CLINICAL ESSENTIALS OF ALZHEIMER'S DISEASE AND RELATED DEMENTIAS (ADRD)

NAD-RCMAR EVENT

Angela Hanson, MD
Geriatrician
UW Medicine, Harborview Medical Center
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Objectives

- Part 1: Brief overview of prevalence of ADRD, focusing on Alzheimer's disease
- Part 2: How do we work up a patient with cognitive impairment?
- Part 3: A few pearls about management

RESOURCES

- Alz.org
- lbda.org
- Aftd.org
- Memory Brain Wellness Center website:
  - http://depts.washington.edu/mbwc/
- HRSA dementia curriculum:
  - https://bhw.hrsa.gov/grants/geriatrics/alzheimers-curriculum
- Area agency on aging in your county

Objectives

- **Part 1: Brief overview of prevalence of ADRD, focusing on Alzheimer's disease**
- Part 2: How do we work up a patient with cognitive impairment?
- Part 3: A few pearls about management

When does it become dementia?

- Presence of cognitive impairment detected via history taking and cognitive assessment
- Decline from previous level of function
- Interference with the ability to function at work or usual activities
- Exclusion of delirium or major psych disorder
- Distinguish from normal aging

Mild Cognitive Impairment

- MCI: problems with memory, language, judgment, and thinking—problems greater than expected for the age of the person, but less than is required for dementia diagnosis
- “Can still carry out everyday activities”
- Not all MCI progresses to dementia
  - About 10–20% a year will progress
- Treatable predictors (or risk or prognostic factors) associated with MCI include diabetes, prediabetes, metabolic syndrome, hypertension, hyperlipidemia, low dietary folate, chronic alcohol abuse, renal failure, depression

Source: HRSA modules on MCI, (Etgen et al., 2011; Langa & Levine, 2014)

Alzheimer's Overview

- Most common cause of dementia:
- Progressive neurodegenerative disease distinct from normal aging
  - Extracellular amyloid plaques and intracellular tau tangles

- Symptoms:
  - Early memory dysfunction (temporal and hippocampal lobe atrophy)
  - Later, dysphasia and dyspraxia
  - Later still, extensive cortical involvement

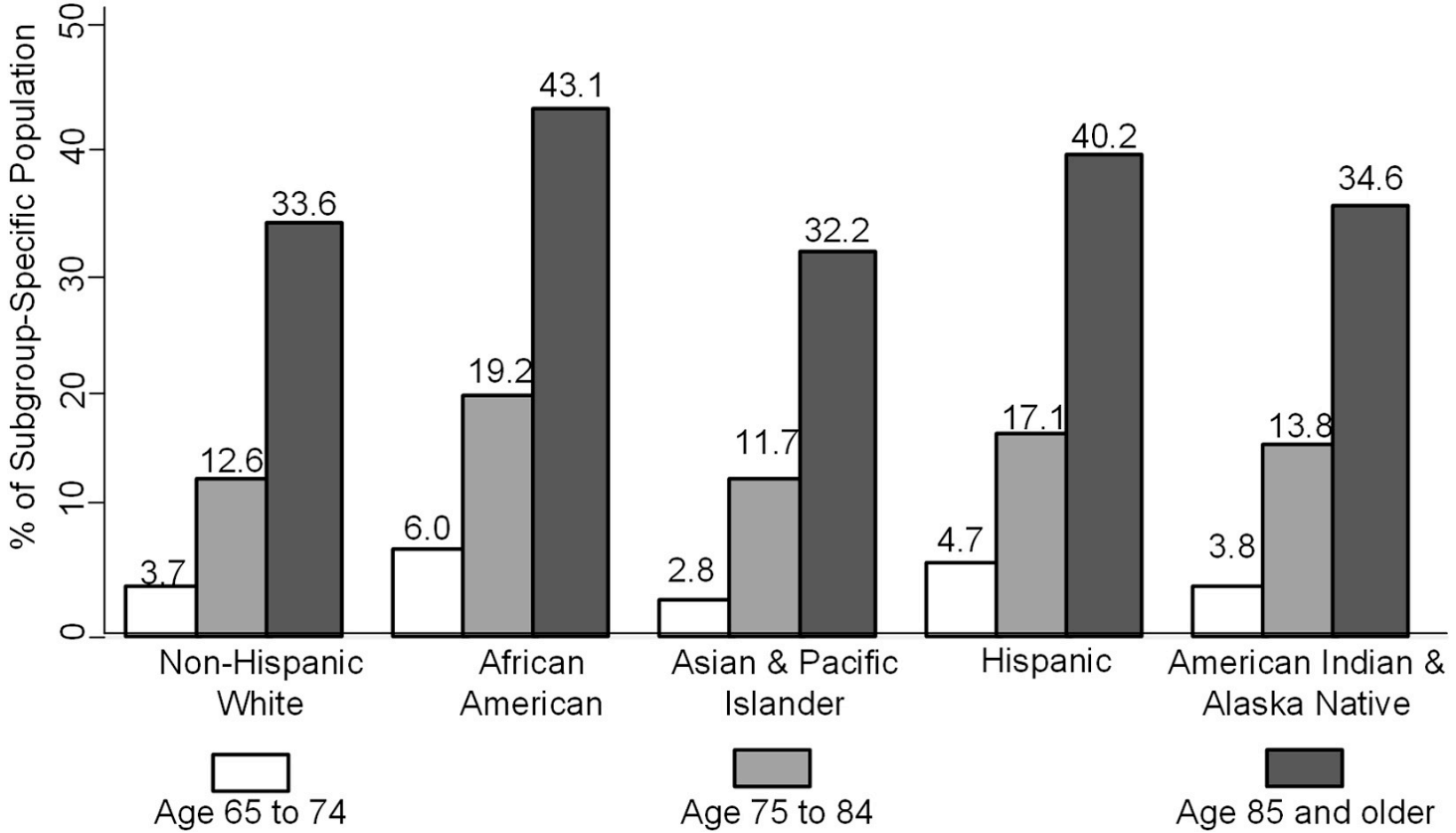
Ellison Neuropathology 3rd Edition 2013

Prevalence of AD

- Burden of ADRD in 2014: **5.0 million adults aged 65 and older (11.5%)**
- Women (13.3%) > men (9.2%)
- Prevalence increases with age:
  - 65-74 years: 3.6%
  - 75-84: 13.6%
  - ≥ 85: 34.6%
- Prevalence by race/ethnicity:
  - Blacks 14.7%
  - Hispanics 12.9%
  - Non-Hispanic whites: 11.3%
  - American Indian/Alaskan: 10.5%
  - Asian/Pacific: 10.1%

Matthews KA, Alz and Dementia 2018

Prevalence of ADRD in USA, 2014



Matthews KA, Alz and Dementia 2018

African Americans and AD risk

- Alzheimer's disease is more prevalent among African-Americans compared to Caucasians
- There is a greater familial risk of Alzheimer's in African-Americans
- Genetic and environmental factors may interact differently to cause Alzheimer's disease in African-Americans (APOE4)
- What role does vascular disease play (high cholesterol, HTN, diabetes)?

