Memory Loss, Alzheimer's disease, & Dementia - Update 2020

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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)

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
- Treat Alzheimer's disease
- Learn about LATE (Limbic-predominant, Age-related, TDP-43 Encephalopathy)
- Diagnose Chronic Traumatic Encephalopathy
- Diagnose & treat other common dementias
- Manage issues of driving, agitation, & pseudobulbar affect
- Know data on diet & exercise for memory

Dementia: Prevalence

- Increases geometrically with age
- 5-10% of individuals > age 65
- 50% of those > age 85
- Approximately 75% of these cases will be Alzheimer’s disease—or LATE.
- (More about LATE later on...)

Patient 1

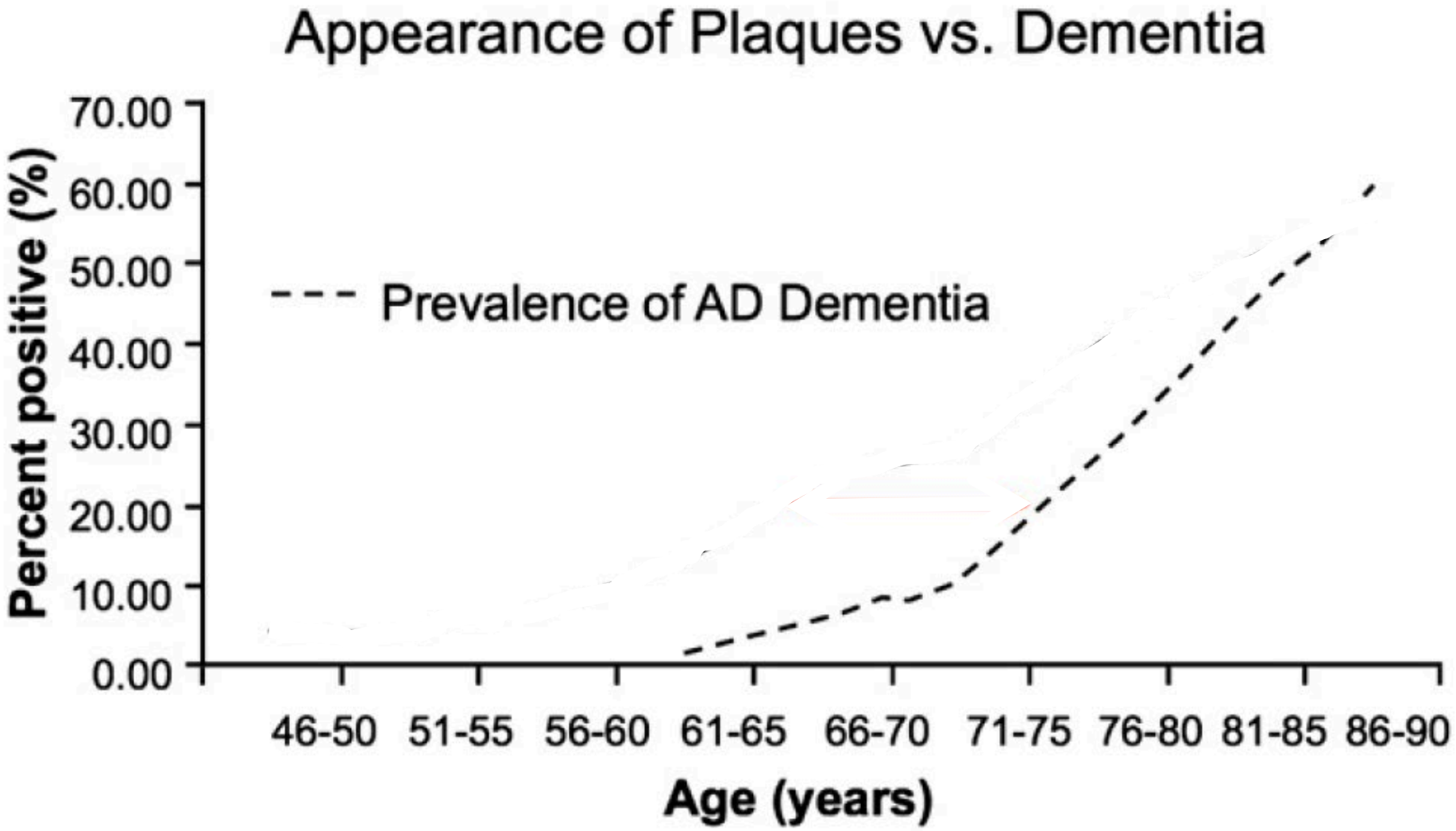
- 81 M with memory difficulties.
- 8 years ago got lost, asked the same questions repeatedly.
- Gradual worsening, last 6-12 mos unable to learn new information
- Prominent word finding difficulties
- Remembers everything about his days during WWII

Alzheimer's disease (probably)

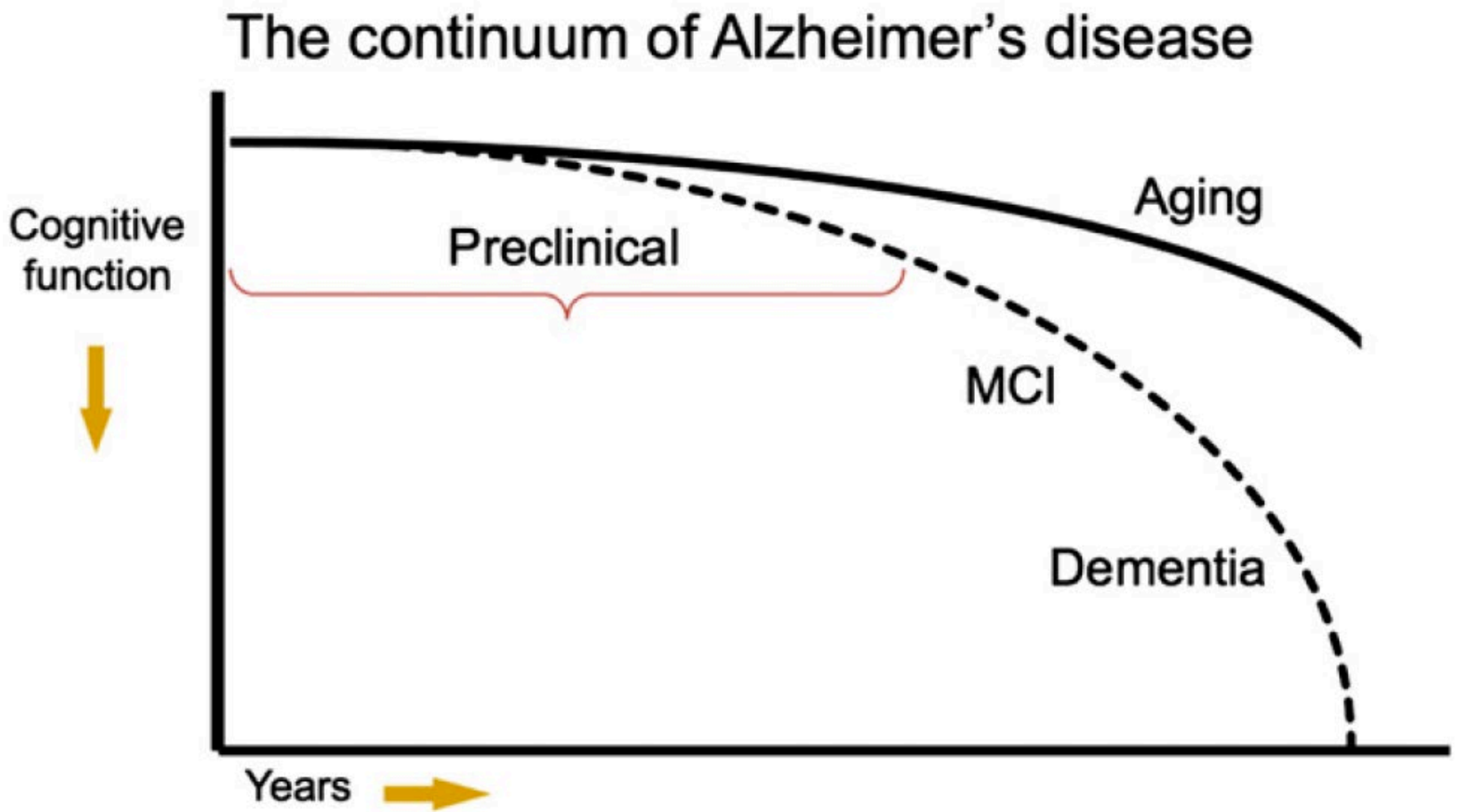
Diagnosis: What's new?

- NIA-AA & DSM-5 Diagnostic Criteria:
  - Dementia / Major Neurocognitive Disorder
  - Alzheimer's disease (AD)
  - Mild Cognitive Impairment due to AD / Mild Neurocognitive Disorder due to AD
- Biomarkers more available & increase level of certainty when present
- Amyloid PET scans detect β-amyloid in brain!
- LATE (Limbic-predominant, Age-related, TDP-43 Encephalopathy) looks like Alzheimer's disease
- Alzheimer's pathophysiology starts decades prior to clinical disease

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

DSM-5 Criteria: Major Neurocognitive Disorder

A. Decline from prior level of function in 1 or more cognitive domains based on:
   1. Concern of individual, informant, or clinician, and
   2. Impairment in cognitive performance

B. Deficits interfere with independence in everyday activities.

C. Deficits do not occur exclusively in delirium

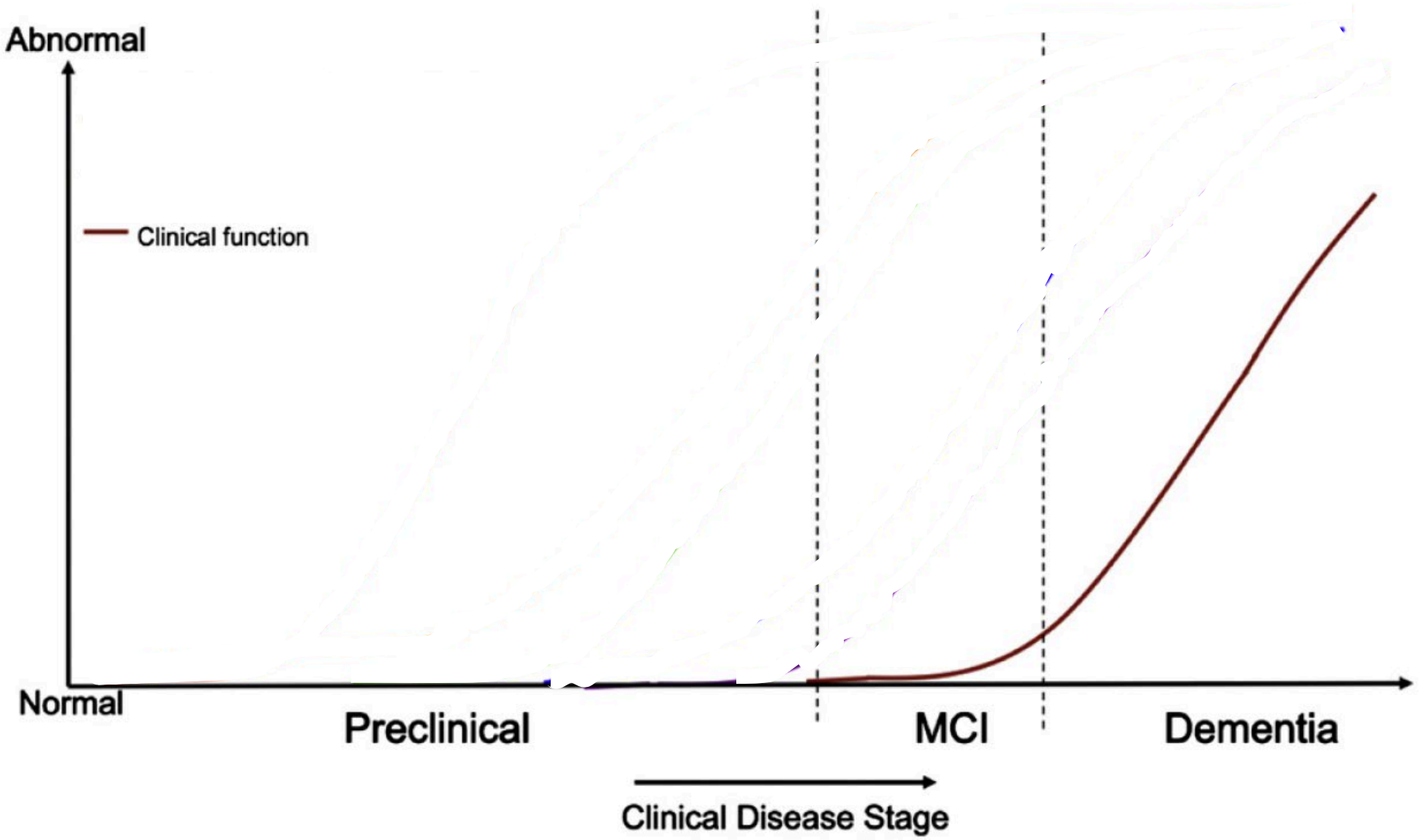
D. Not better explained by another mental disorder

- Specify whether due to AD, FTD, LBD, VaD, etc.
- Specify w/ or w/o behavioral disturbance
- Specify mild (IADL), moderate (BADL), Severe

NIA-AA Criteria: Alzheimer's disease dementia

- Dementia present using All-Cause Dementia criteria
- Insidious onset over months to years
- Progressive cognitive impairment
  - Amnestic presentation
  - Non-amnestic presentation
    - Language: word finding
    - Visuospatial: getting lost, impaired face recognition
    - Executive dysfunction: reasoning, judgment, problem solving
- Exclusionary criteria
  - Other dementia or disorder affecting cognition: vascular, dementia with Lewy bodies, frontal temporal dementia, other

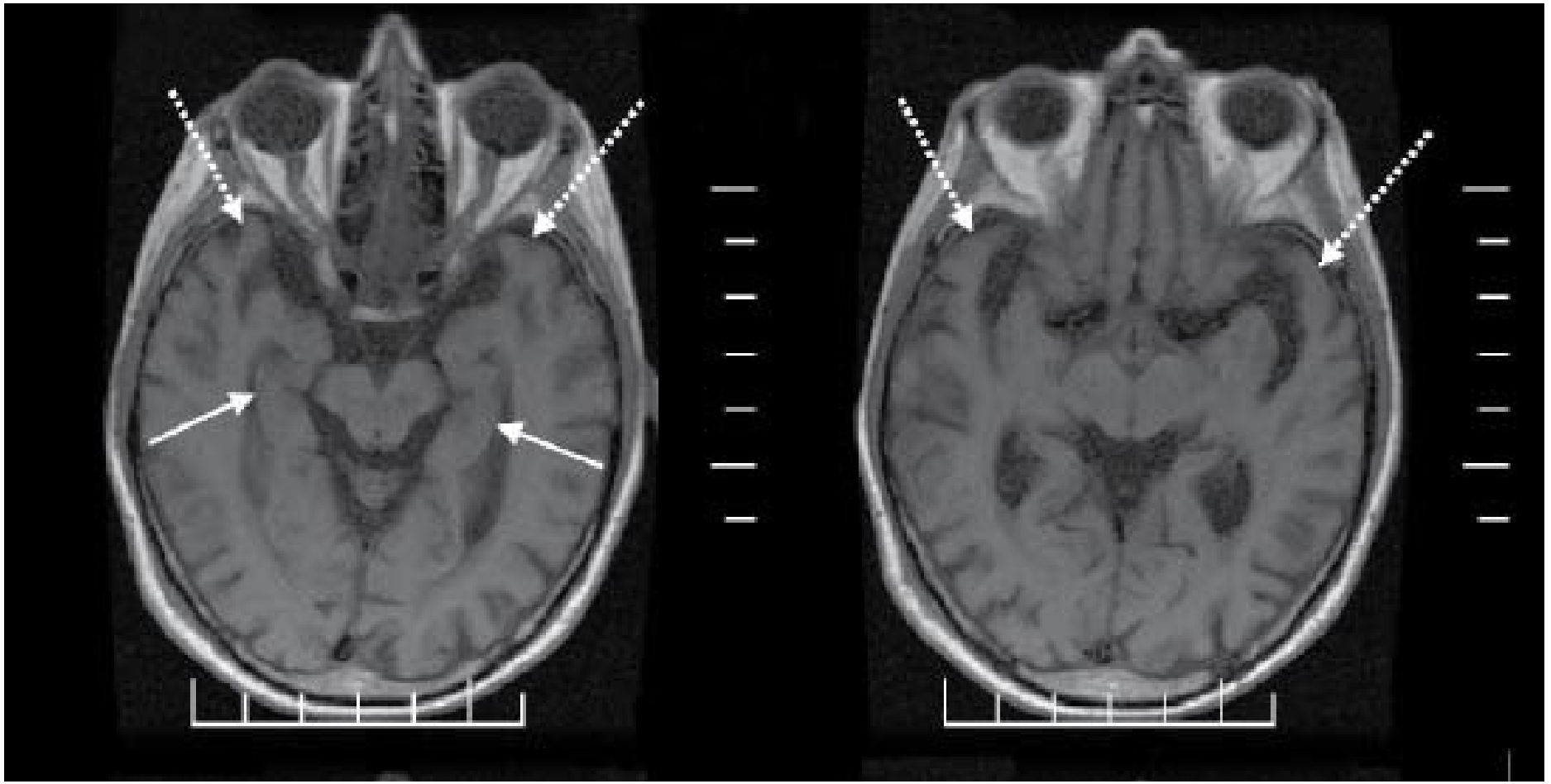
Biomarkers



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

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)



