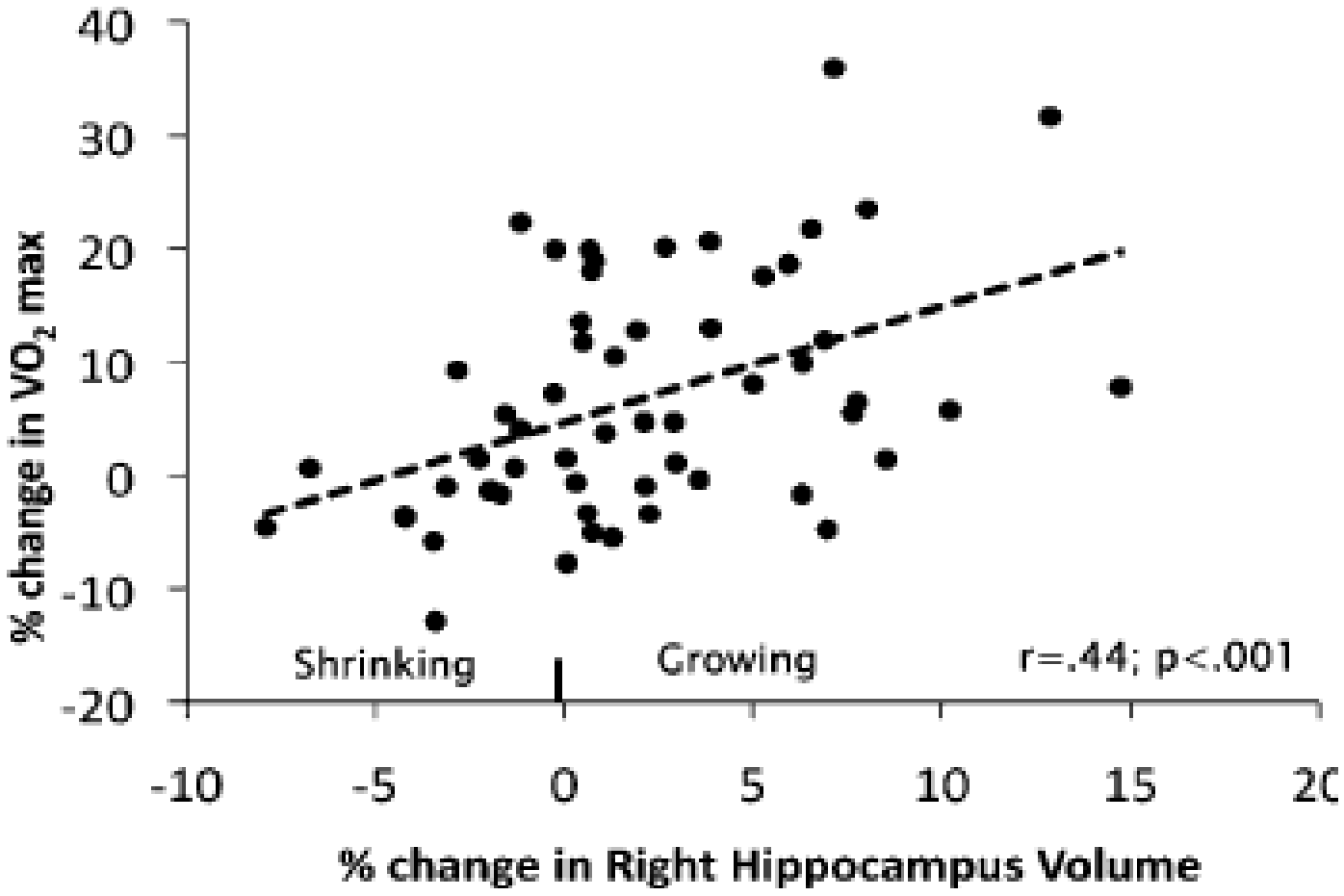
- 120 older adults 55-80, mean 66 years
- Randomized to 1 yr of exercise or stretching