Native people and AD Risk

- More research is needed to understand the differences in risk factors/dx/treatment
- Smith and colleagues (2008) reported the prevalence of dementia by DSM-IV criteria to be 27% among Australian Aborigines $\geq$ 65, which is 5x higher than overall Australian population.
  - USA data I presented earlier does not show that same pattern: a lot of variability in the studies
- A couple of studies mention that the Alzheimer's risk gene APOE4 was not a risk factor for AD in the Yoruba population in Africa or in those with Cherokee ancestry

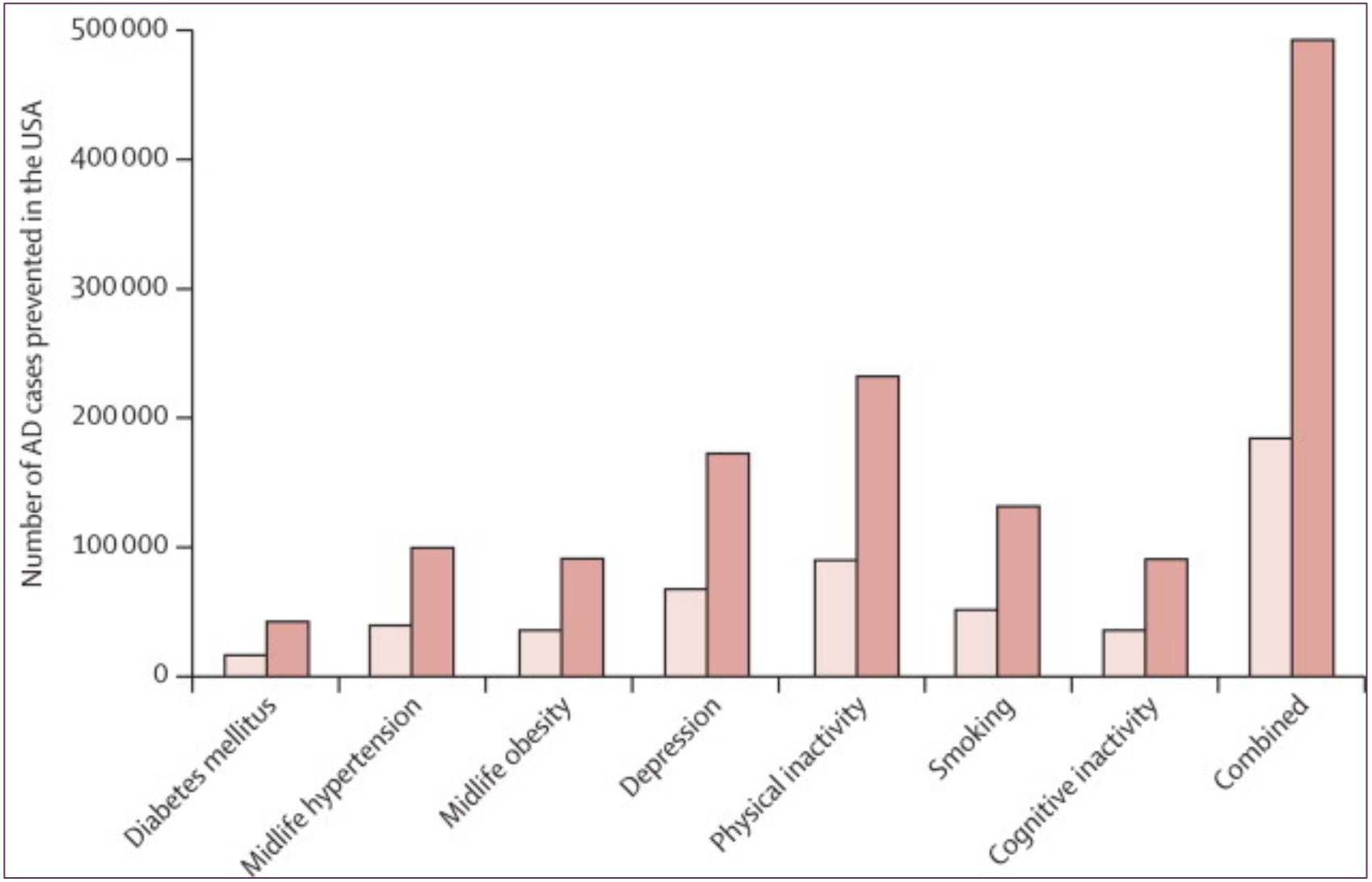
Arch Neurol 1996, Am J Geriatr Psychiatry 2006

Risk Factors for AD in the USA

- 2011 study by Barnes and Yaffe
- What they did: Derived a list of risk factors, based on population studies
  - Diabetes
  - Hypertension
  - Obesity
  - Current smoking
  - Depression
  - Cognitive inactivity
  - Physical inactivity

Barnes, Yaffe. The Lancet Neurology, Volume 10, Issue 9, 2011, 819 - 828

AD Cases Preventable: USA



Risk Factor Reduction and AD

- Up to half of AD cases are potentially attributable to modifiable risk factors
  - Large caveat: Risk factors are not independent
- USA: Smoking and physical inactivity
- Worldwide: Low education
- “Education and mental stimulation throughout life are believed to lower the risk of AD...by helping to build a cognitive reserve that enables individuals to continue functioning at a normal level despite experiencing neurodegenerative changes”

Barnes, Yaffe. The Lancet Neurology, Volume 10, Issue 9, 2011, 819 - 828

PART 1 SUMMARY

- Age and APOE4 are two ‘unchangeable’ risk factors (APOE4 might not increase the risk of AD equally in all populations)
- Modifiable risk factors is something we all share as Americans and can work on together
  - Reducing smoking, increasing exercise and treating high blood pressure can reduce dementia and Alzheimer’s risk

OBJECTIVES

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- **Part 2: How do we work up a patient with cognitive impairment?**
- Part 3: A few pearls about management

Mr. Jones

- 75 year old man with hypertension, heartburn (GERD) new to clinic
- He wants to discuss his medications, seasonal allergies, and heartburn symptoms
- Triage vitals: BP 160/90
- Near end of visit, as you are prescribing an additional blood pressure med, his daughter says, “I’m worried about my dad’s memory, he might not be taking his medications properly. Do you think he has dementia?”
- What do you do?

Contributors to Cog Impairment

Medical disease: Diabetes, ↓ glu, ↓ Na, thyroid, OSA

Neurologic disease: AD, TBI, LBD, stroke

Medications: anti-cholinergics, sedatives, EtOH, MJ

Psychosocial: Caregiver and social supports (or lack of)

Psychiatric: Depression, anxiety, poor sleep

Tools for a dementia provider

- History
- Physical Exam
- Cognitive exam
  - Short tests you can do in clinic
  - Longer tests – neuropsych or speech/cog eval
- Blood work
- Imaging/EEG
- Spinal fluid analysis
- (Which tests depends on the individual patient)

Mr. Jones has cognitive impairment...now what?