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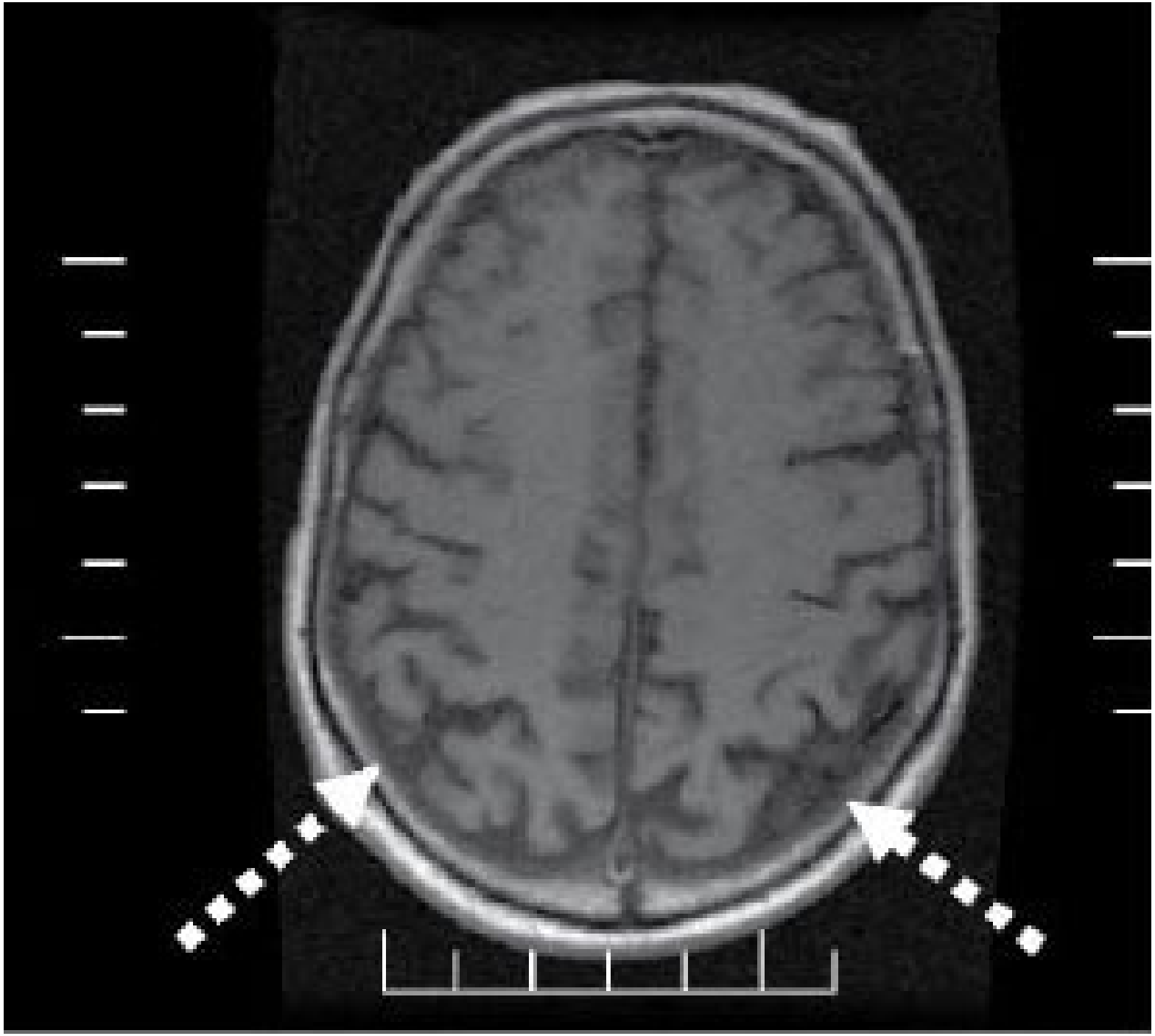

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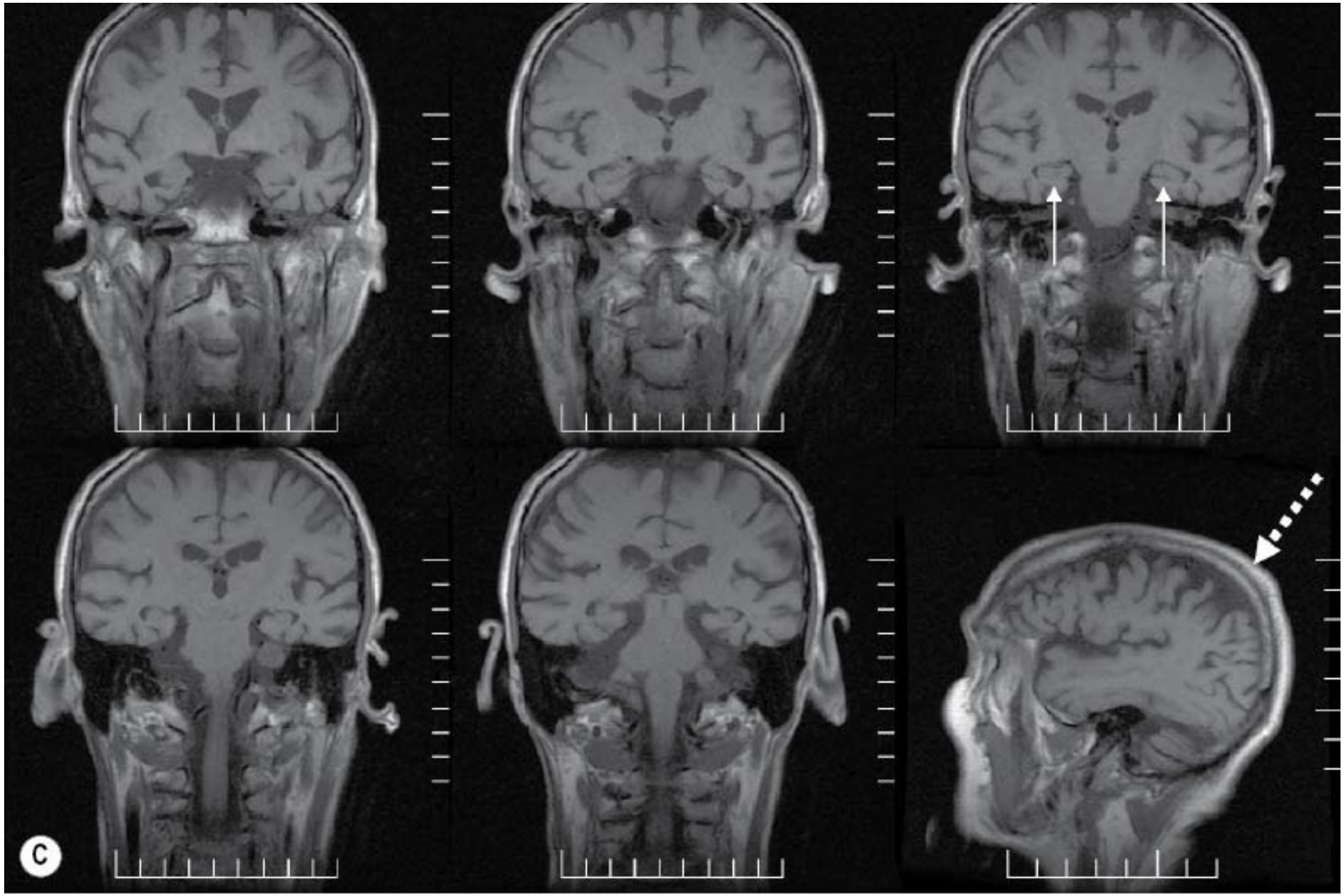

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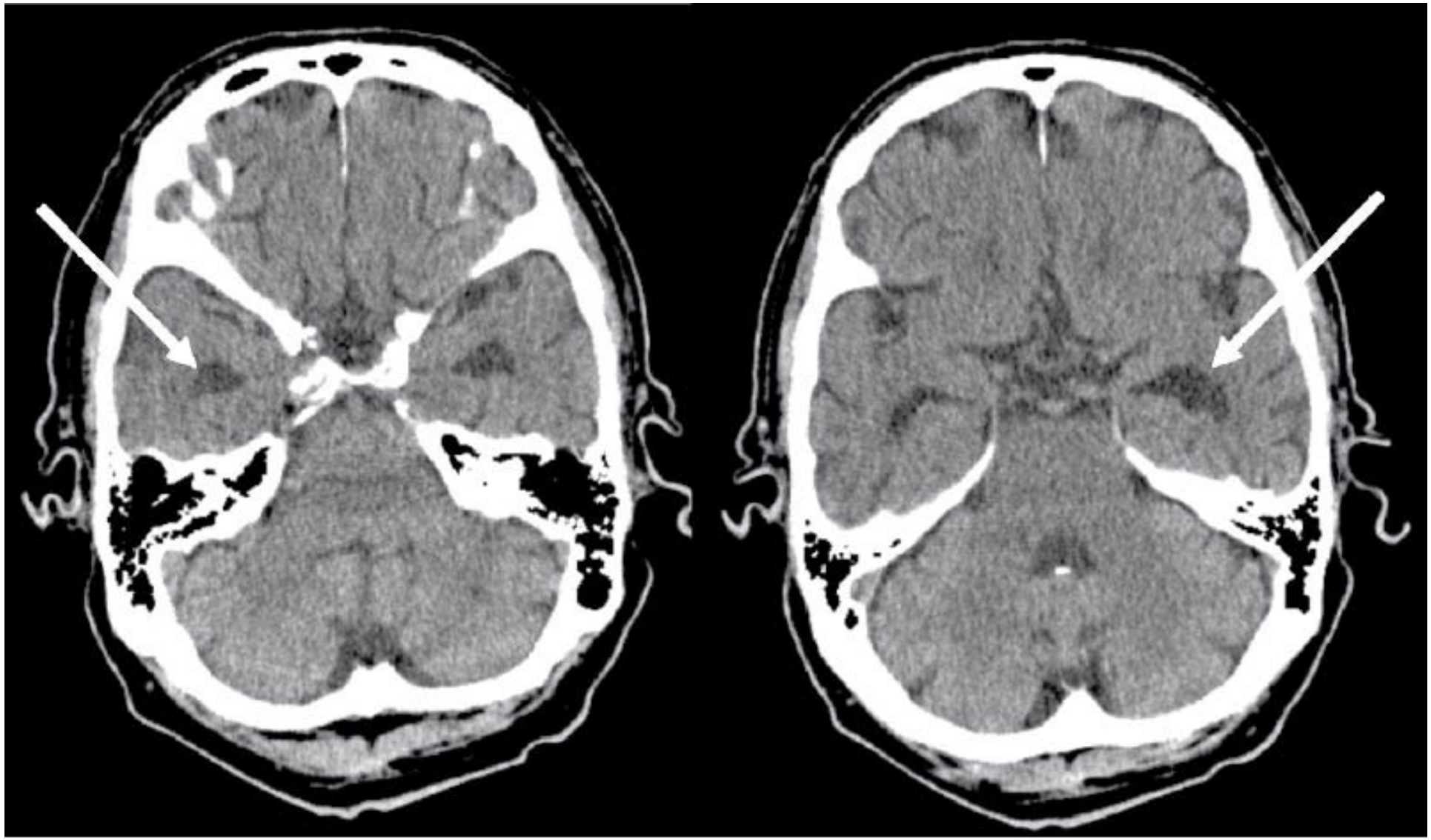

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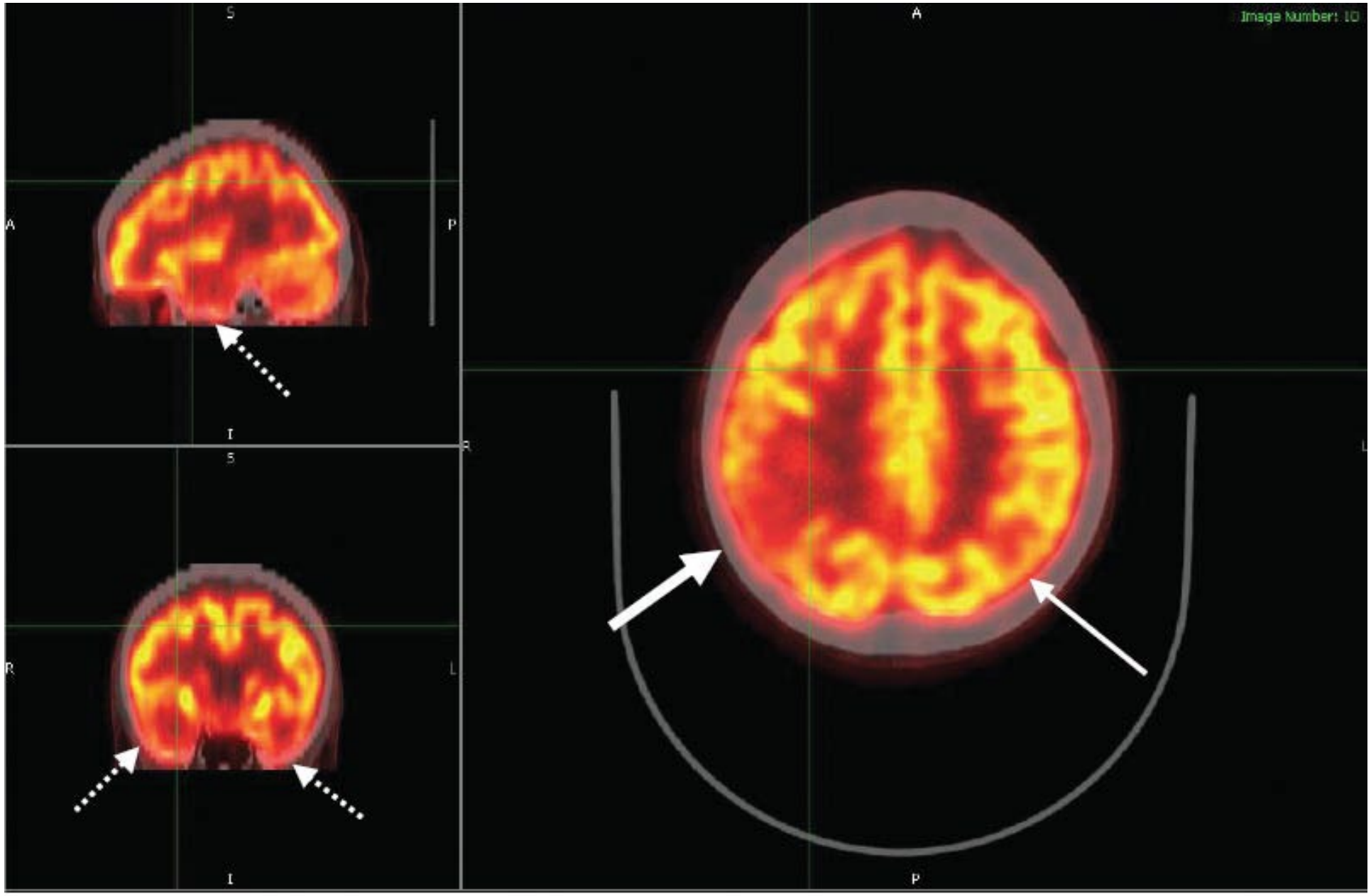
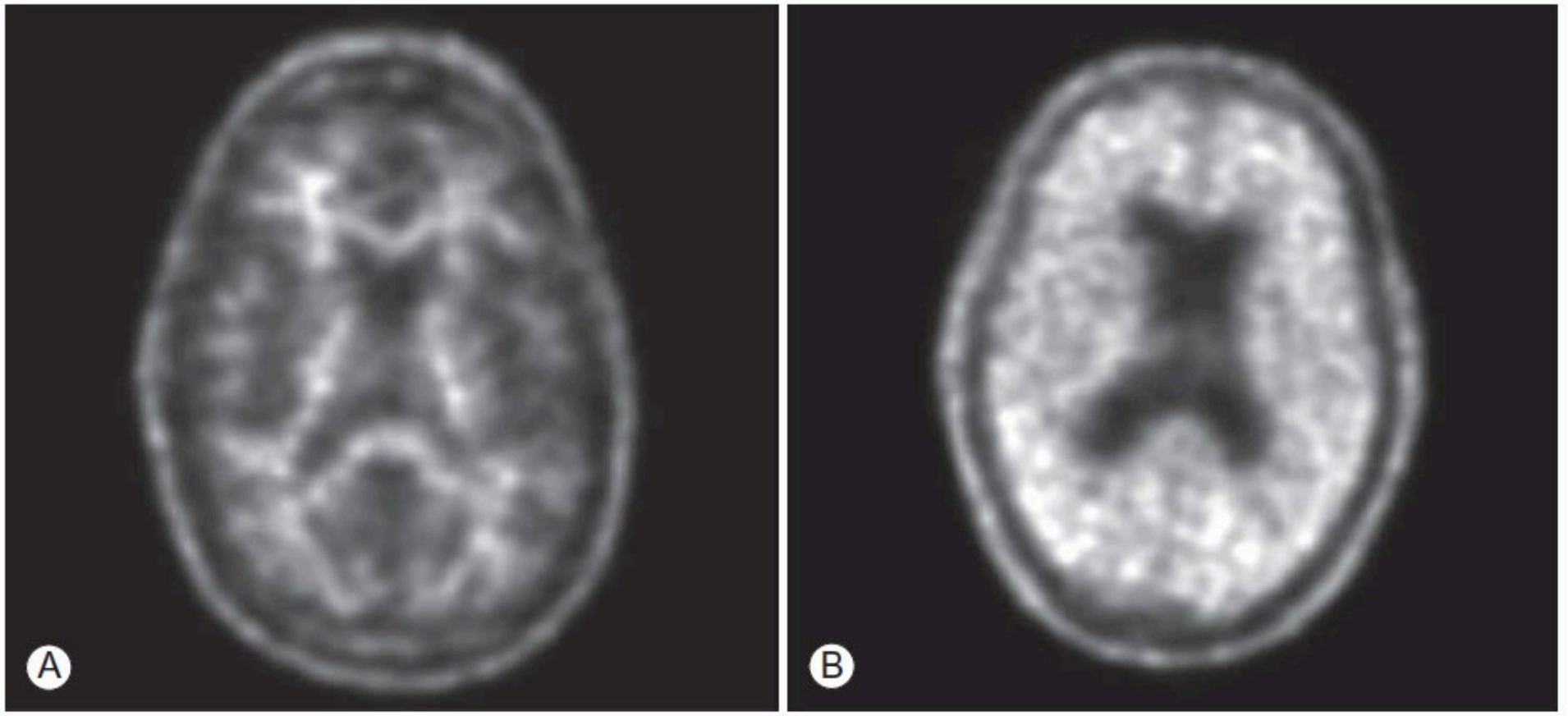
Biomarkers: what to look for / when to use them

- 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, 2016

Amyloid Imaging



- Use when knowing that AD pathology is present in symptomatic patient would change management.
- May detect AD pathology in asymptomatic patients who may not develop disease for 10-15+ years
- Will have broader use when disease modifying therapies are available.

From Budson & Solomon, 2016

Alzheimer's disease-like disorder with negative amyloid biomarkers?