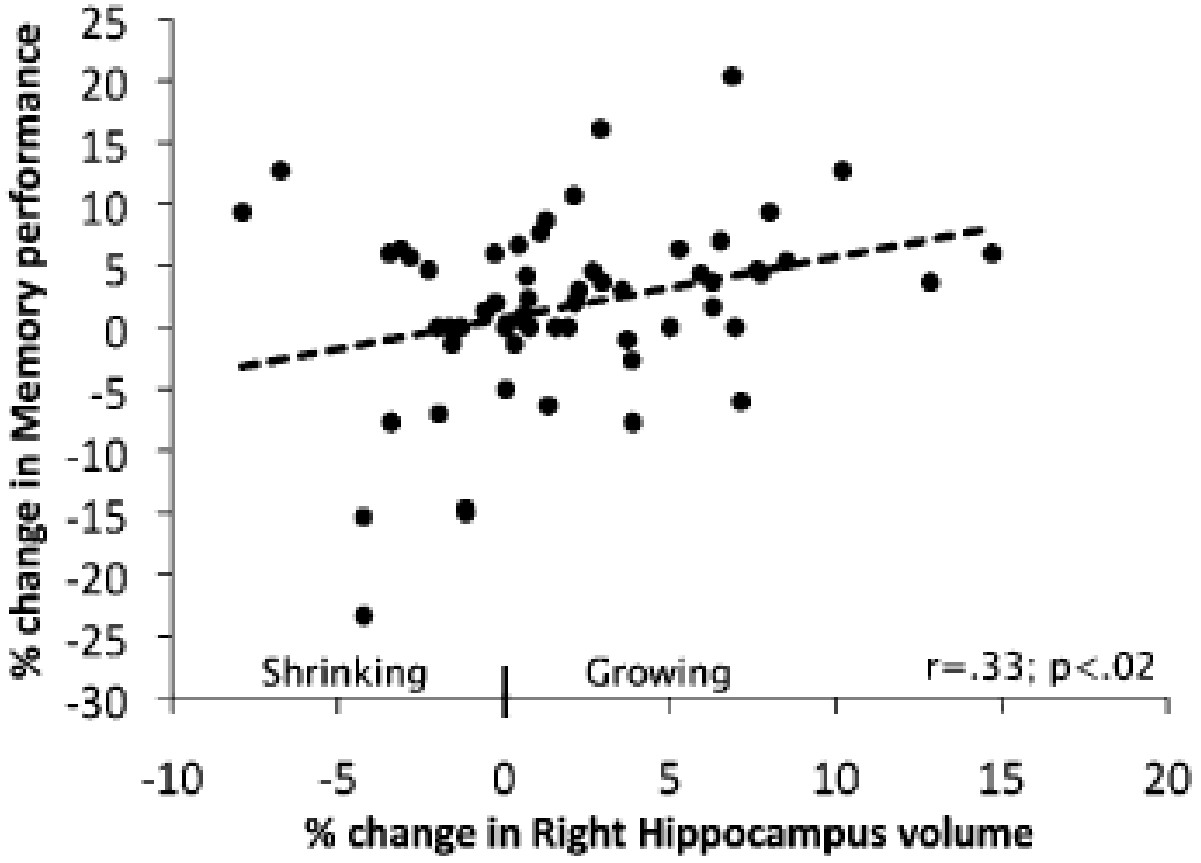
PNAS | February 15, 2011 | vol. 108 | no. 7 | 3017–3022

ΔVO_2 max correlates with Δ hippocampal volume



PNAS | February 15, 2011 | vol. 108 | no. 7 | 3017–3022

∆memory performance correlates with∆ hippocampal volume



PNAS | February 15, 2011 | vol. 108 | no. 7 | 3017–3022

Non-pharmacologic approaches

- Exercise, exercise, exercise
- Mediterranean diet
- Social activities
- Engage in novel, stimulating cognitive activities—including crossword puzzles!
- Keep a positive mental attitude
- TV is bad for your brain

Key Points

- ~70% of dementias are Alzheimer's disease (AD)—or LATE (Limbic-predominant, Age-related, TDP-43 Encephalopathy).
- LATE looks like AD (but without amyloid & tau biomarkers)
- AD pathology begins 10 to 20 years prior to symptoms.
- FDG PET can distinguish between different dementias.
- Cholinesterase inhibitors "turn the clock back" on memory loss 6-12 months and improve quality of life in patients with mild, moderate, & severe AD.
- Cholinesterase inhibitors are FDA approved for AD and Parkinson's disease dementia/dementia with Lewy bodies; there is good "off label" evidence for their use in vascular dementia & MCI.
- Memantine is only for patients with moderate to severe dementia; watch for drowsiness and confusion.
- Not enough evidence for aducanumab but lecanemab looks promising

Next Best Steps

- Use the 2011 criteria to diagnose AD dementia & MCI.
- Think about dementia w/Lewy bodies, vascular dementia, & chronic traumatic encephalopathy.
- Consider dextromethorphan / quinidine (Nuedexta) for pseudobulbar affect & agitation.
- Consider prazosin for anger & pimavanserin for agitation.
- Use the 4Rs for agitation:
  - Reassure, Reconsider, Redirect, Relax
- Encourage exercise, Mediterranean diet, social activities, novel activities, & positive attitude to reduce risk of AD.
- Refer families to the Alzheimer's Association www.alz.org.

End