- Look for reversible causes (less likely)
  - Rare but important workup: B12, TSH, (RPR, HIV)
  - Drugs/EtOH/Medications
  - Urgent imaging or delirium workup needed?
- Look for contributing factors (LIKELY)
  - Mood disorders, medical disorders, medications
- Ultimately the question is...**does this patient have a neurodementing illness**?
  - No one test rules dementia in or out
  - It's ok to diagnose over time

Short Screening Tests

Test	Items	Time	Sen/Spec	Notes
Mini-Cog	2 (6 points)	3 min	76/89	Clock + recall
AD8	8 items	3-5 min	74-84/80-86	Caregiver assessment only
GPCOG	6 items	5-6 min	85/86	Cog test + caregiver assessment

- There are lots of other tests...these are some recommended ones
- Hanson's pearl: Mini-Cog or GPCOG preferred as they test >1 domain and the clock draw is very visual for families (if abnormal)
- These can all be administered by non-physician staff (LPNs, MA, etc)

Alzheimers Dement. 2013 Mar;9(2):151-9

Int J Geriatr Psychiatry. 2010 Feb;25(2):111-20

(Longer) tests: Still do-able in clinic

Test	Items	Time	Sen/spec	Notes
MoCA	12 (30 points)	10-15 min	90% MCI, 100% AD (spec=90-94)	Can detect MCI, less biased for cultural, education level
Short Blessed	6 (12 points)	6-8 min	82/88	Visually impaired Validated in ER
RUDAS	6 (30 points)	10-15 min	89/98	Less affected by education level, language.
SLUMS	30 points	10-12 min	?? [Improved over MMSE]	Validated in veterans
CDIS	32 cog items, 26 cv	30 minutes	Brief version has 7, 6 items	Increasingly validated and studied in several world populations

Alzheimers Dement. 2013 Mar;9(2):151-9

Int J Geriatr Psychiatry. 2010 Feb;25(2):111-20

NATIVE PEOPLE AND DIAGNOSIS

- “Our instrument, The Community Screening Instrument for Dementia (CSID) was developed during the course of the Cree studies to provide a culturally fair, reliable, and valid screening instrument for dementia, which could be used in the culturally, linguistically, and educationally distinct Cree and English-speaking populations of Manitoba.”

Am J Geriatr Psychiatry 2006; 14:480–488

SCREENING TESTS IN SPECIAL POPULATIONS

- Visual impairment
  - MoCA without the vision questions: 63% sens for MCI, 94% sens for AD, 98% spec AD (≥ 18/22 questions is normal)
  - Short Blessed test, AD8 alternatives
- Hearing impairment
  - Ensure hearing aids in, pocket talker
  - AD8: caregiver. Some tests have a written version (RUDAS)
- Non-English speaking patients
  - mocatest.org : translated in 37 different languages
  - CDIS developed in Cree-speaking population, has a short and long version. RUDAS also validated in several populations
  - Caveat: different words in *English* score differently, so interpret test scores with caution
- Avoid MMSE as screening: better alternatives

Neuropsych testing

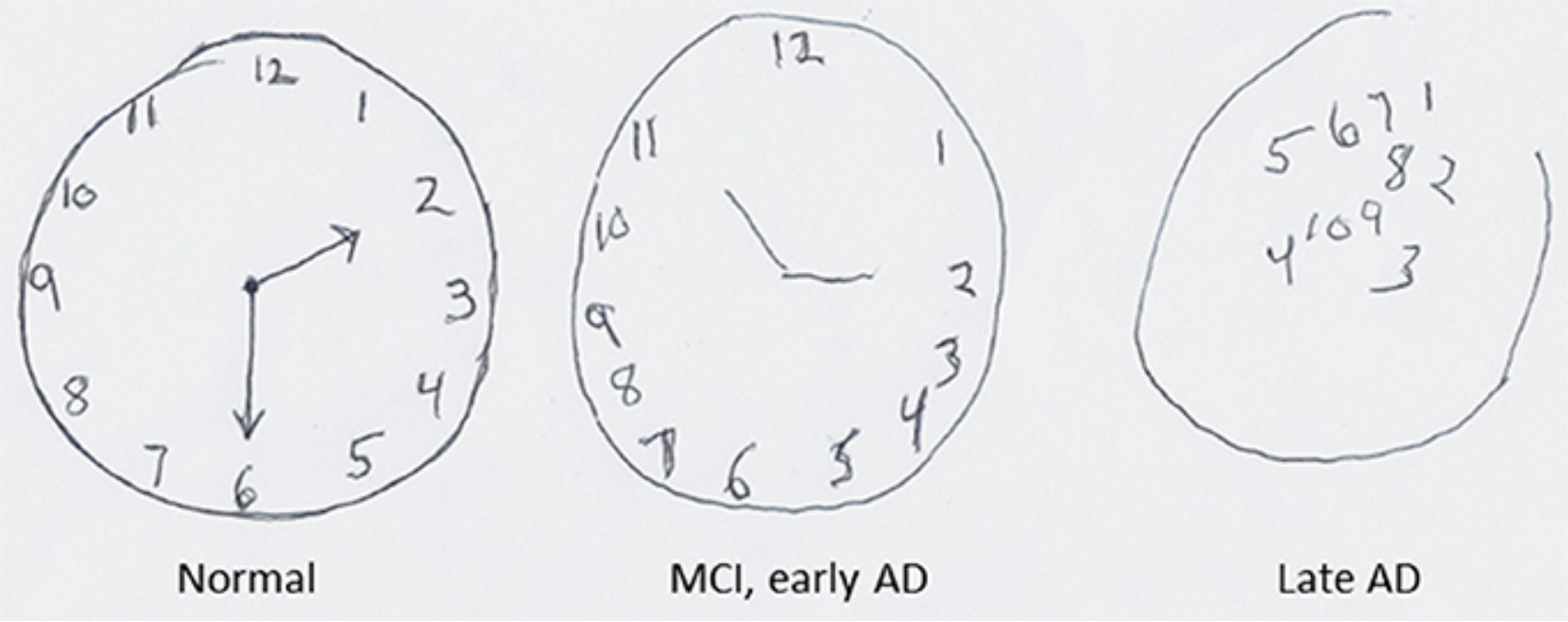
- 3-4 hours of history and cognitive testing
- Much more information about the specific domains affected
- Can compare scores to age and education-adjusted norms
- Identify strengths and weaknesses for patients

Imaging

- Head CT: Can look for big strokes, obvious findings
- Brain MRI much more sensitive and can see a fuller picture of the brain, more subtle findings
- PET scans: tracers for glucose, amyloid
- Be aware that an MRI in early stage dementia might appear ‘normal’ because atrophy hasn’t happened yet

Mr. Jones: Mini-Cog

- Mr. Jones struggles with the clock draw portion, and draws a clock similar to the middle one below:
- He recalls only 1 of 3 words



Causes of Dementia [in older adults]

- #1:
  - Alzheimer's disease: 60-70%
- #2 & 3:
  - Lewy Body Dementia/Parkinson Disease Dementia and Vascular Dementia, in some order (depending on study)
- Frontotemporal dementia
- TBI
- EtoH related dementia
- Normal Pressure Hydrocephalus
- Rare cases of rapidly progressive (see next slides)
- **Mixed etiologies common (esp in older adults)**
- Diagnosis will change management/prognosis

Things don’t always match up...