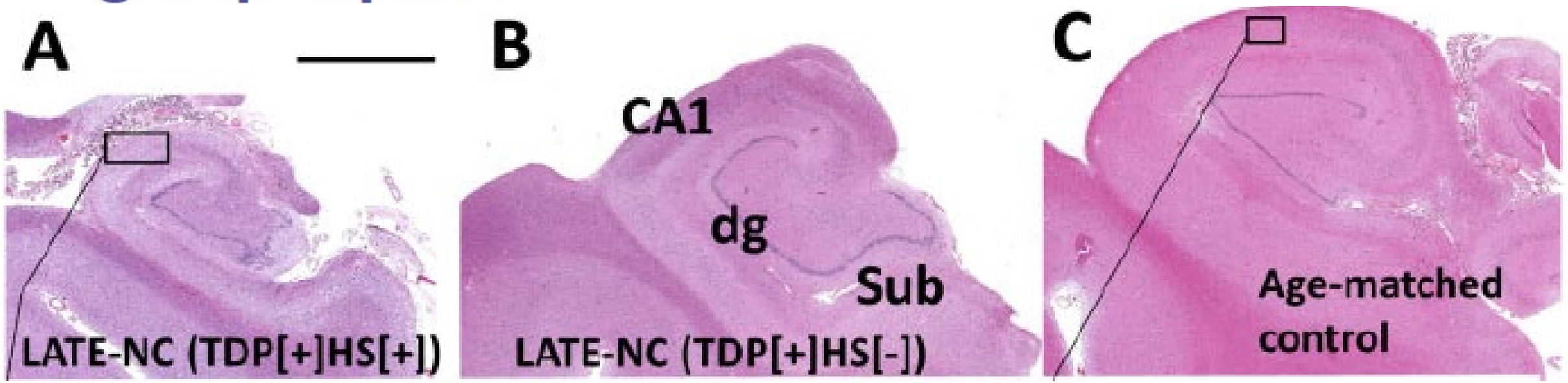
- Some patients appear to have Alzheimer's disease clinically but do not have amyloid biomarkers—part of the pathologic definition of Alzheimer's.
- Could the biomarkers not be sensitive to pathology?
- Maybe…but the pathology should be very prevalent by the stage of clinical symptoms.
- Maybe these patients have another disorder…

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

BRAIN
A JOURNAL OF NEUROLOGY

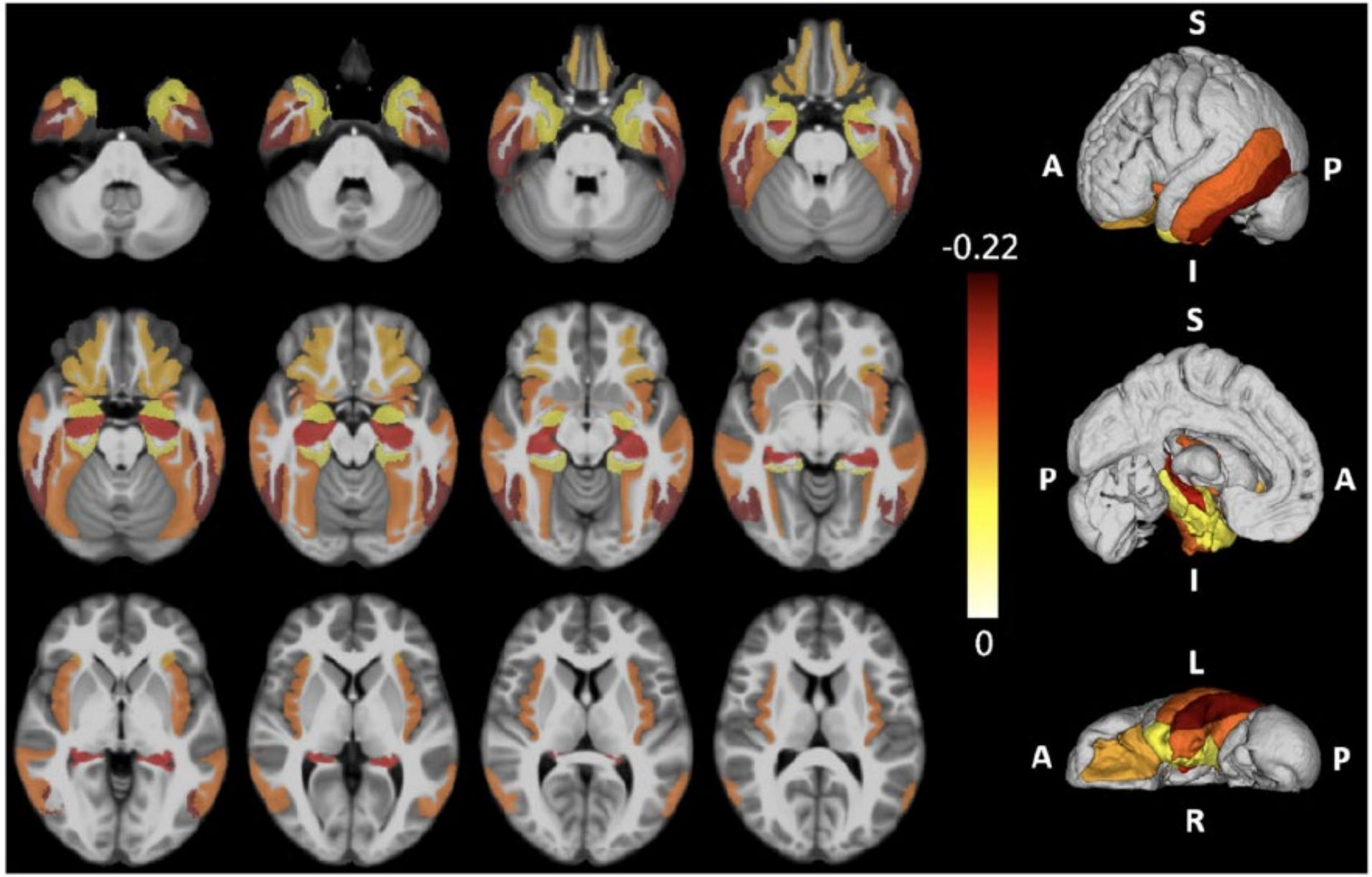
REVIEW

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

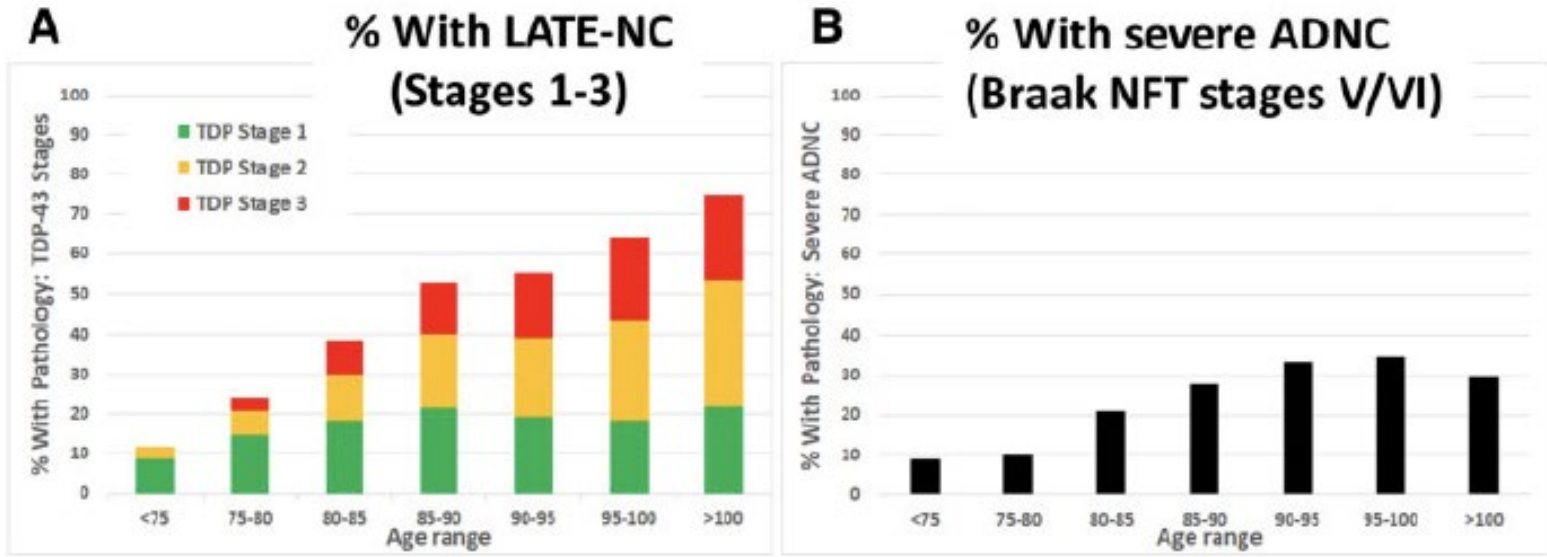


A

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)



NACC multicentre autopsy cohort data (*n* = 806)

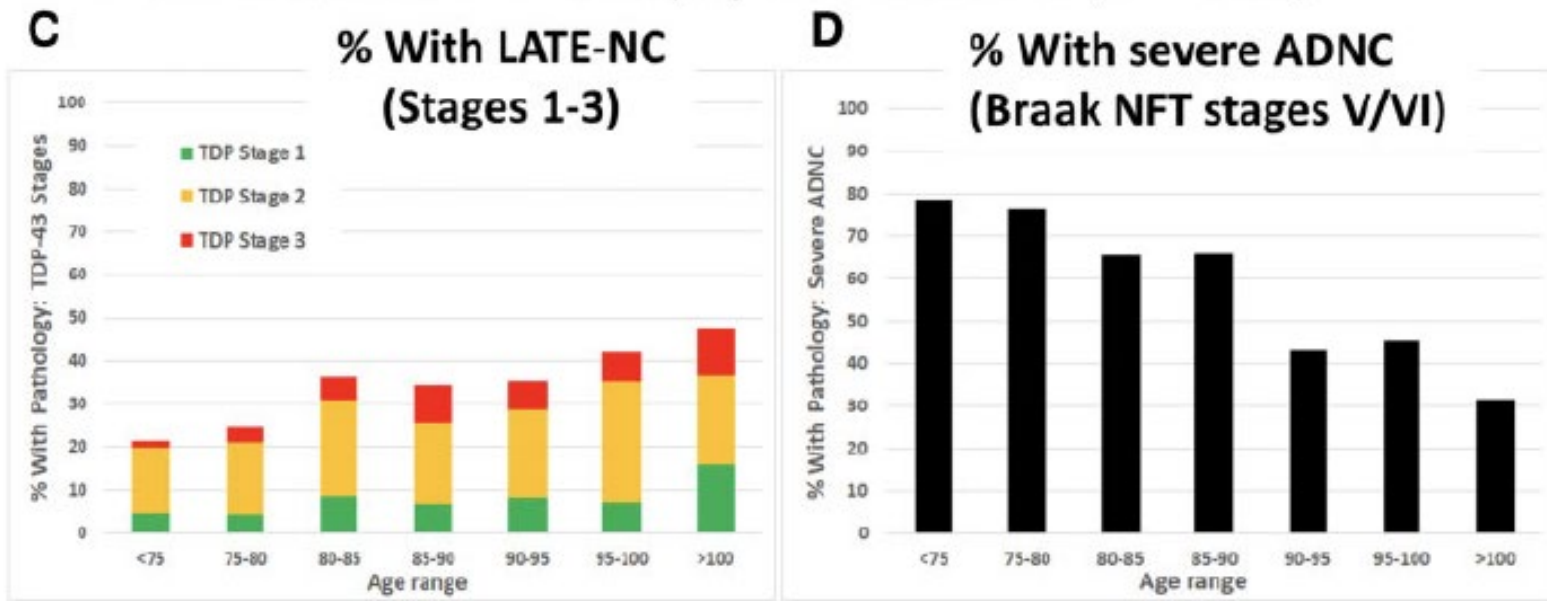


Table 2 **A statistical analysis of attributable risk from research volunteers in two clinical-pathological studies of ageing from Rush University**

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
  - Enzyme inhibitors that stop the formation of β-amyloid
  - Monoclonal antibodies directed against β-amyloid plaques and tau tangles
  - Trials on-going in patients with mild AD, MCI due to AD, *and* healthy individuals with memory complaints & + amyloid PET scan.

Treatment: currently available for AD (& LATE)

- Why will they likely work for LATE? Because participants with LATE were included in all of 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.
- 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