Clinical diagnosis

- What domains are affected?
- What are the symptoms ?
- Age and rapidity of onset?

Pathologic diagnosis

- Plaques and tangles (AD)
- Tau only (FTD/TBI)
- Lewy Bodies
- Vascular strokes/damage

Diagnosis of Alzheimer's Disease

- Three stages of AD:
  - Pre-clinical (research definition)
  - Mild Cognitive Impairment (mild neurocognitive disorder, DSM-V)
  - Alzheimer's Dementia (major neurocognitive disorder, DSM-V)
    - Probable
    - Possible
- Rare < age 60 (unless familial)

NIA/AA Diagnostic Guidelines for Alzheimer's Disease

Overview of Alzheimer's disease

- Early onset AD (FAD): <5% of all AD: autosomal dominant inheritance, onset 30s-60s, genes involved in amyloid processing
- Late onset AD (LOAD): Onset >60s typically
  - Increased in individuals with the E4 allele of the APOE gene: lipid transport protein
- Extracellular amyloid plaques, intracellular tau tangles, neurodegeneration
- Other pathologies: Inflammation, synapse loss, mitochondrial dysfunction

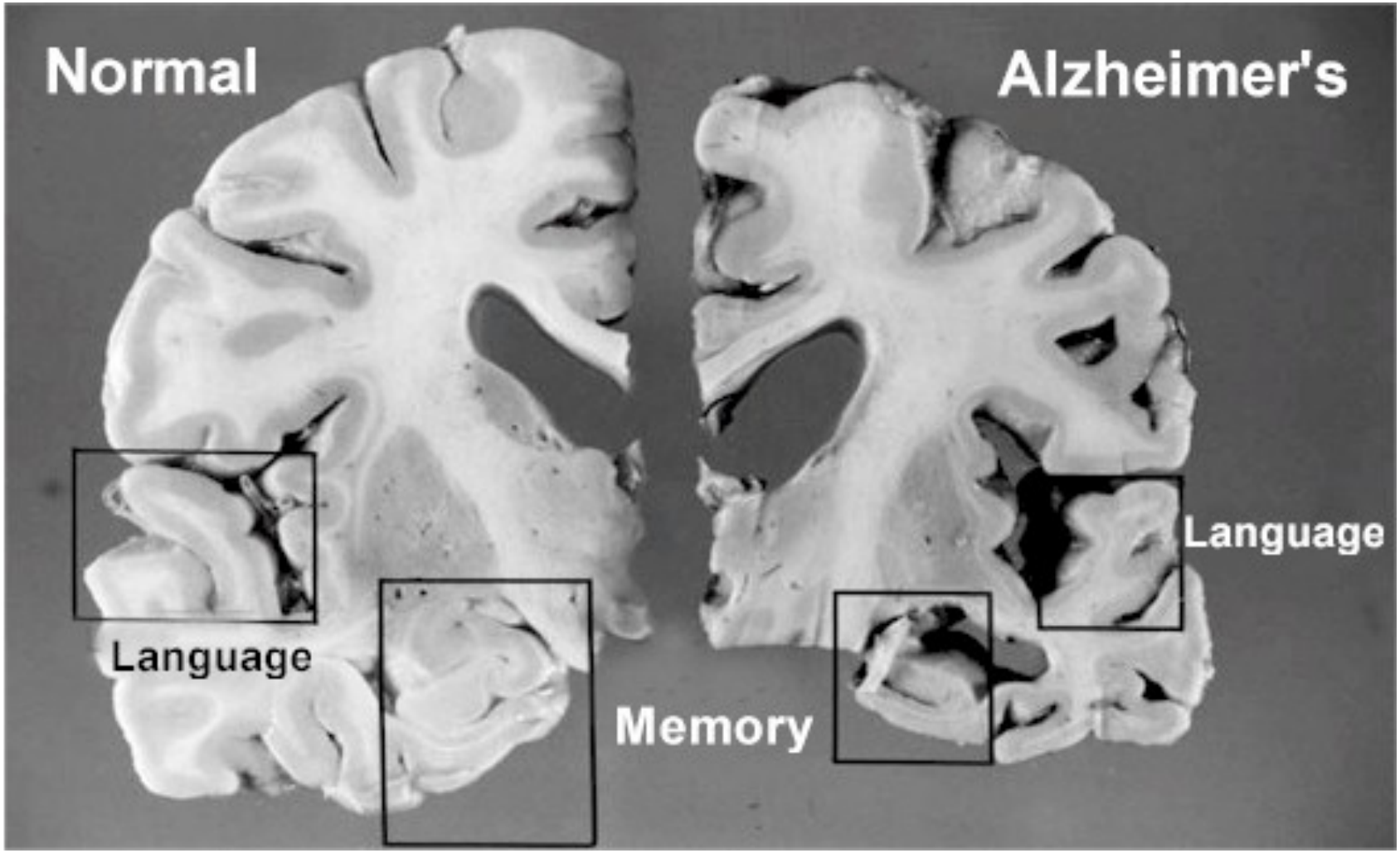
Probable Alzheimer's Dementia

- Interference with work, usual activities
- Decline from previous level of function
- Sx not better explained by delirium, stroke, etc
- Insidious onset and progressive course
- Objective cognitive impairment, at least 2 domains:
  - Impaired ability to acquire and remember new information (most common first symptom: "amnestic" presentation)
  - Impaired visuospatial abilities (predominant in PCA variant)
  - Impaired language functions (predominant in logopenic variant)
  - Impaired reasoning/handing of complex tasks, poor judgment
  - Changes in personality, behavior, or comportment

General dementia

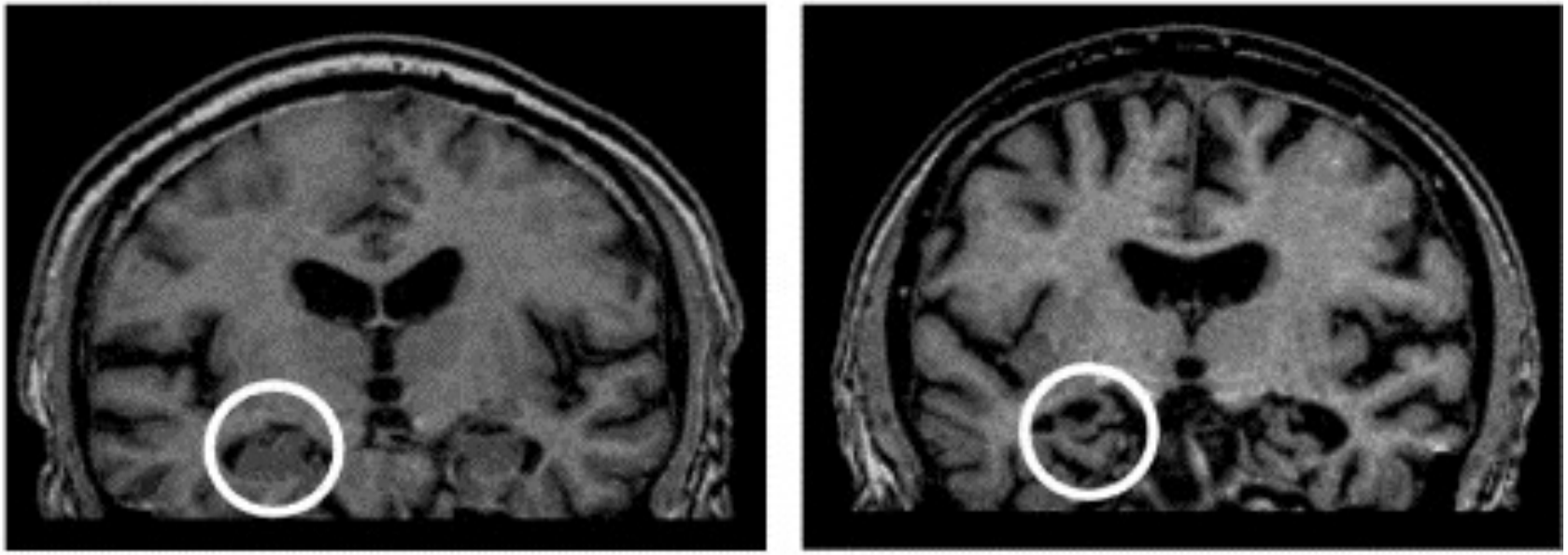
NIA/AA Diagnostic Guidelines for Alzheimer's Disease

Hippocampal Atrophy in AD



Hippocampal Atrophy in AD

(A) Hippocampus



Normal

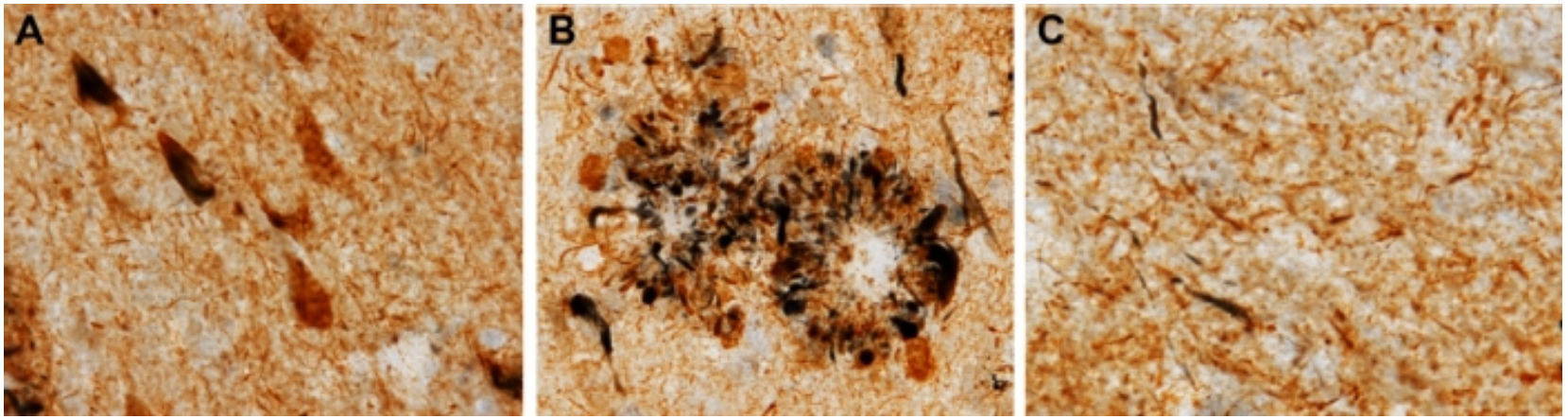
Severe Atrophy

http://radiopaedia.org/cases/

neurofibrillary tangle

neuritic plaque

neuropil thread



Immunohistochemistry (IHC) staining

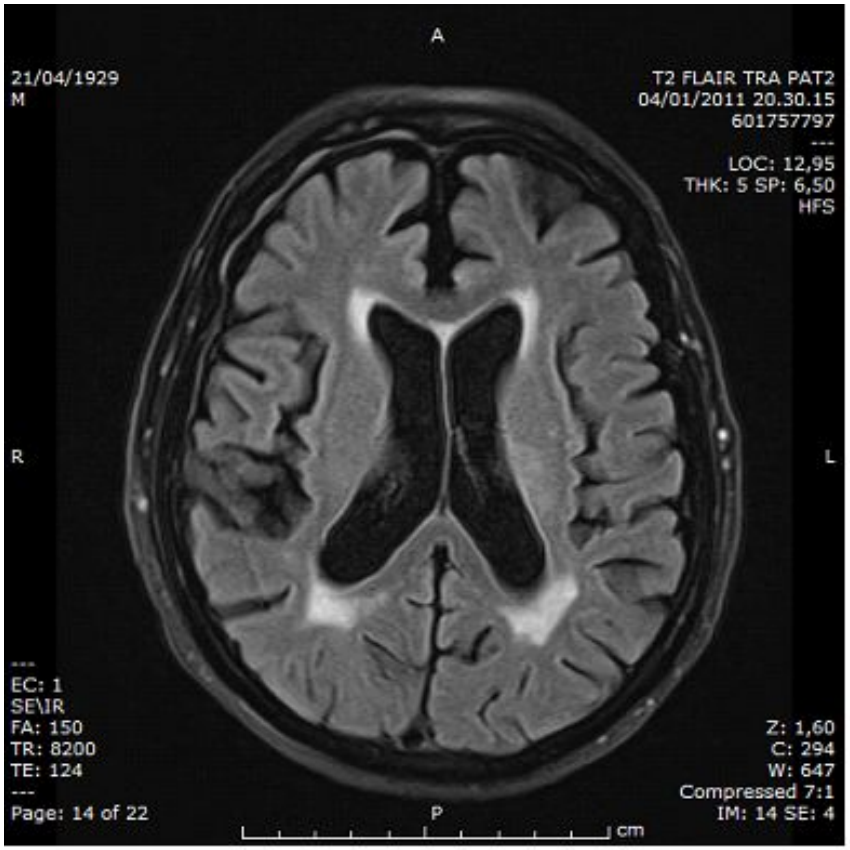
http://translationalscience.msu.edu/research/NMKlab.htm