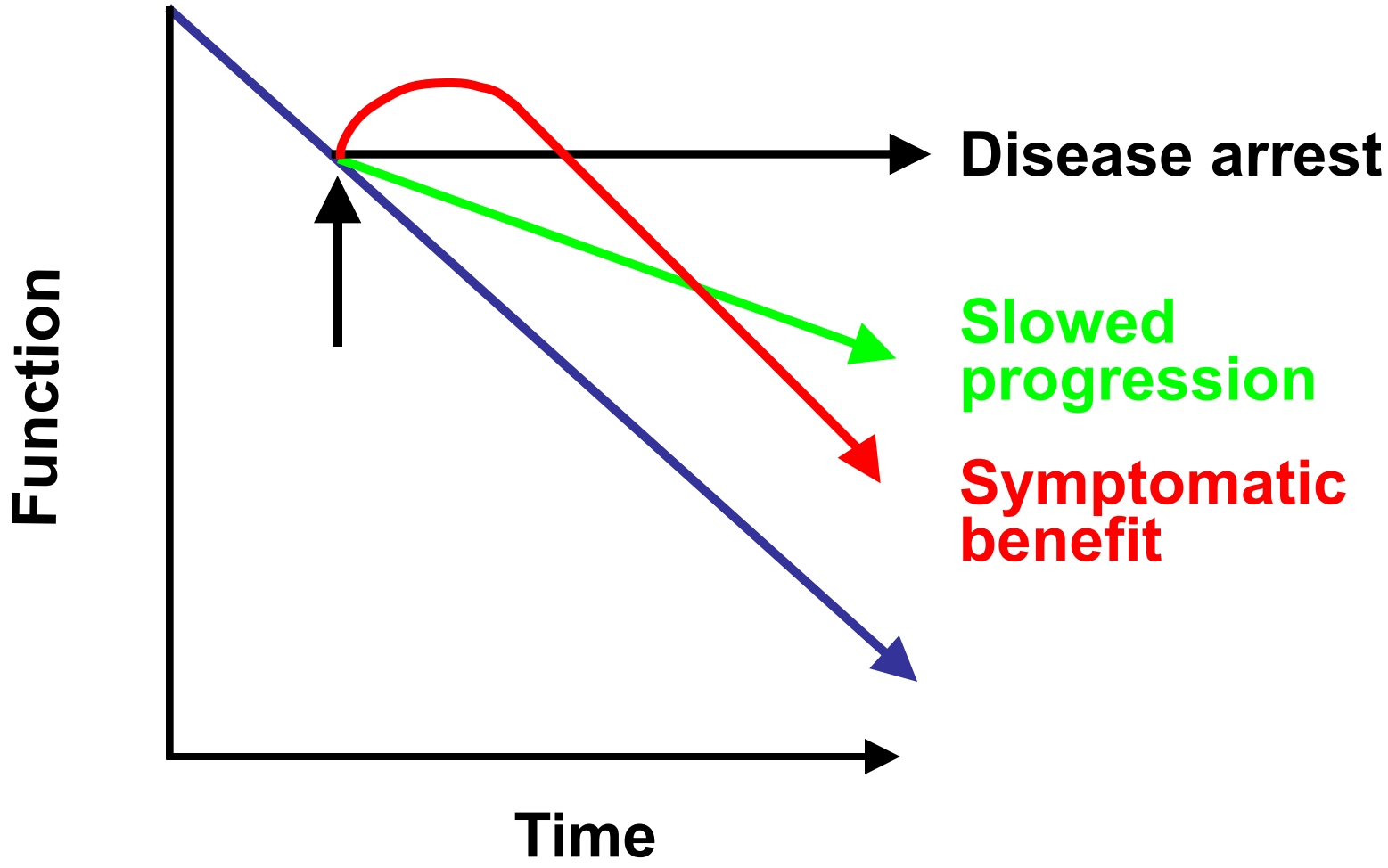
Treatment expectations

- 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, 2016

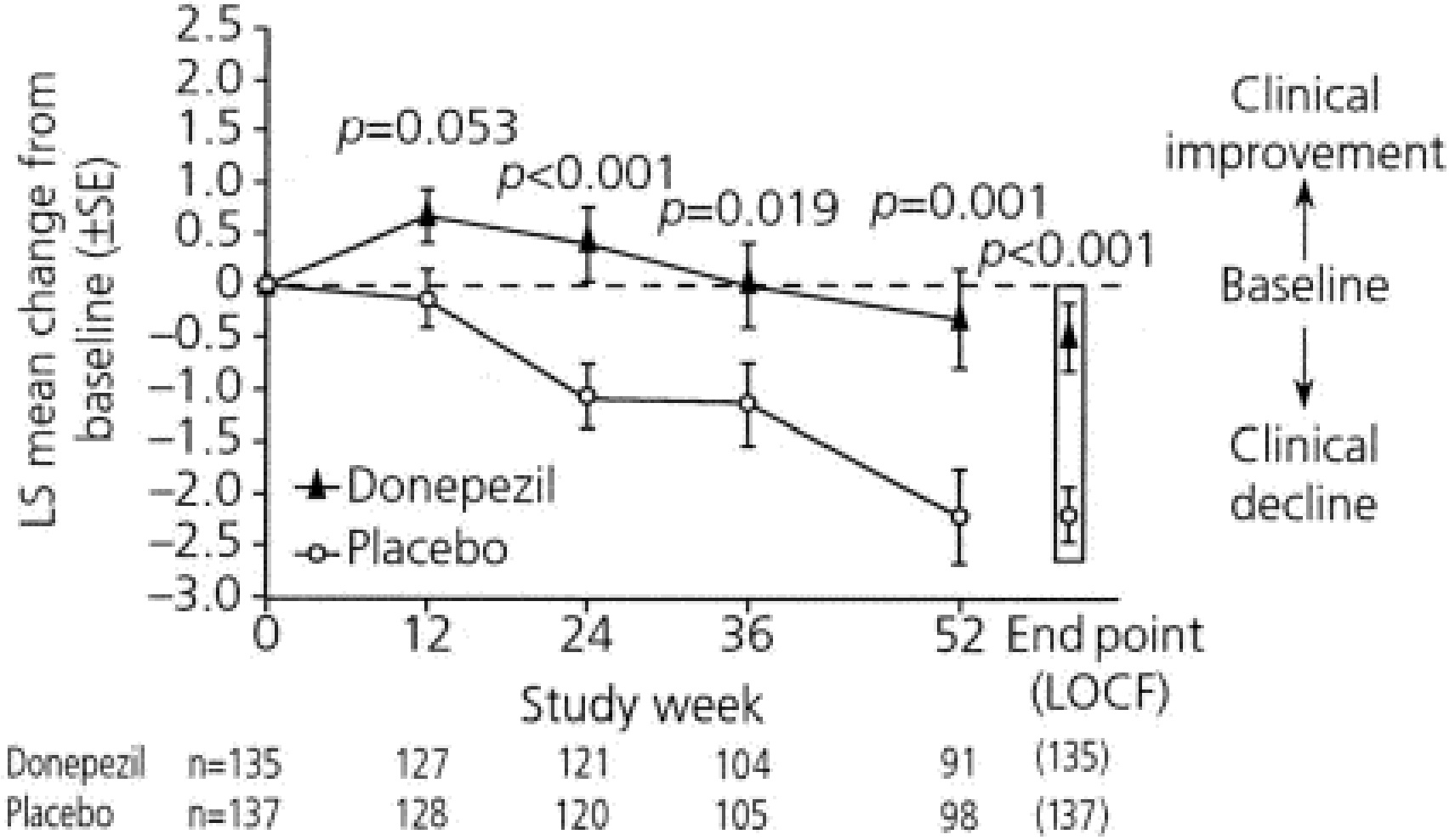
Turning back the clock

- 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

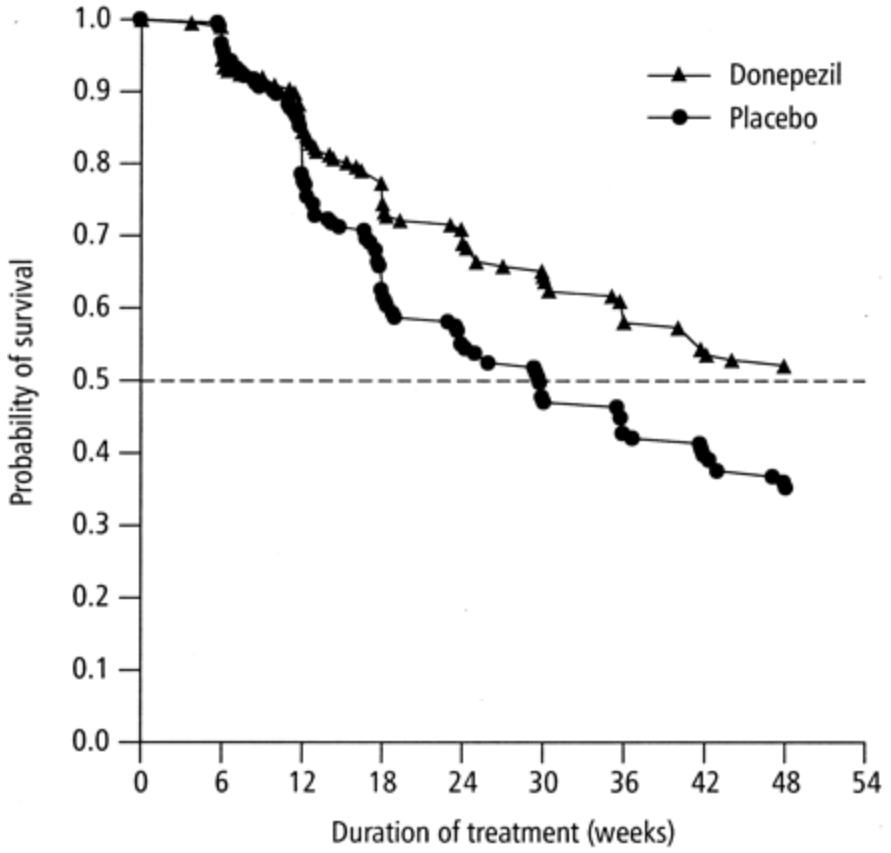
Change in MMSE in mild to moderate Alzheimer's disease



Neurology 2001 57:489-95

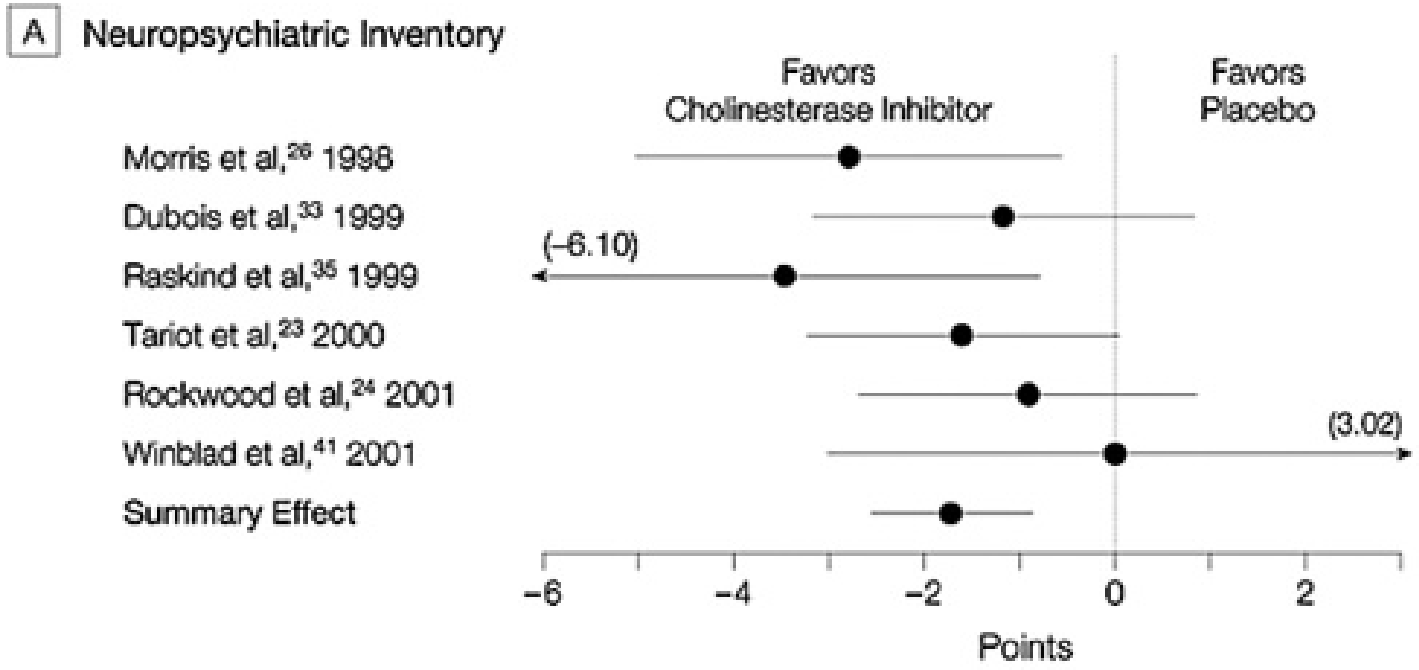
Time to clinically evident functional decline

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



Neurology 2001 57:481-8

Meta analsysis: neuropsychiatric symptoms in AD

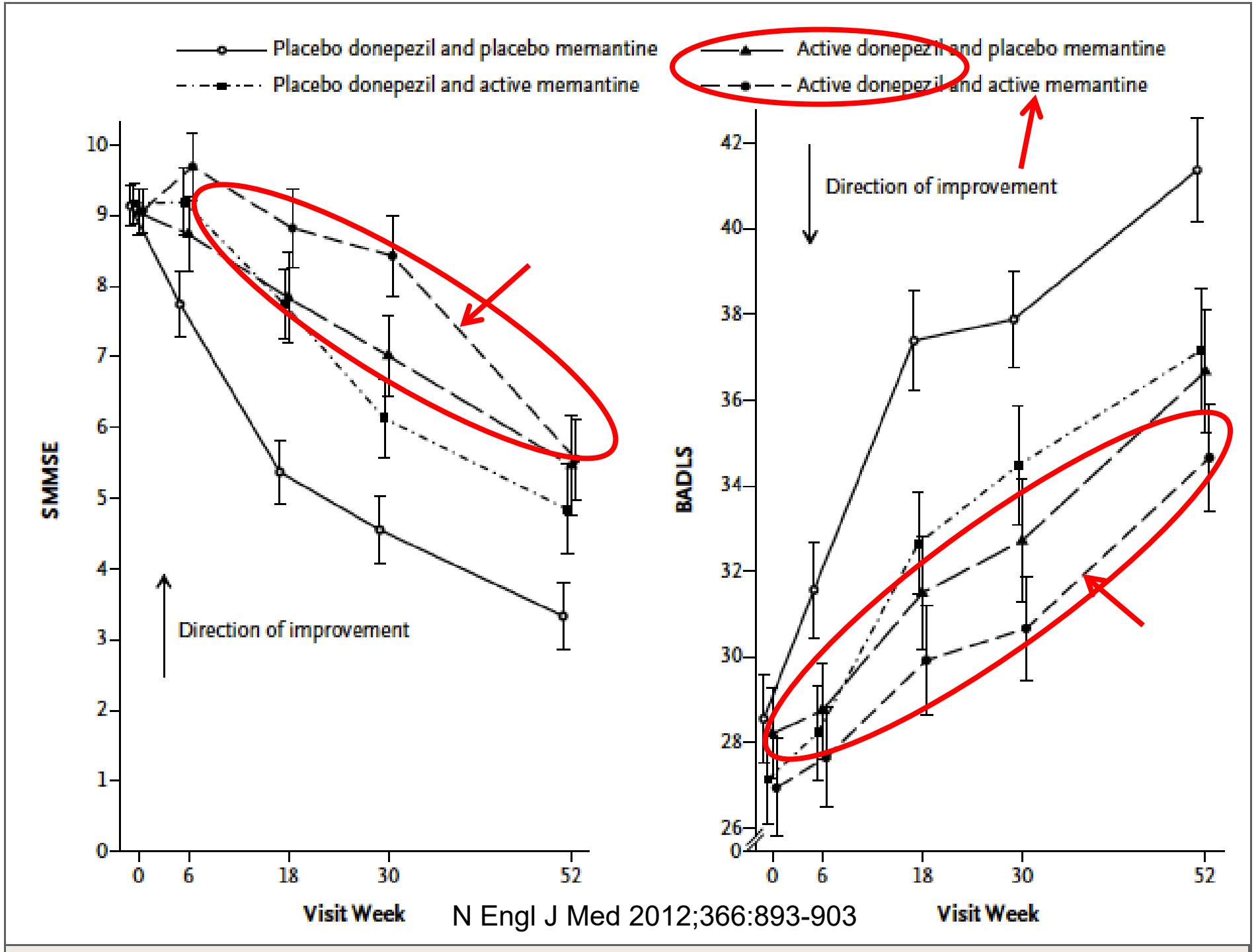


JAMA 2003 289: 210-16

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?

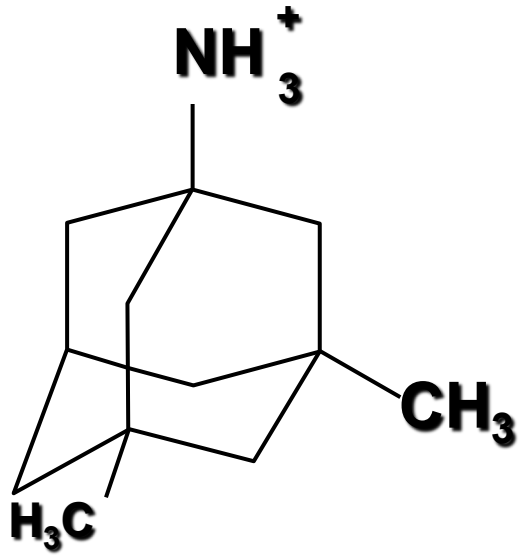


N Engl J Med 2012;366:893-903

- “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

Memantine uses

- FDA: moderate to severe AD (MMSE <16)
- Patients with AD or vascular dementia at any stage who are a bit Parkinsonian, or who are not depressed but appear withdrawn, not taking initiative, not talking much
- Patients with Lewy Body Dementia
- Try in patients with Frontotemporal Dementia

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

DSM-5 Criteria: Mild Neurocognitive Disorder

A. Modest decline from prior level of function in 1 or more cognitive domains based on:
   1. Concern of individual, informant, or clinician, and
   2. Modest impairment in cognitive performance

B. Deficits *do not* interfere with capacity for independence in everyday activities.

C. Deficits do not occur exclusively in delirium

D. Not better explained by another mental disorder

- Specify whether due to AD, FTD, LBD, VaD, TBI, Substance/medication use, HIV, Prion, PD, HD, medical condition, multiple etiologies, etc.
- Specify w/ or w/o behavioral disturbance

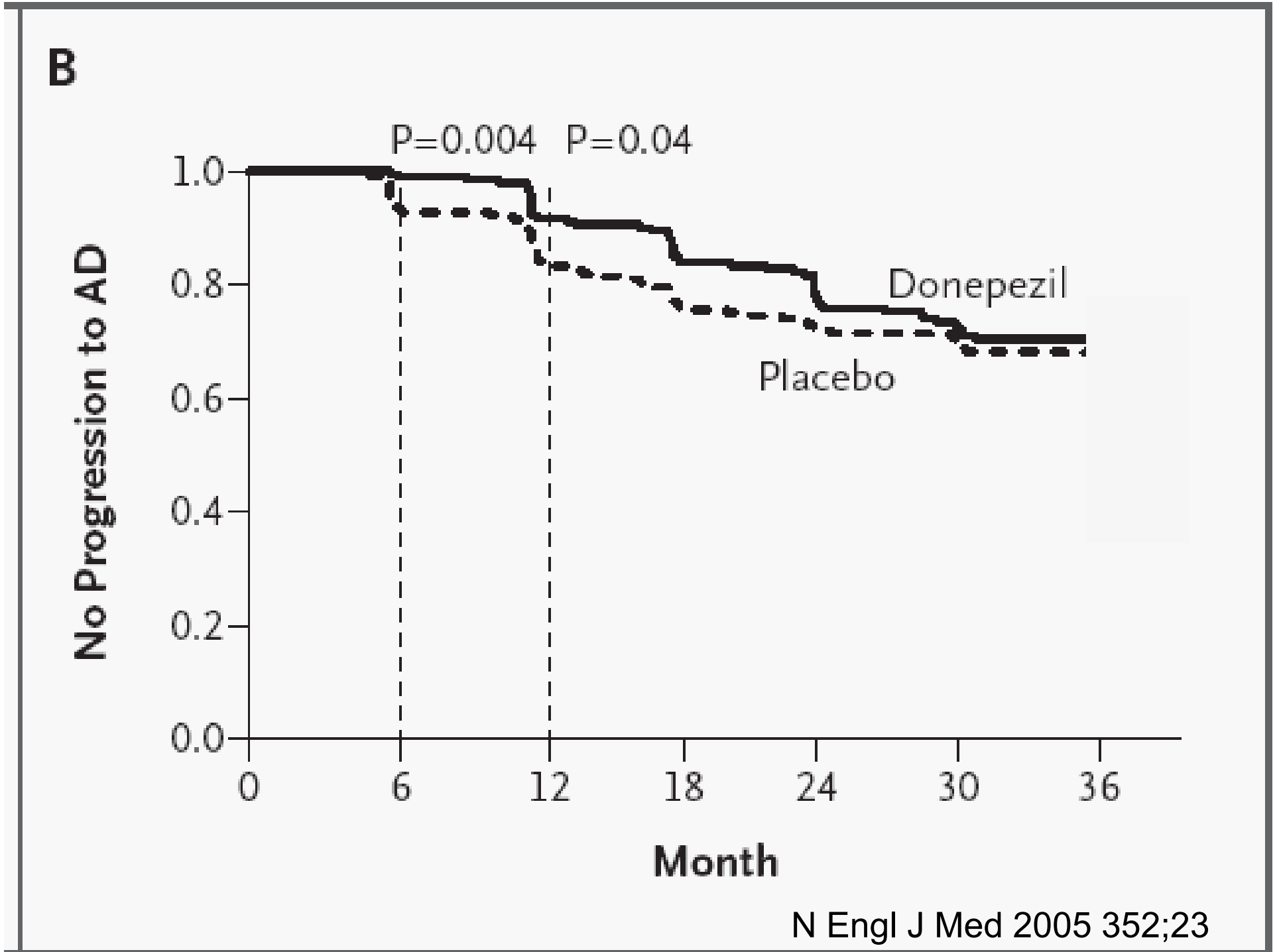
MCI: Prognosis & Treatment

- 50-70% progress to AD 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 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



N Engl J Med 2005 352;23

MCI: Prognosis & Treatment

- 50-70% progress to AD 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

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

Vit E does nothing in MCI; what about in mild to moderate AD?

- JAMA 2014;311:33-44
- Vit E 2000 IU, memantine 20 mg, both, placebo
- ADL scores declined 6.2 mo less in Vit E group
- No difference in memantine alone or memantine plus Vit E

- Unclear whether Vit E is helpful in AD.