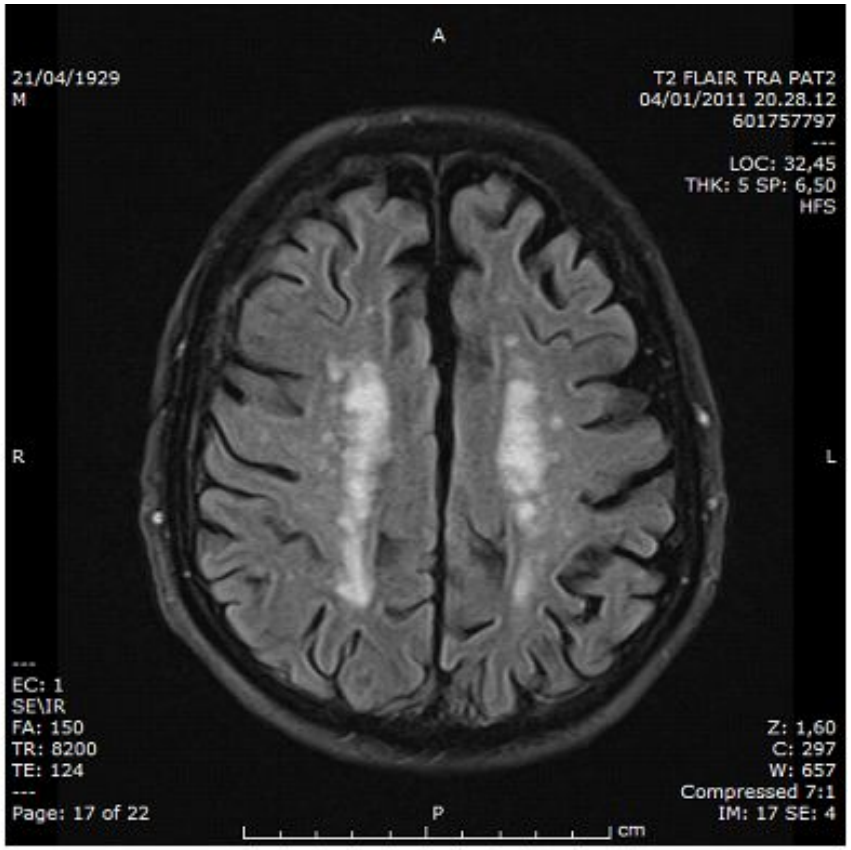
VASCULAR DEMENTIA: NINDS CRITERIA

- Large vessel stroke OR
- Small vessel strokes
  - Bilateral thalamic lesions OR
  - Multiple basal ganglia, thalamic and frontal WM lacunar stroke: need at least 2 in the BG area and at least 2 in the frontal white matter OR
  - “Extensive” periventricular WM lesions
- These patients may look more like AD in terms of progression (gradual rather than stepwise)

NINDS-AIREN criteria

WHITE MATTER DISEASE





An 82 yo man with slowly progressive memory impairment

Mental and Behavioural Disorders and Diseases of the Nervous System, 2013

NINDS-AIREN criteria

DIAGNOSIS OF LEWY BODY DEMENTIA

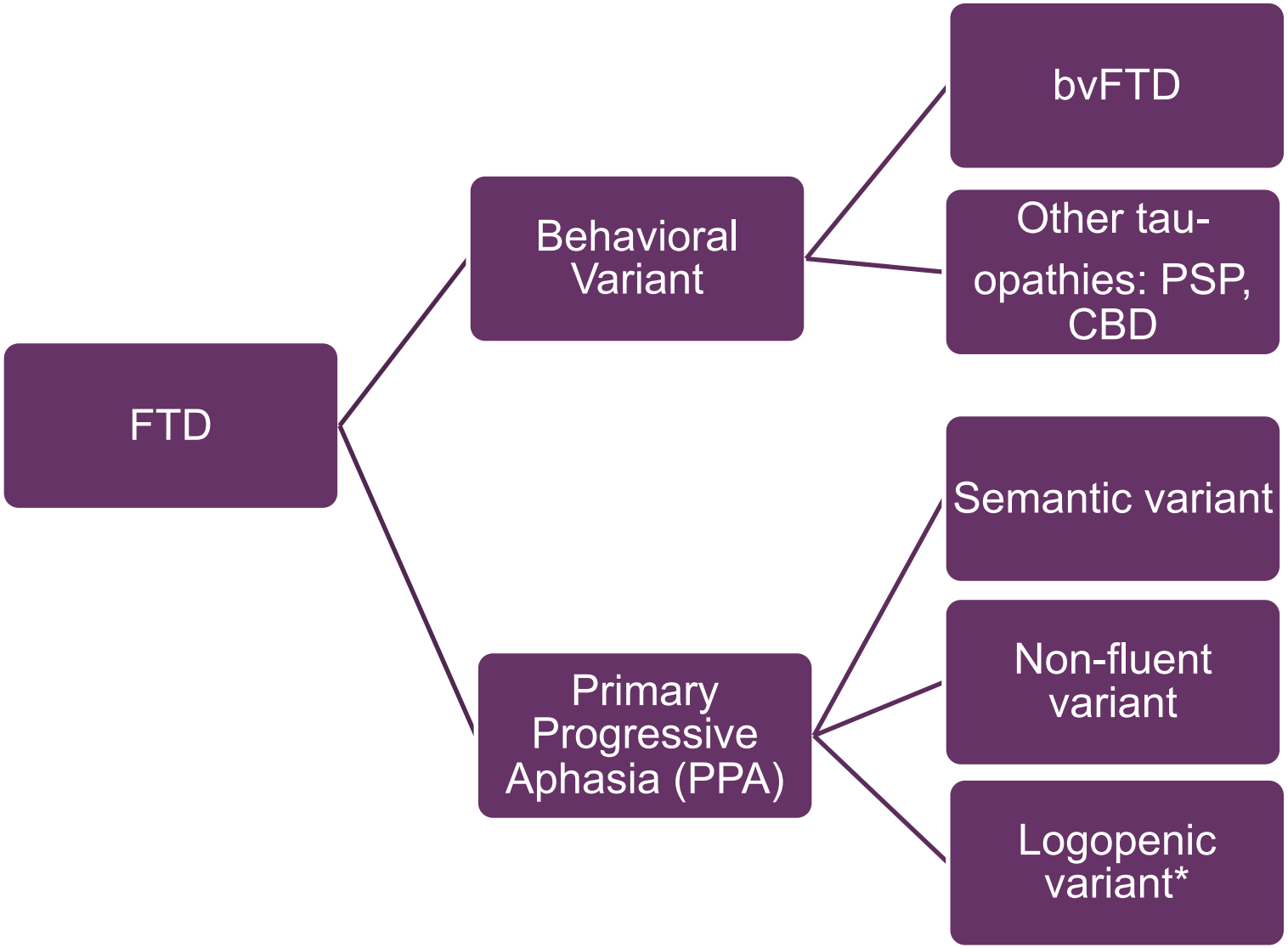
- Consensus criteria for DLB 2017: Core features
  - Fluctuating cognition with variation in attention/alertness: 60-80%
  - Recurrent well formed visual hallucinations: 50-75%
  - REM sleep behavior disorder
  - Parkinsonism features (onset within 1 year of dementia, otherwise it's PDD): 80-90%
- Suggestive features: neuroleptic sensitivity, low dopamine uptake on SPECT/PET, falls
- May respond better to Acetylcholinesterase Inhibitors
- Age of onset: range 50-85, Survival < AD, median<5y
- Pathology: Lewy body inclusions
- Cog testing: more impaired on attention, exec fxn, visuospatial