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

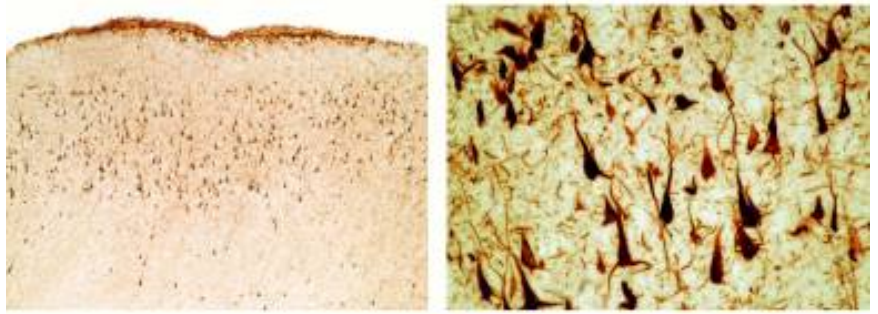
Chronic Traumatic Encephalopathy

Chronic Traumatic Encephalopathy (CTE) vs. Alzheimer's Disease

control

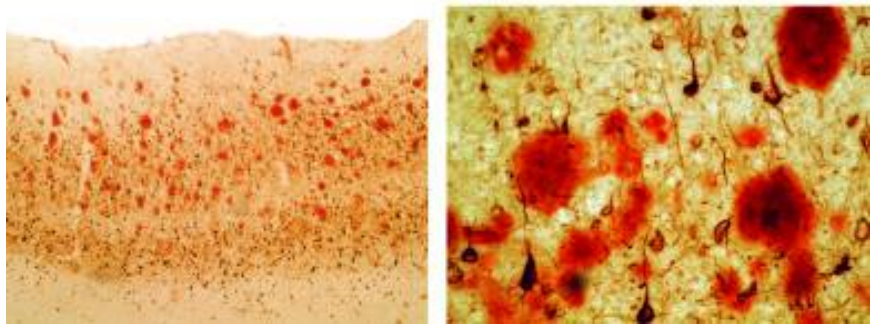
no tau,
no Aß

CTE

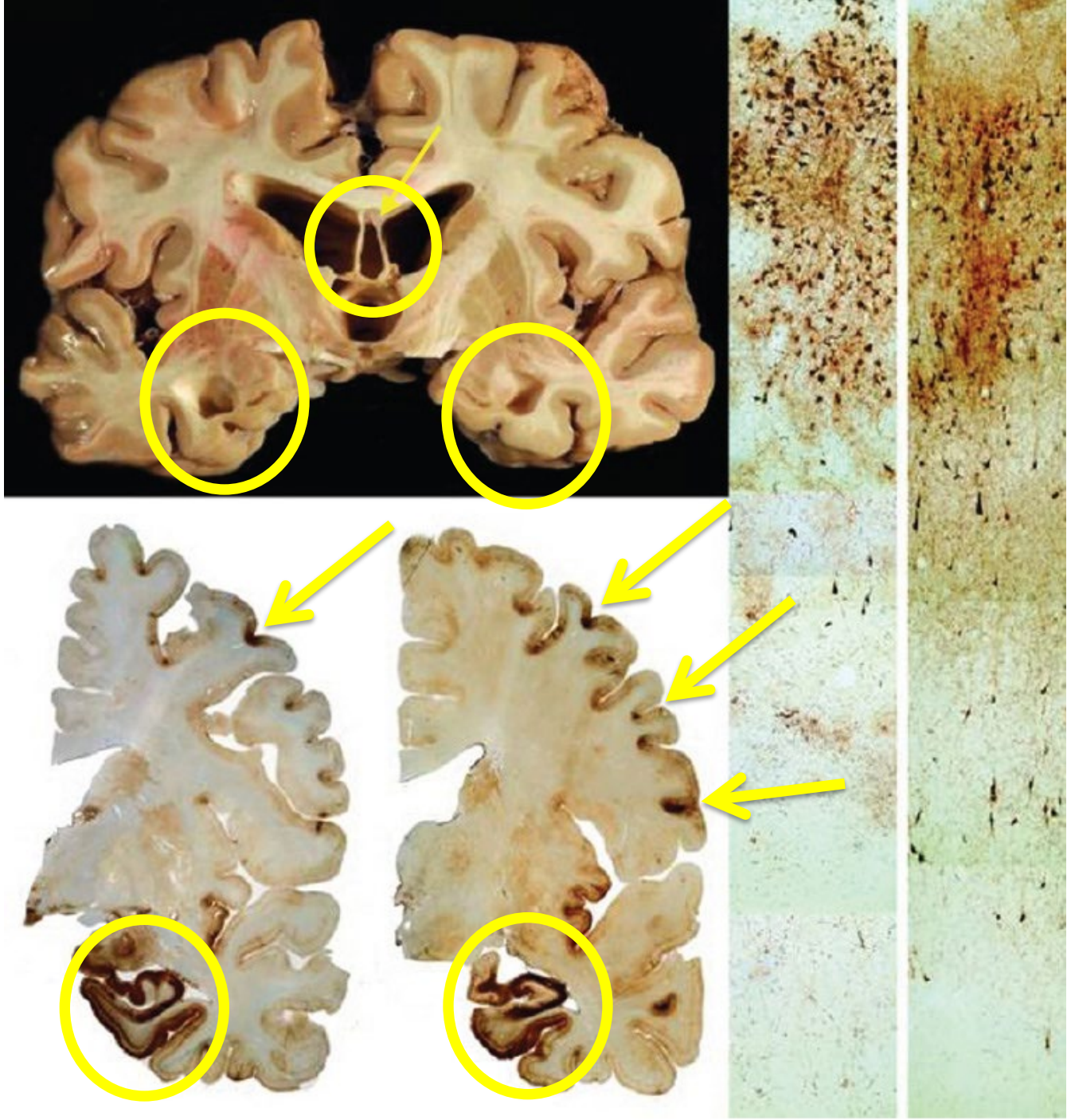


tau, no Aß

AD



tau & Aß

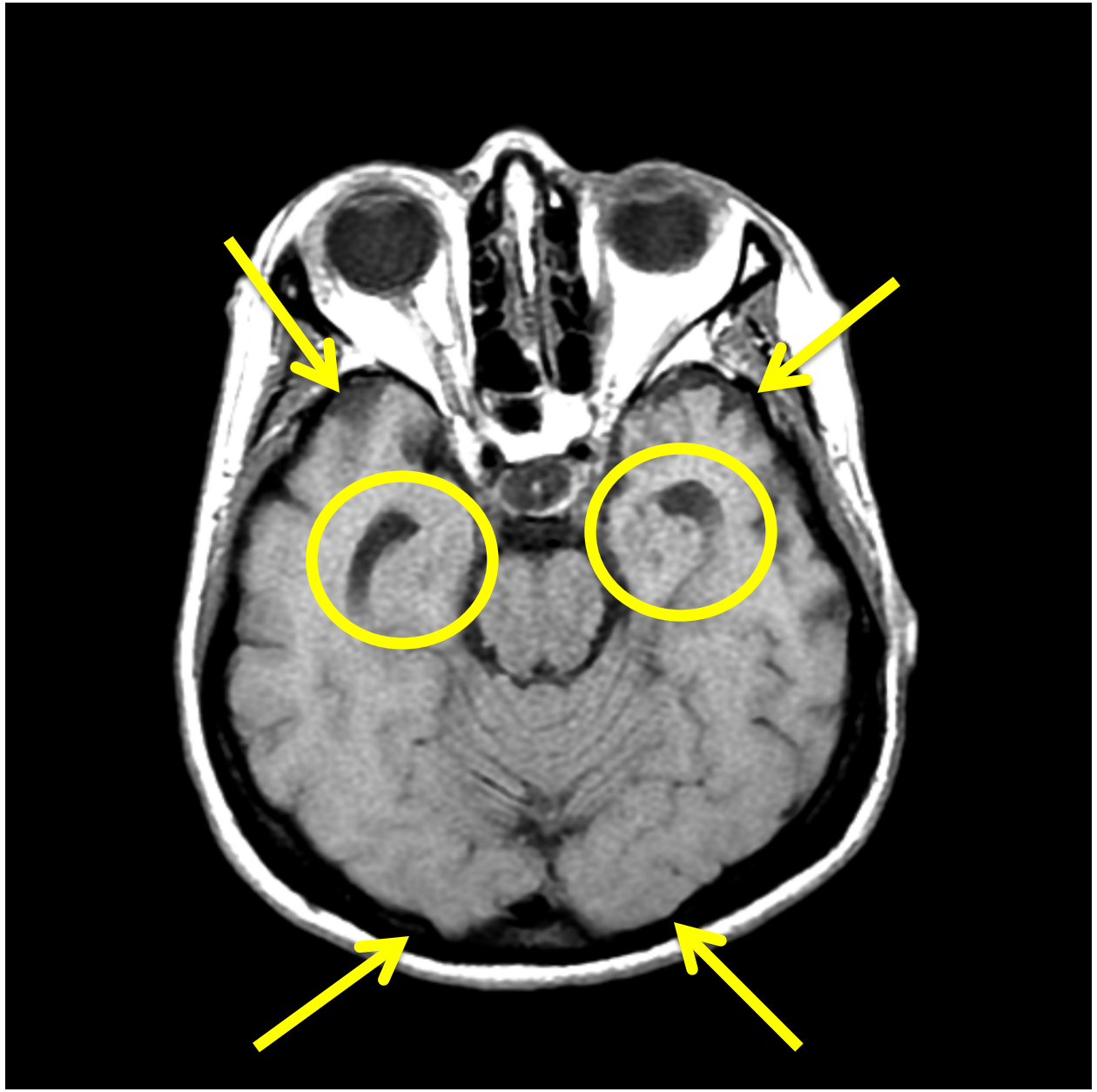


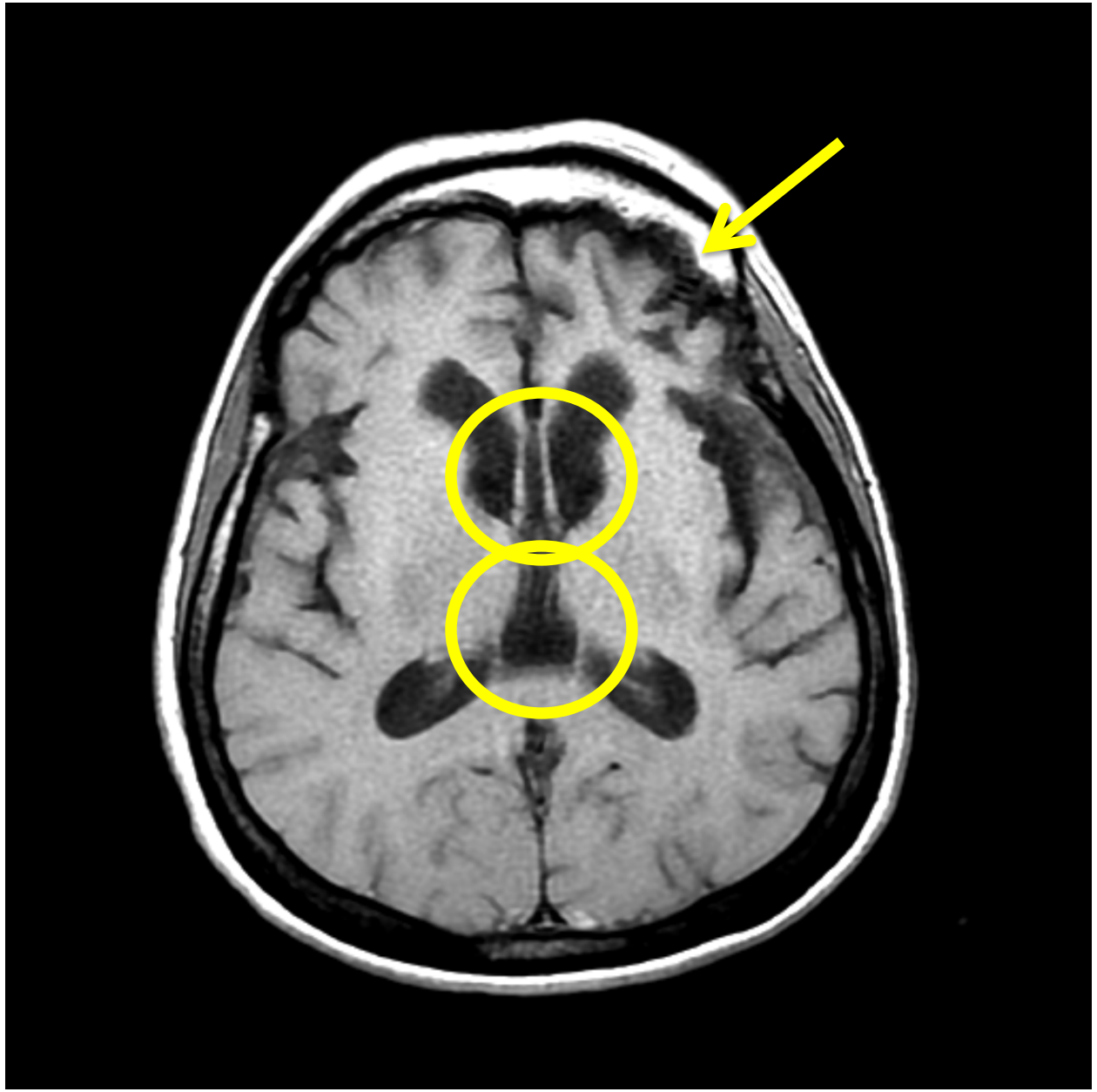
From Budson & Solomon, 2016

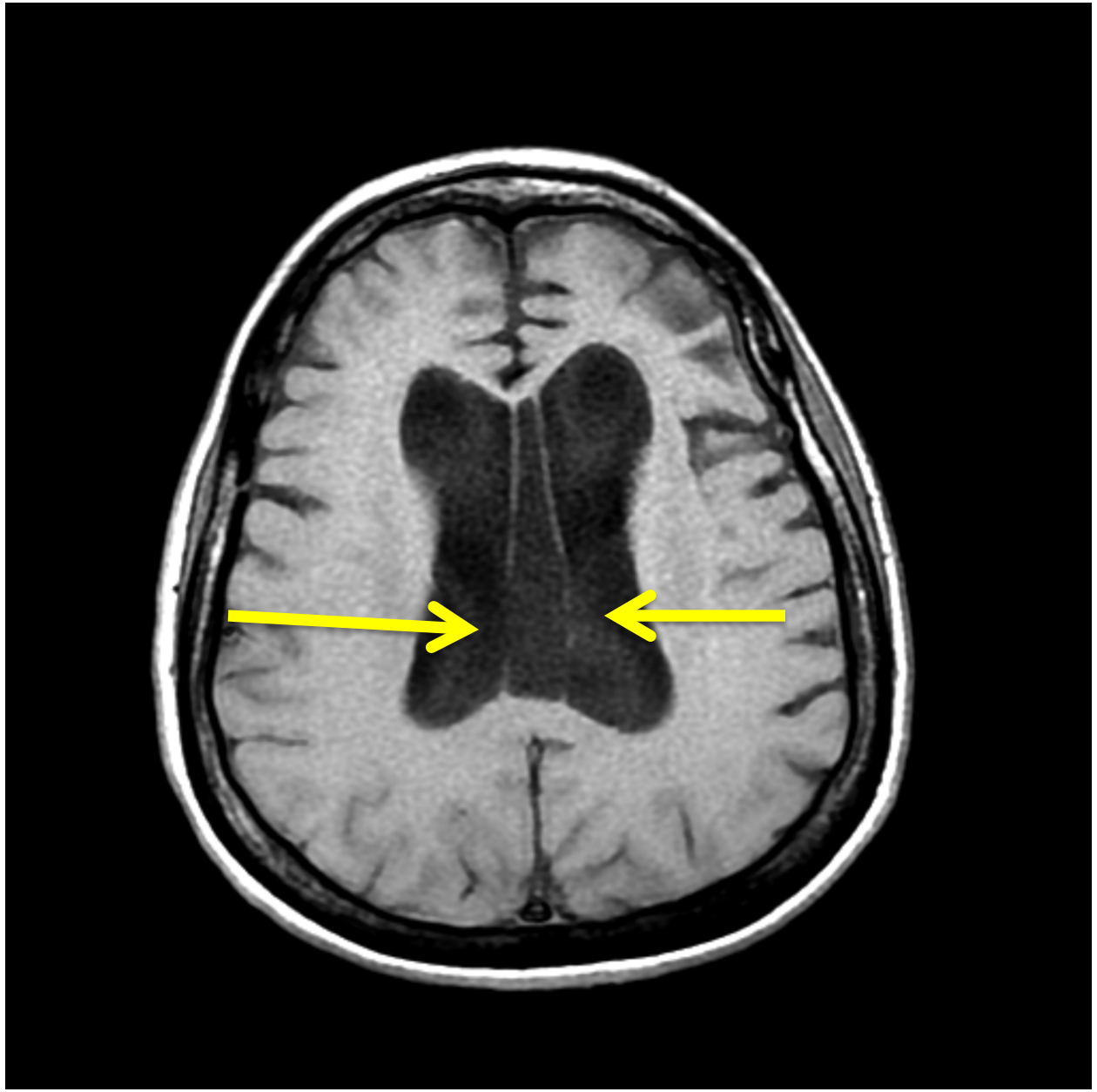
CTE Brief Summary

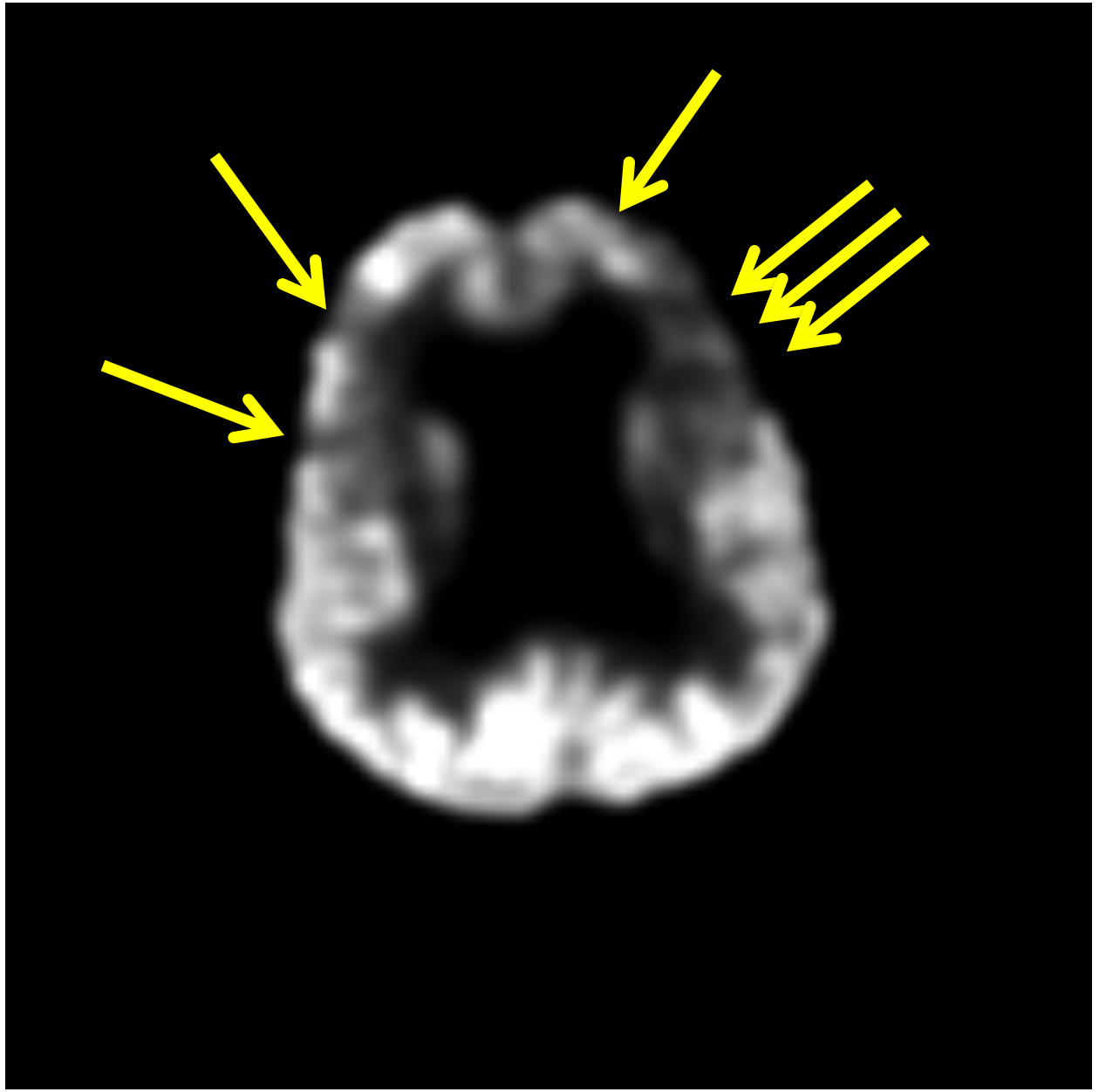
- Caused by multiple impacts to the head
- Characterized by perivascular accumulation of tau irregularly in the depths of cortical sulci
- Two main syndromes (also mixed & dementia):
  - Behavioral/Mood Variant (younger, m=35 yrs)
  - Cognitive Variant (older, m=59 yrs)
- Commonly initial features include: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