McKeith IG et al, Neurology 2005; 65:1863, updated 2017

FRONTOTEMPORAL DEMENTIA

- As common as AD in younger patients
  - Mean age of onset: 58 (reports age 20-80)
- Up to 30% of cases are familial/genetic
  - Tau, TDP-43, FUS, others
  - Some overlap with ALS in families (TDP-43)
  - Pathology: tau/tdp43 tangles only
- Two main variants:
  - Behavioral: Often mistaken for mental illness
  - Language: can be subtle early on in the illness

Brain 2011: 134,2456-2477



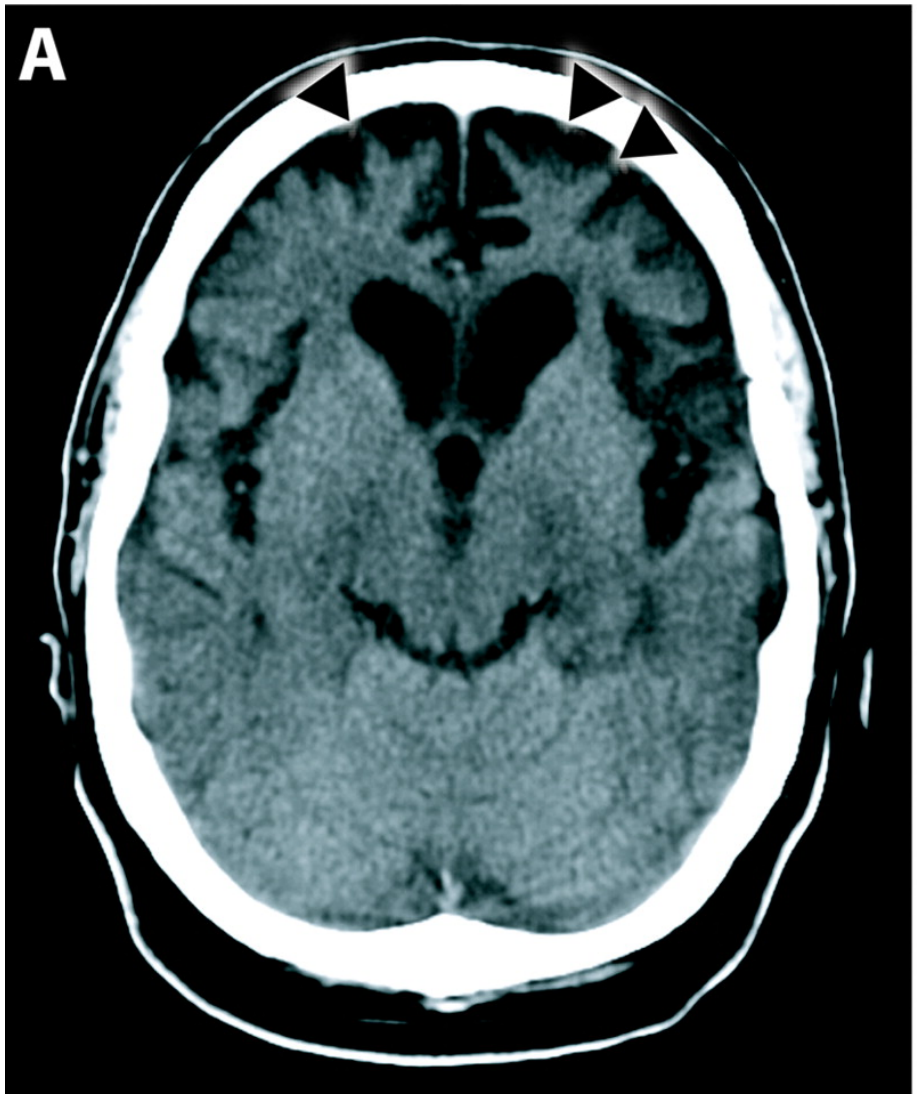
* Pathologically this is a form of AD (plaques and tangles)

BV FTD: Need 3 of 6 criteria:

- Early behavioral disinhibition: socially inappropriate behavior, loss of decorum, impulsivity
- Early apathy or inertia
- Loss of empathy: ↓ response to others' needs
- Early perseverative, stereotyped, compulsive behavior or speech
- Hyperorality, diet change: binge eating, pica
- Neuropsych profile: executive function deficits with relative sparing of episodic and visuospatial memory