T1
MRI
scan







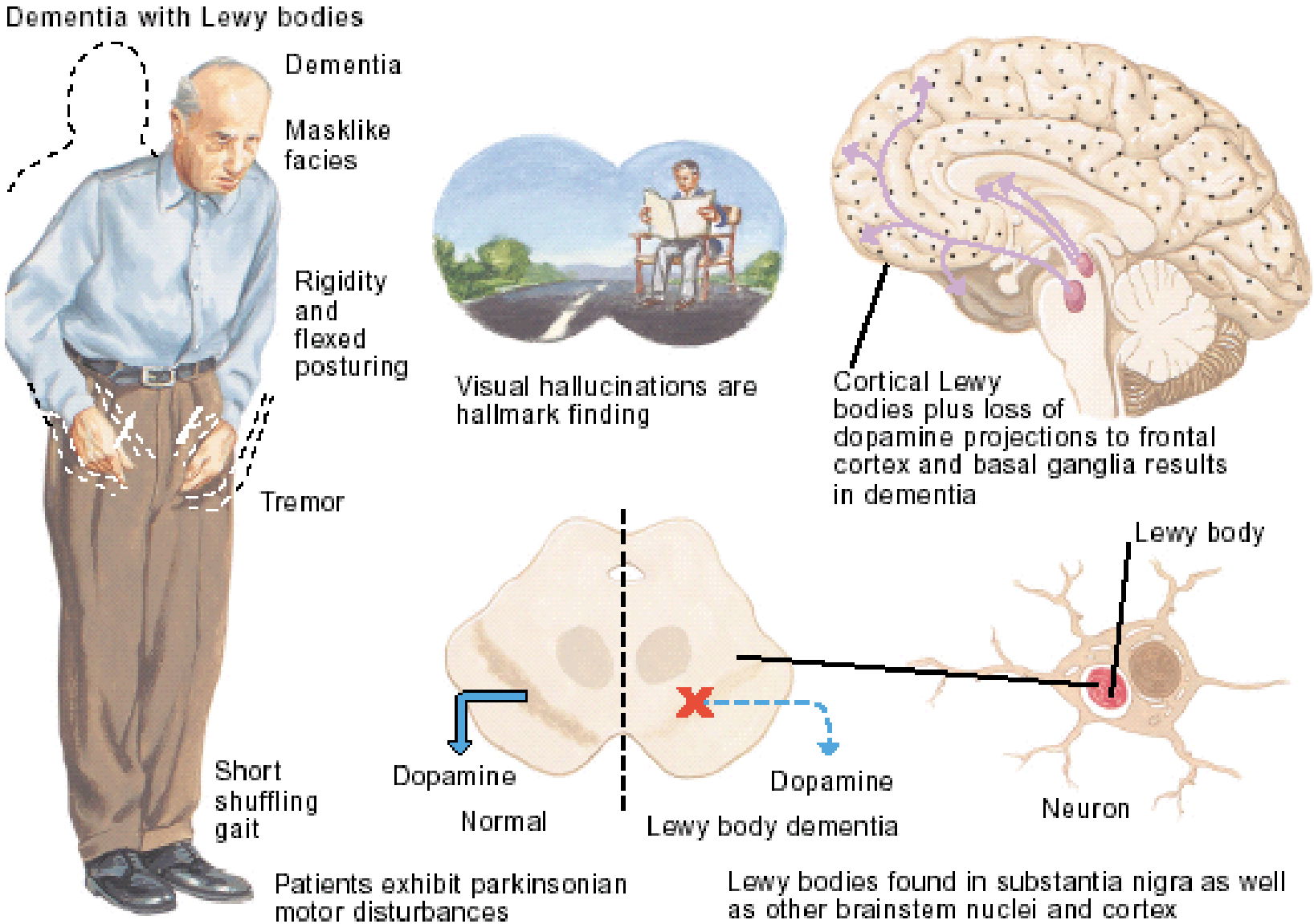


Patient 4

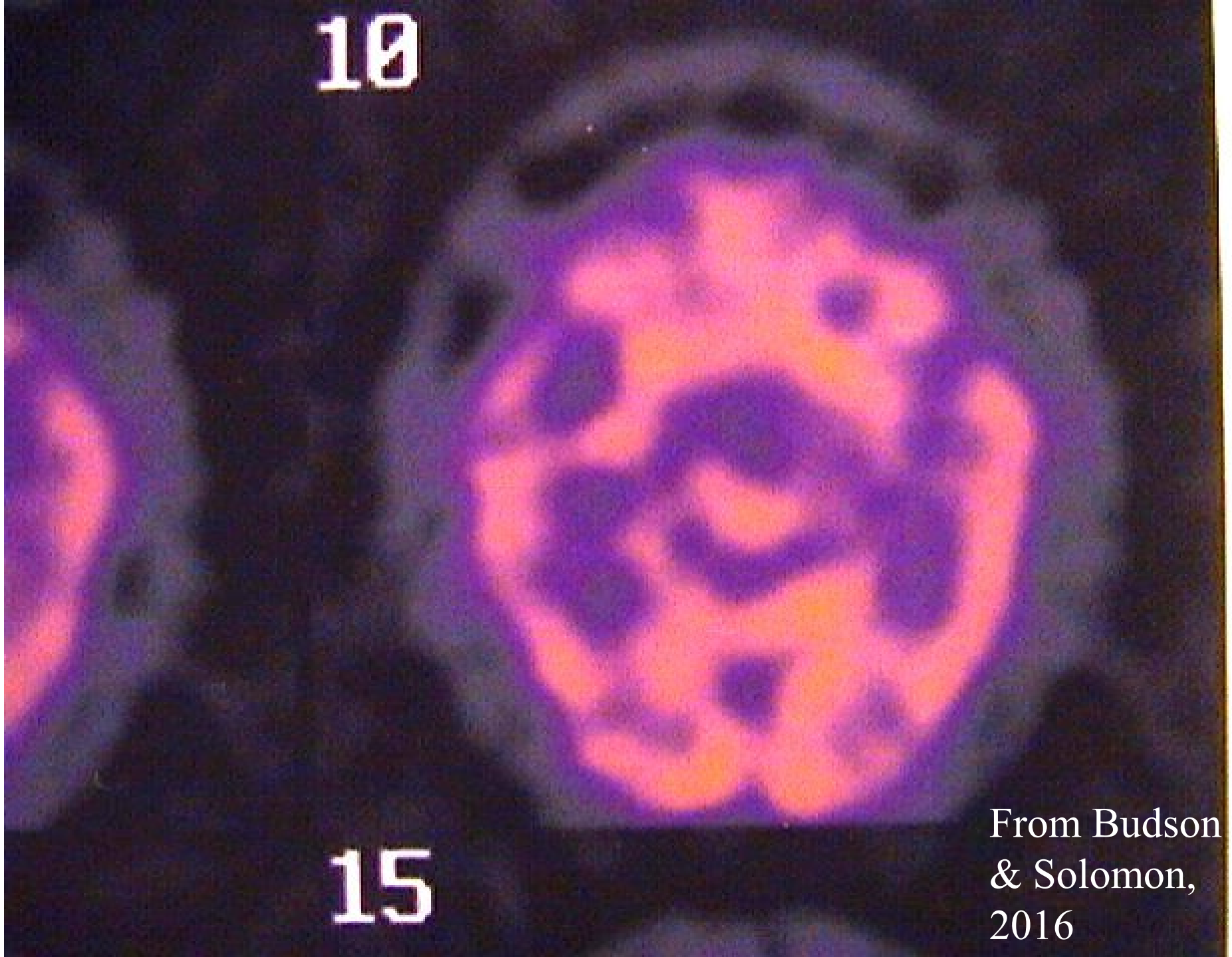
- 65M with memory problems.
- Also Parkinsonism
  - Masked faces, shuffling gait, cogwheeling
- Visual hallucinations of people and animals
- Visual perceptual defects
- Wife complains he is waking her up moving & kicking her in his sleep

Dementia with Lewy Bodies / Parkinson's Disease Dementia

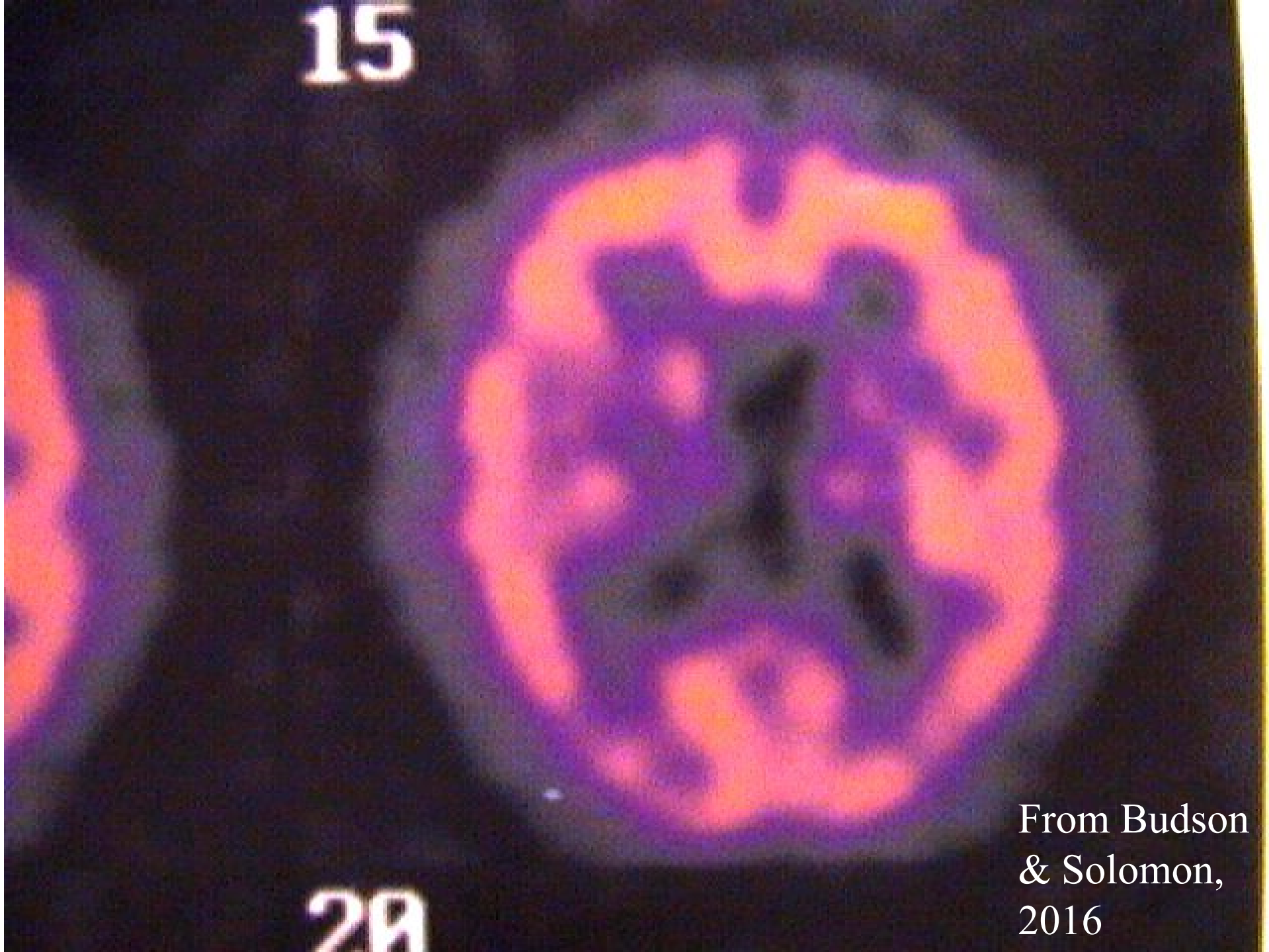
Dementia with Lewy Bodies



From Budson & Solomon, 2016

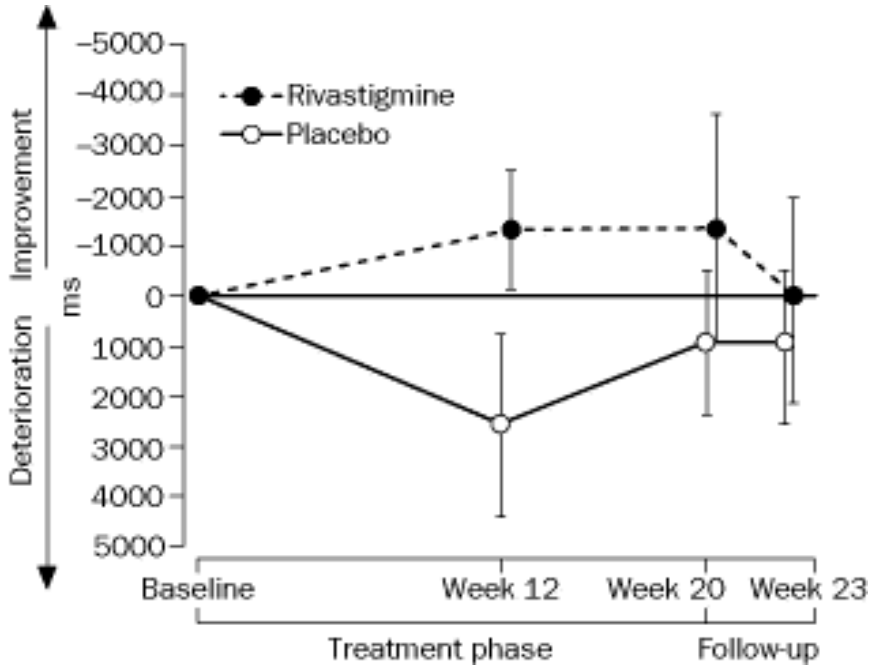


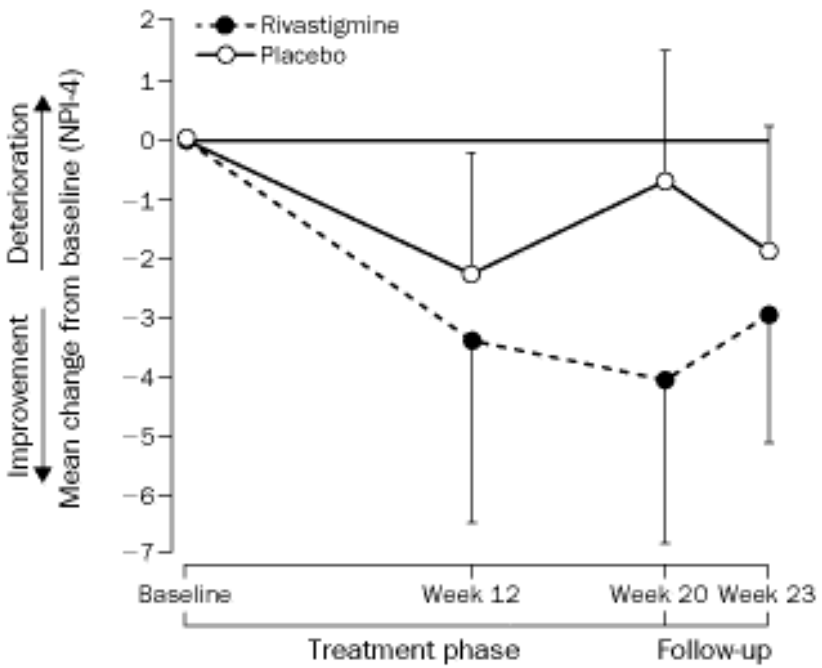
From Budson & Solomon, 2016



From Budson & Solomon, 2016

Rivastigmine in Dementia with Lewy Bodies





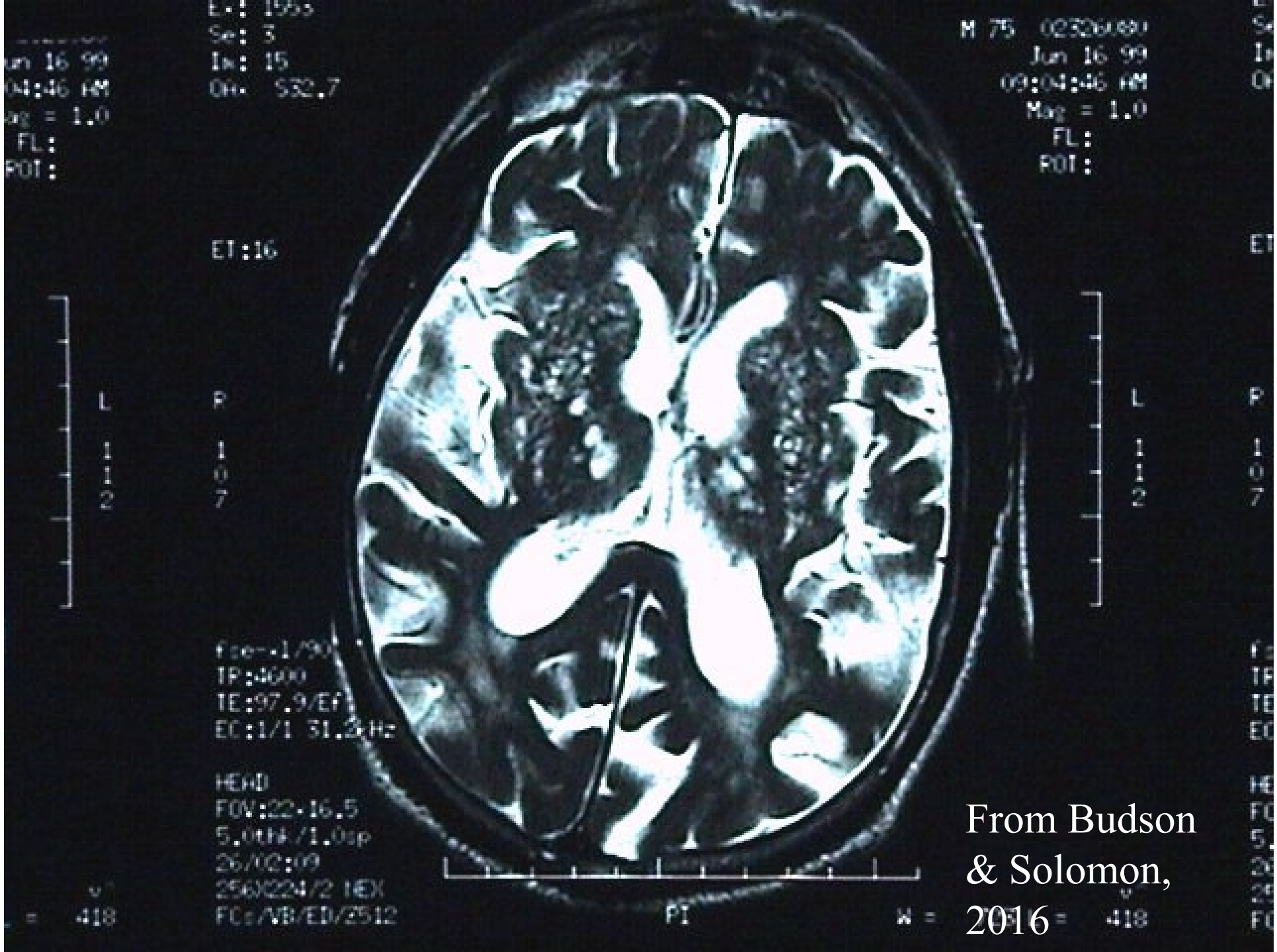
Rivastigmine patch is FDA approved for Parkinson's Disease Dementia

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



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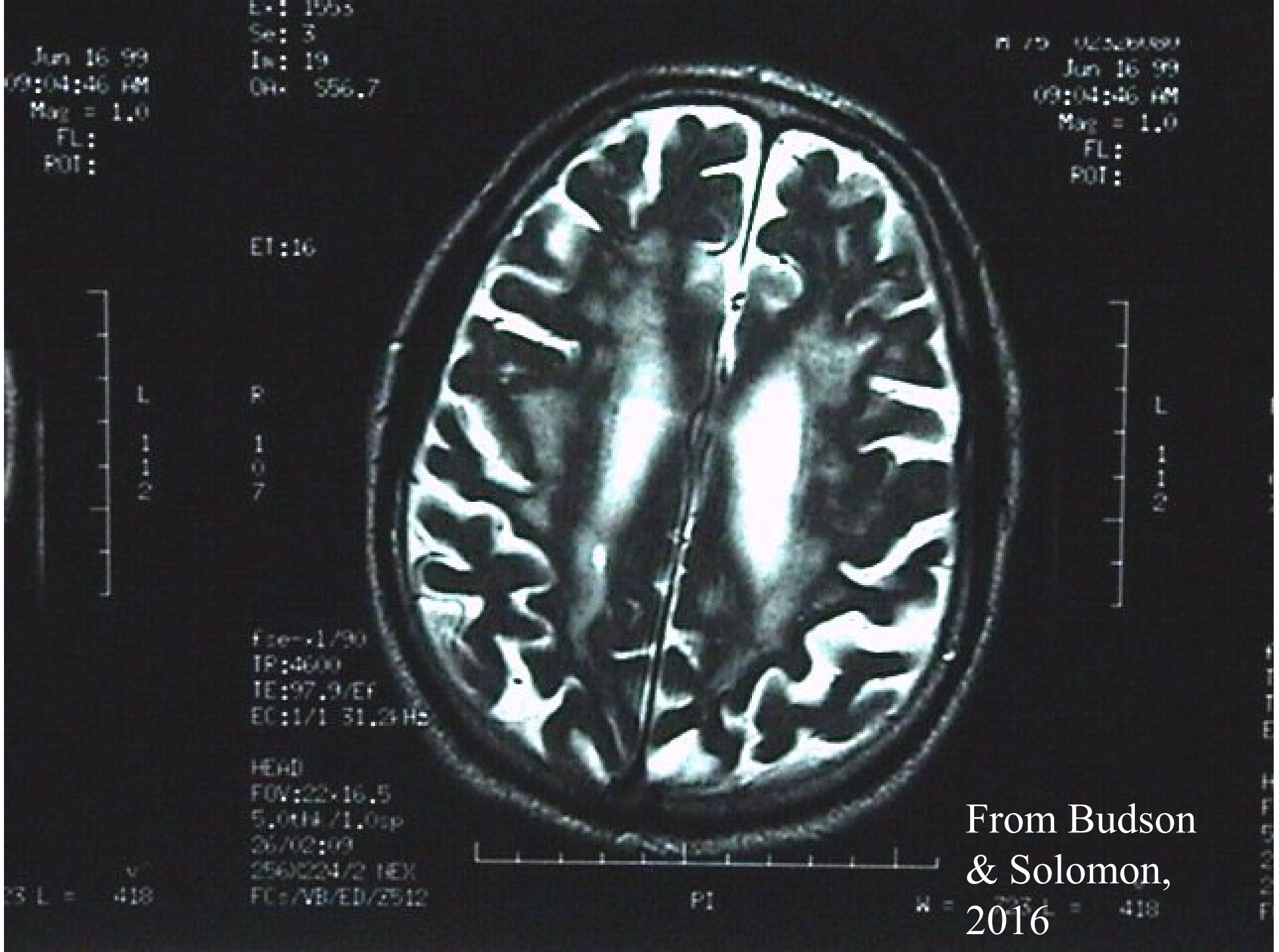
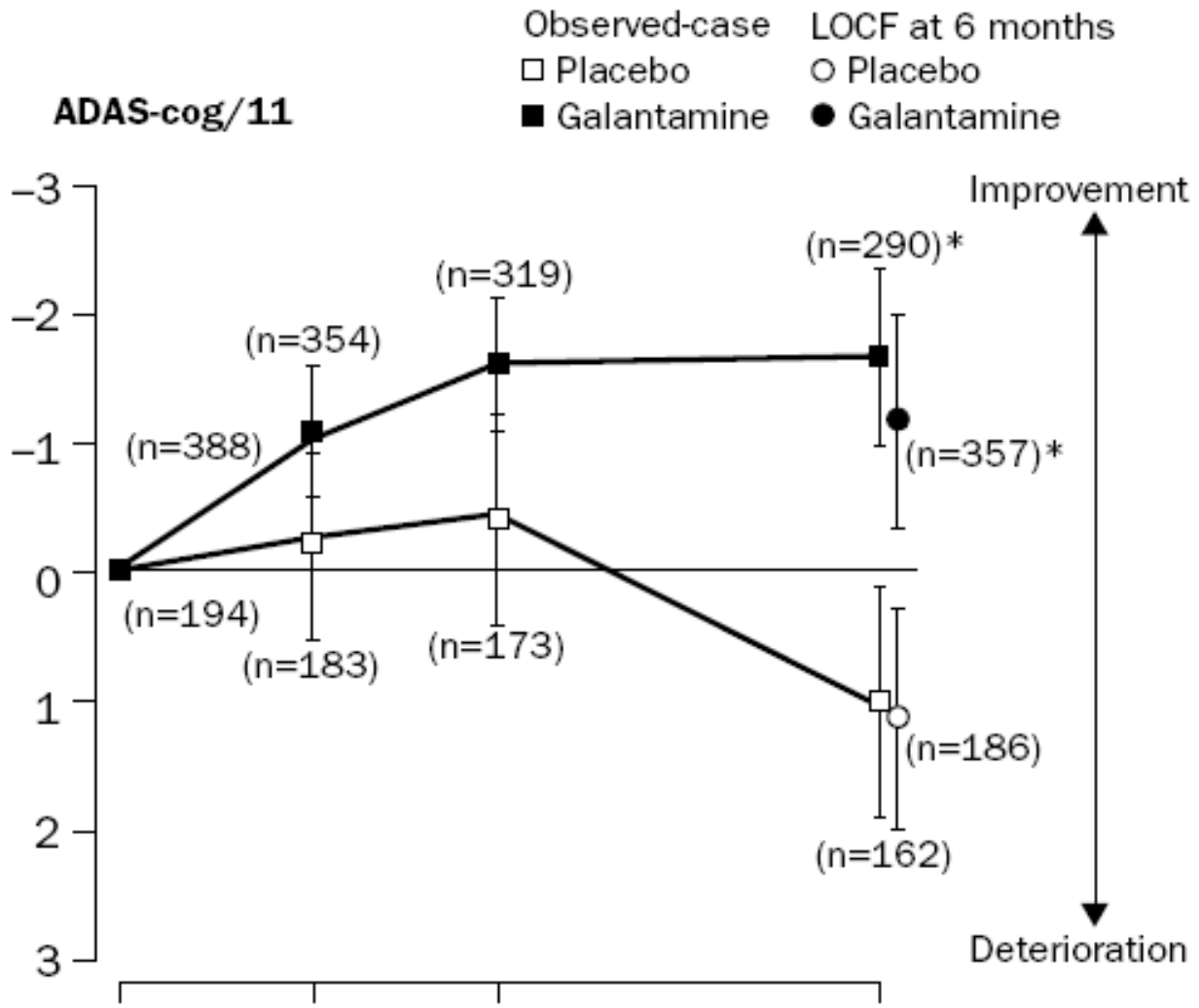


From Budson & Solomon, 2016

Galantamine in vascular dementia



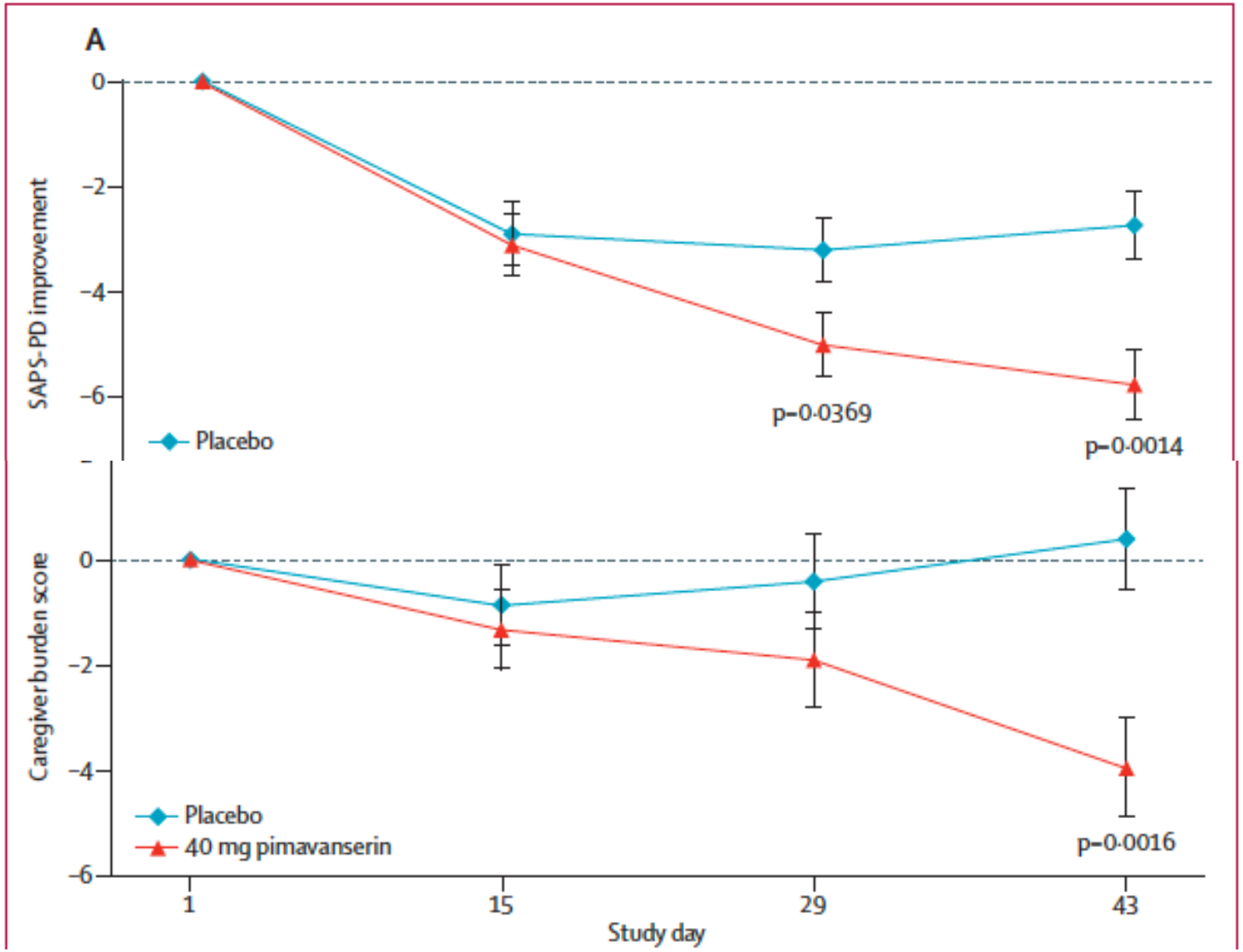
Lancet 2002 359:1283-90

Managing agitation

- Try to determine the underlying cause of agitation
- 4 R's: Reassure, Reconsider, Redirect, Relax
- 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
- Daytime agitation
  - risperidone/Risperdal: start 0.25 mg QD
- Nighttime agitation
  - quetiapine/Seroquel: start 25 mg QHS
- Pimavanserin (Nuplazid) 40 mg QD for PDD
- 20 mg Dextromethorphan HBr/10 mg Quinidine sulfate (Nuedexta)
- Prazosin: start 1 mg, increase 1 mg/wk. Watch BP.

Pimavanserin for psychosis in PDD

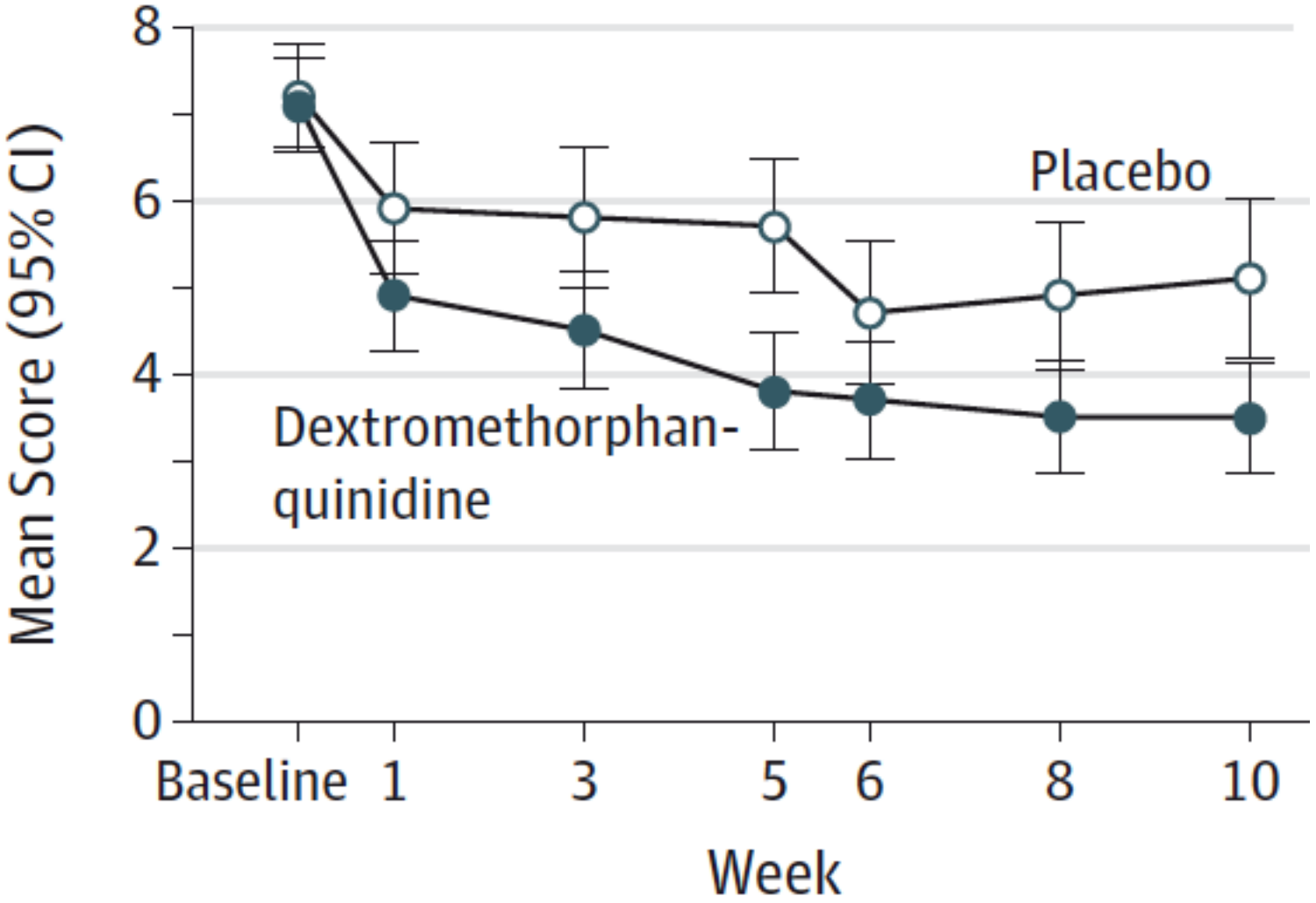
selective serotonin 5-HT2A inverse agonist



Trials on-going in Alzheimer's disease

Cummings et al., Lancet. 2014 383(9916):533-40

NPI Aggression Domain Scores in AD



Weeks 1: 20/10 QD, 2-3: 20/10 BID, 4+: 30/10 BID

JAMA. 2015;314:1242-54

Pseudobulbar Affect (PBA)

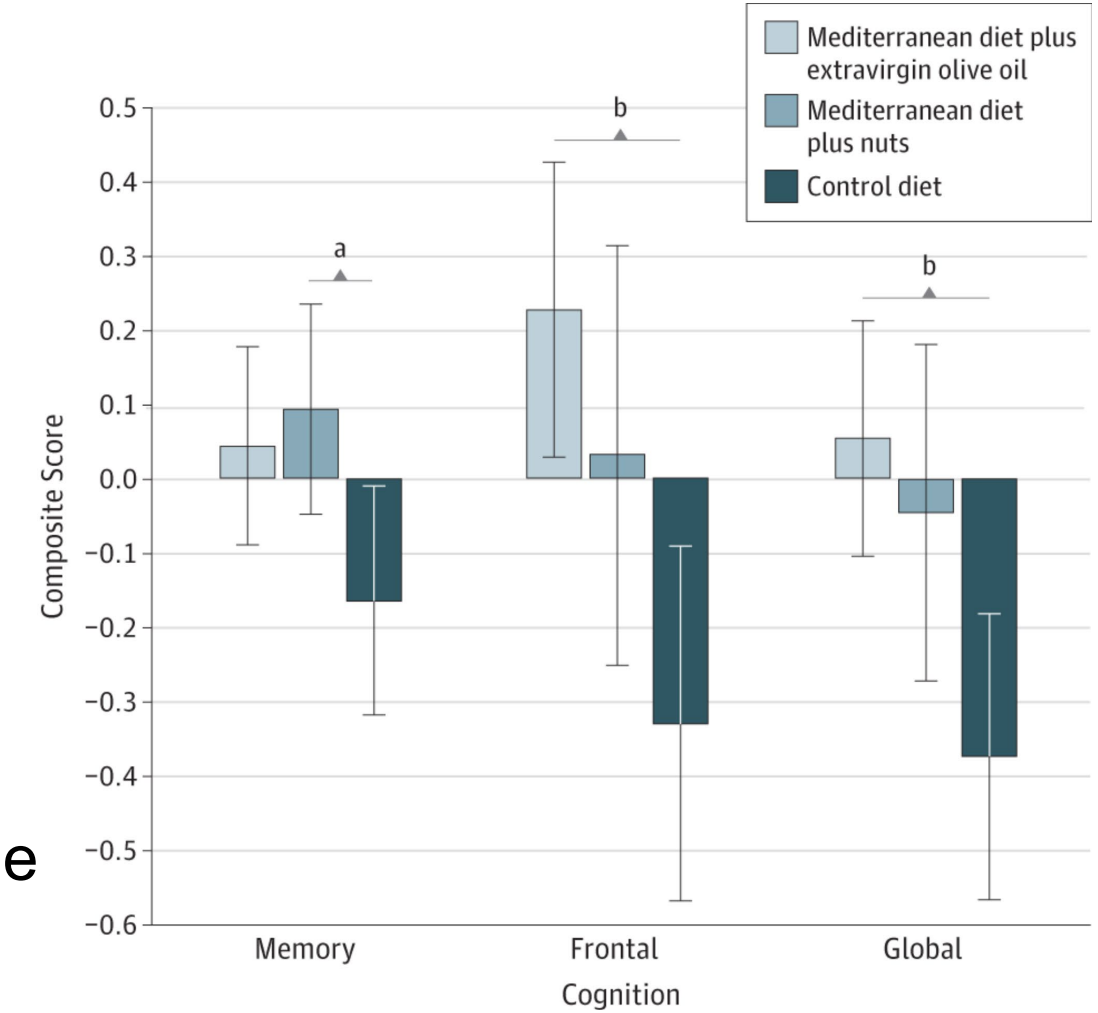
- Crying or laughing for little or no reason.
- Very common in AD, VaD, & other dementias
- New medication FDA approved to reduce PBA:
  - 20 mg Dextromethorphan HBr / 10 mg Quinidine sulfate (Nuedexta)
  - 1 capsule daily x 7 days, then 1 capsule Q12H
  - Common adverse reactions: falls, diarrhea, UTI, dizziness, cough, vomiting, asthenia, peripheral edema, influenza, ⇧GGT, & flatulence
  - Serious side-effects/contraindications from quinidine

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

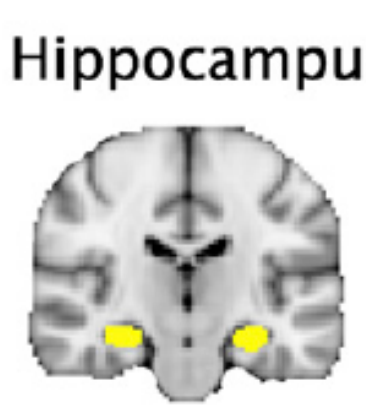
- 334 cognitively healthy adults
- Mean age 67 years
- Randomly assigned
  - Med diet + olive oil
  - Med diet + nuts
  - Control
- Fish, olive oil, avocado, fruit, vegetables, beans, nuts, whole grains, red wine

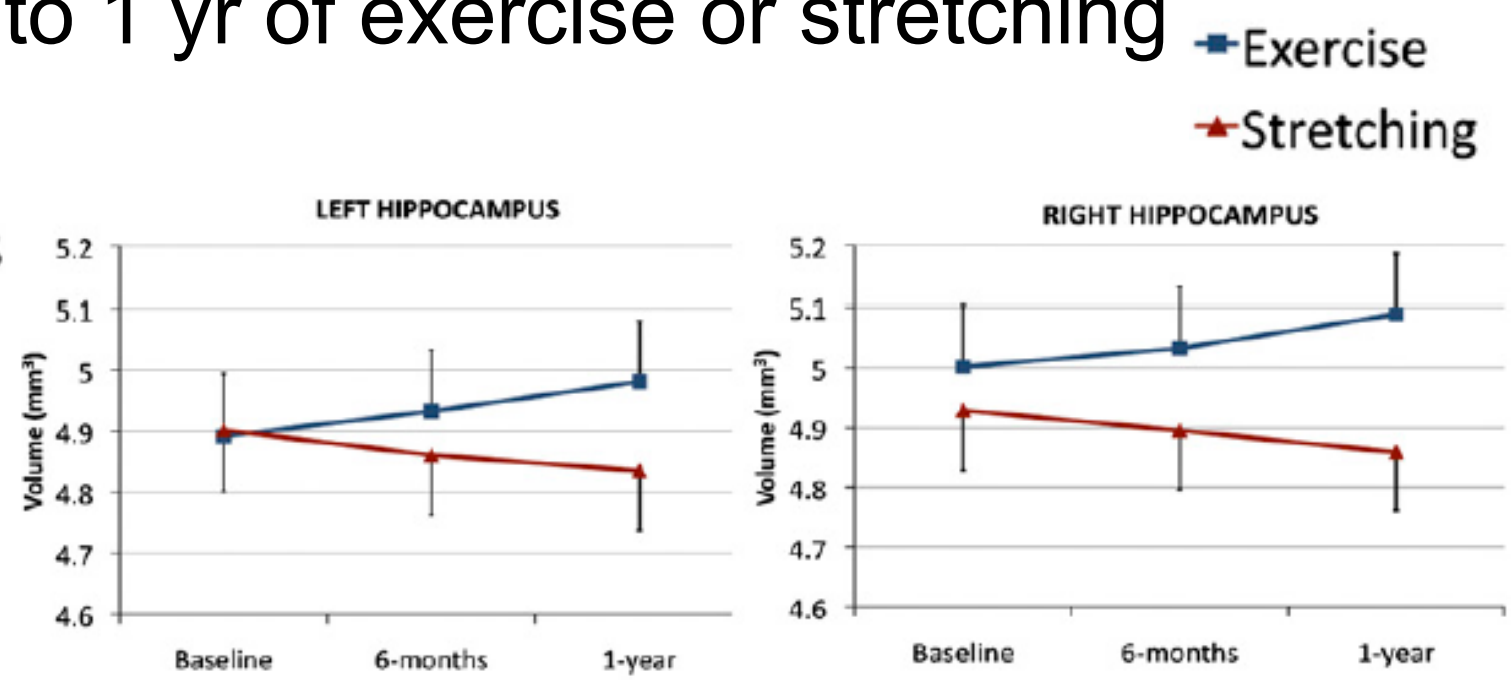


From: **Mediterranean Diet and Age-Related Cognitive Decline: A Randomized Clinical Trial**
JAMA Intern Med. 2015;175(7):1094-1103. doi:10.1001/jamainternmed.2015.1668

Exercise increases hippocampal volume in older adults

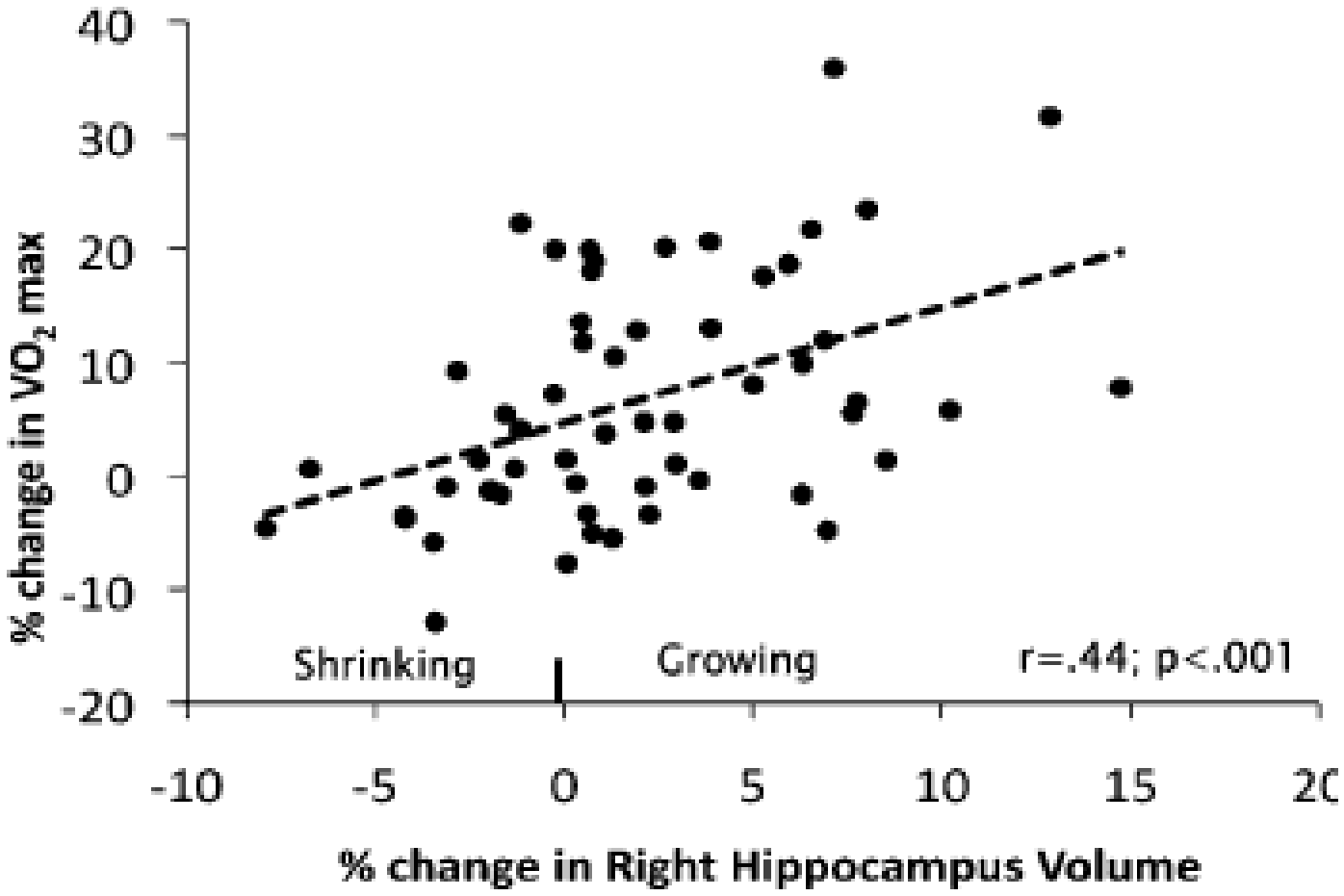
- 120 older adults 55-80, mean 66 years
- Randomized to 1 yr of exercise or stretching





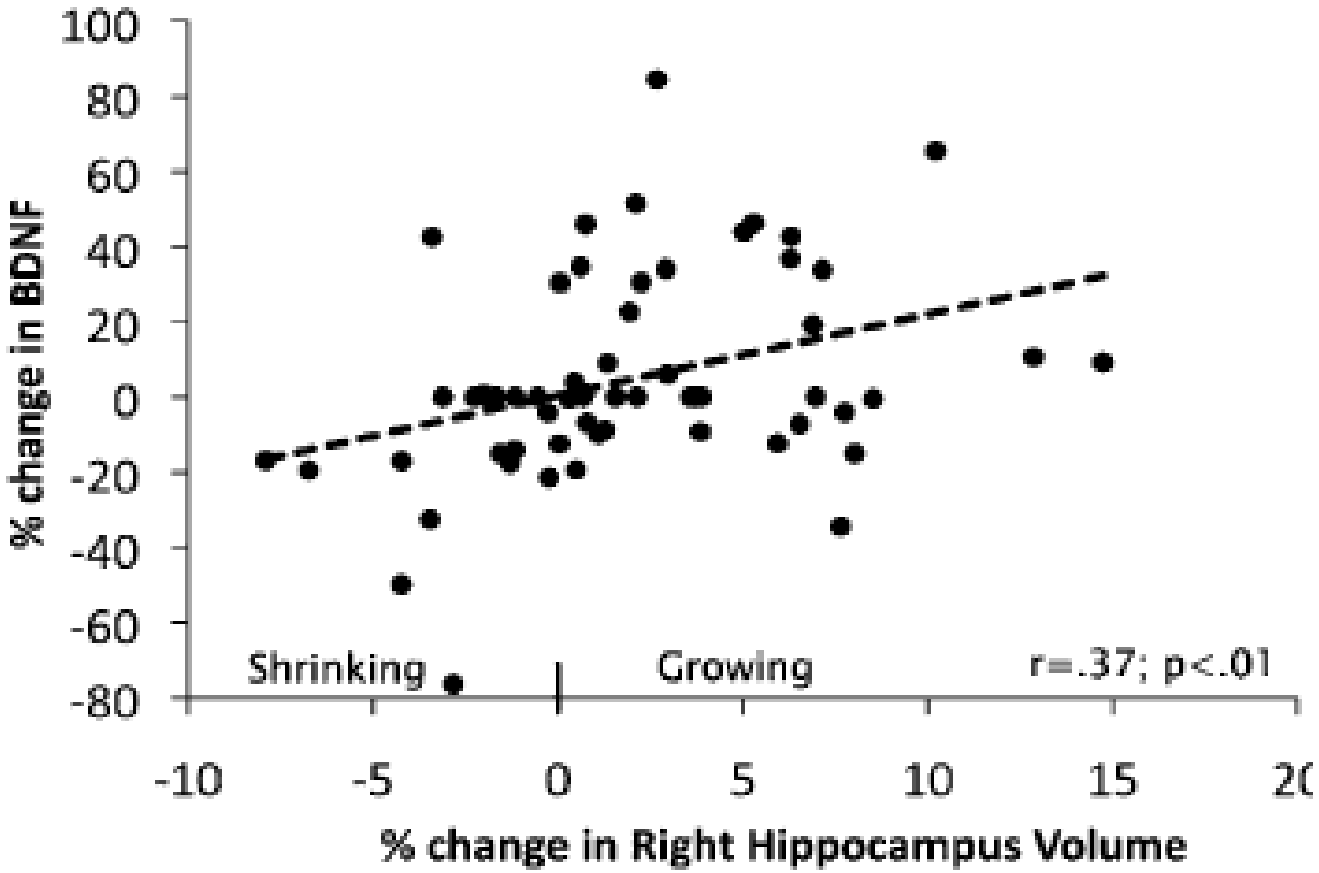
PNAS | February 15, 2011 | vol. 108 | no. 7 | 3017–3022

ΔVO_2 max correlates with Δ hippocampal volume



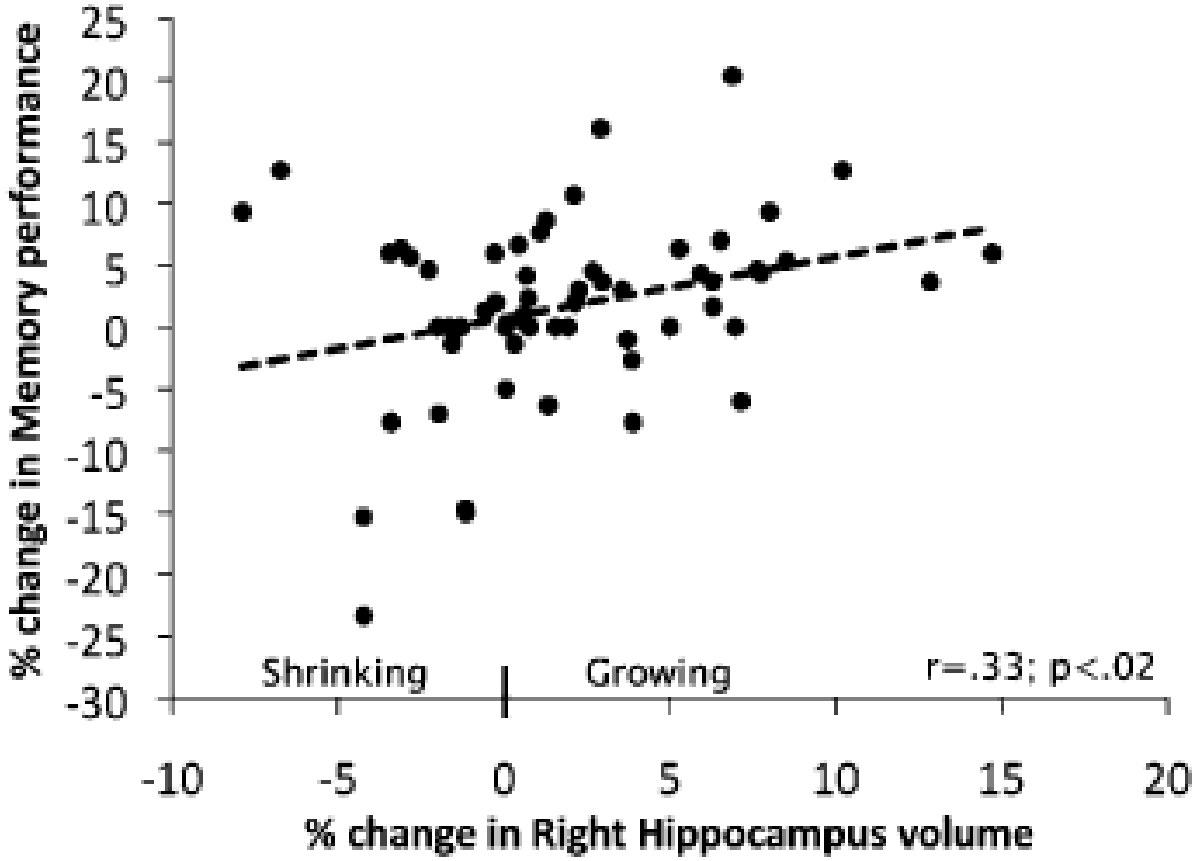
PNAS | February 15, 2011 | vol. 108 | no. 7 | 3017–3022

Δ BDNF 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
- Keep a positive mental attitude

- “Should I do crossword puzzles, doc?”
  - If you want to get better at them…
  - Better than TV…

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 parietal atrophy)
- 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 & mild cognitive impairment (MCI).
- Memantine is only for patients with moderate to severe dementia; watch for drowsiness and confusion.

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