Brain 2011: 134,2456-2477

Frontotemporal Dementia

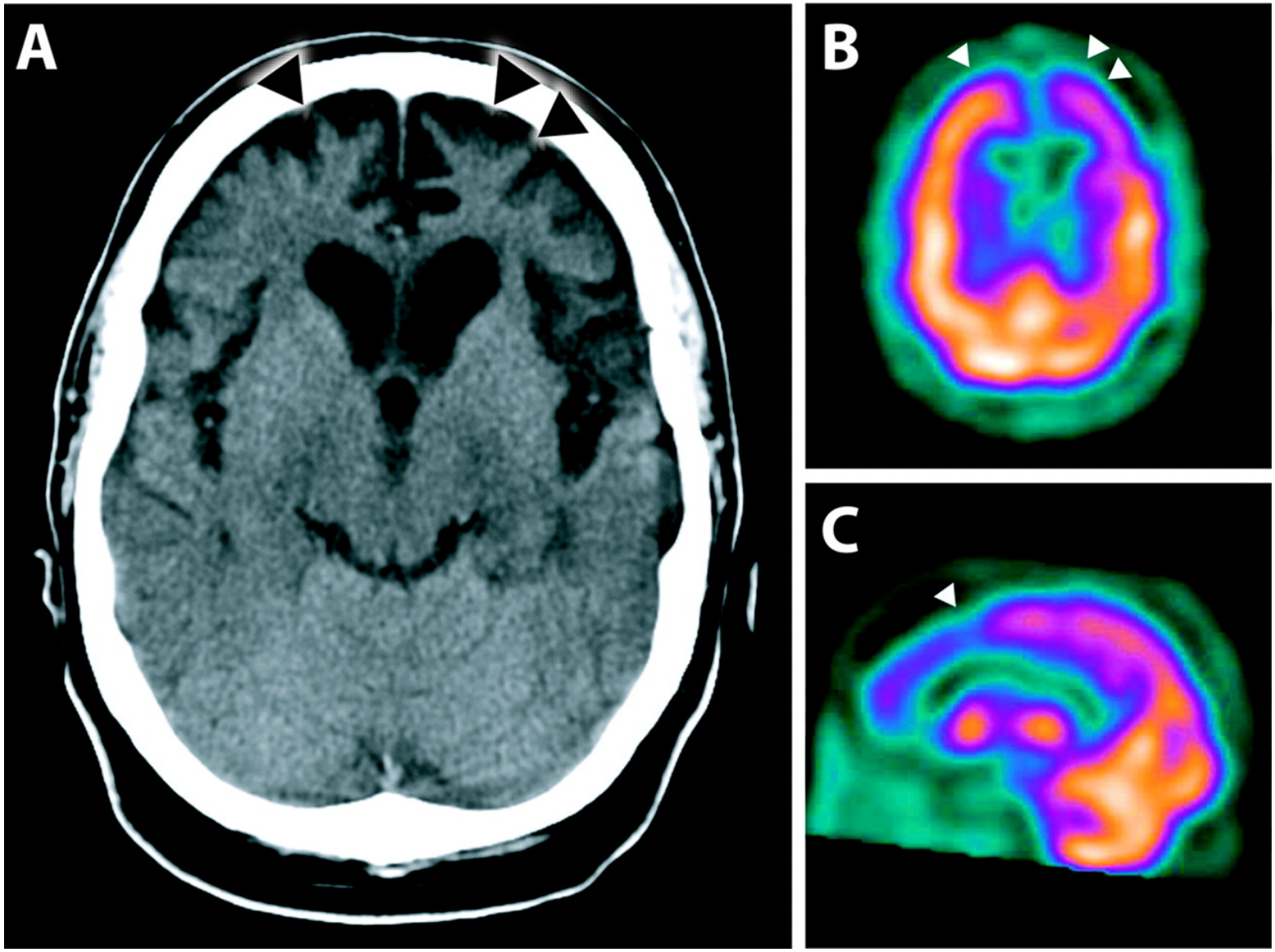


Note the jagged edges, and the asymmetry

Relative sparing of hippocampus

http://radiopaedia.org/cases/

Frontotemporal Dementia



Part 2 Summary

- To formally diagnose dementia:
  - Work up in a standardized way: Labs, exam, imaging, when to refer
  - Know the criteria for the most common forms of dementias
  - Many patients will have mixed dementia
- Ok to diagnose over time
- History often the most important piece
- Cognitive impairment is a geriatric syndrome

Objectives

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- Part 2: How do we work up a patient with cognitive impairment?
- **Part 3: A few pearls about management**

Cultural factors and dementia

- Cultural and societal differences with how people view aging, caregiving, memory loss
  - Urban vs rural, different cultural groups
- Wendy Hulko et al-wrote a nice paper about First Nation communities in British Columbia, Canada and ways that memory loss and aging might be viewed differently in Native populations
- Broad topic – hard to distill to a few bullet points, but a lesson I keep trying to follow is to avoid assumptions and allow families to express their ideas and questions in a safe environment

Wendy Hulko et al, J Cross Cult Gerontol 2010

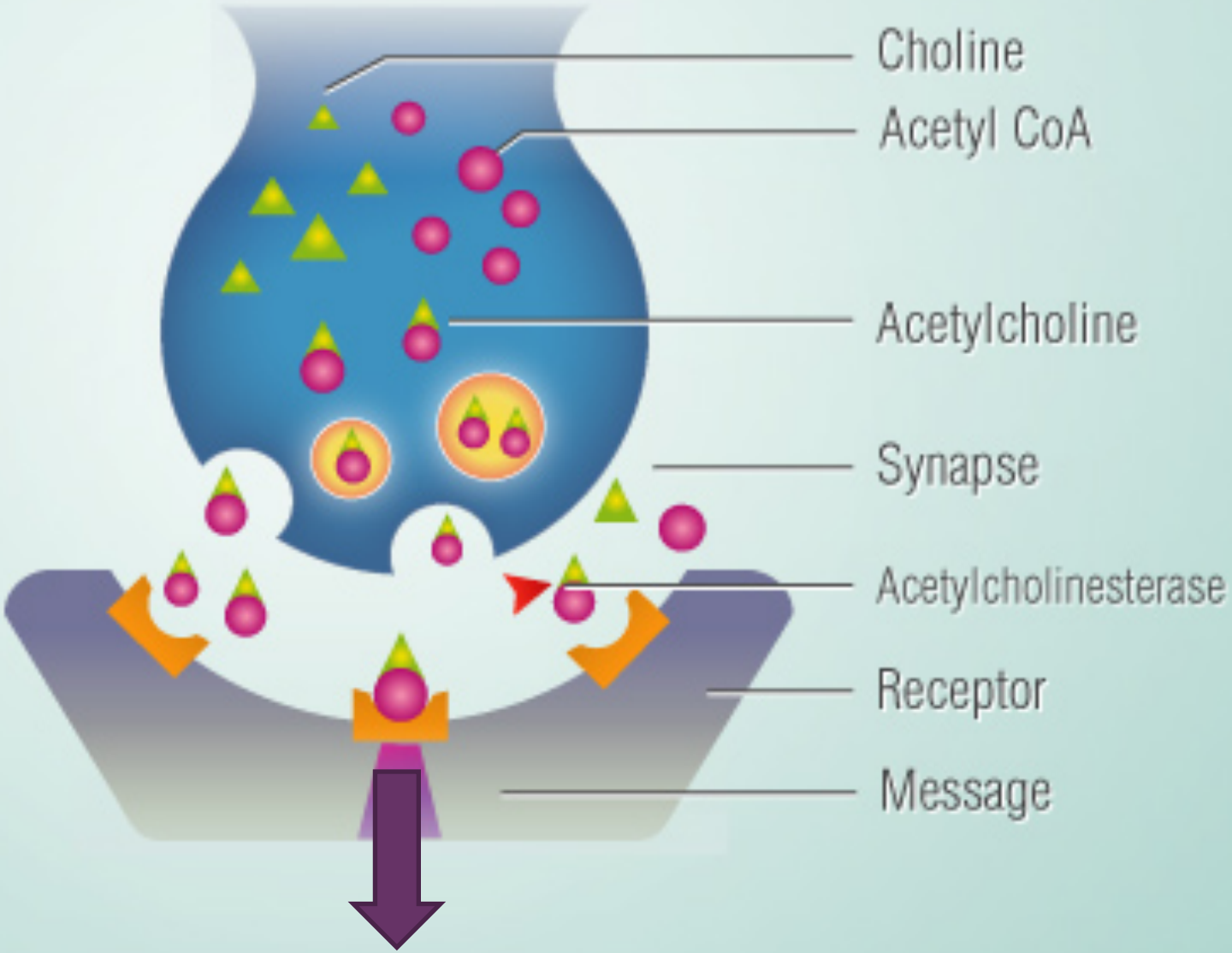
Caregiver assessments

- Can formally assess with various tools/surveys
- Informal assessments
- Practicing patient-centered care while also addressing caregivers:
  - Address the patient as much as possible even when you're talking to the caregiver

Medications for Alzheimer's

- First, a brief review of the neurotransmitter acetylcholine

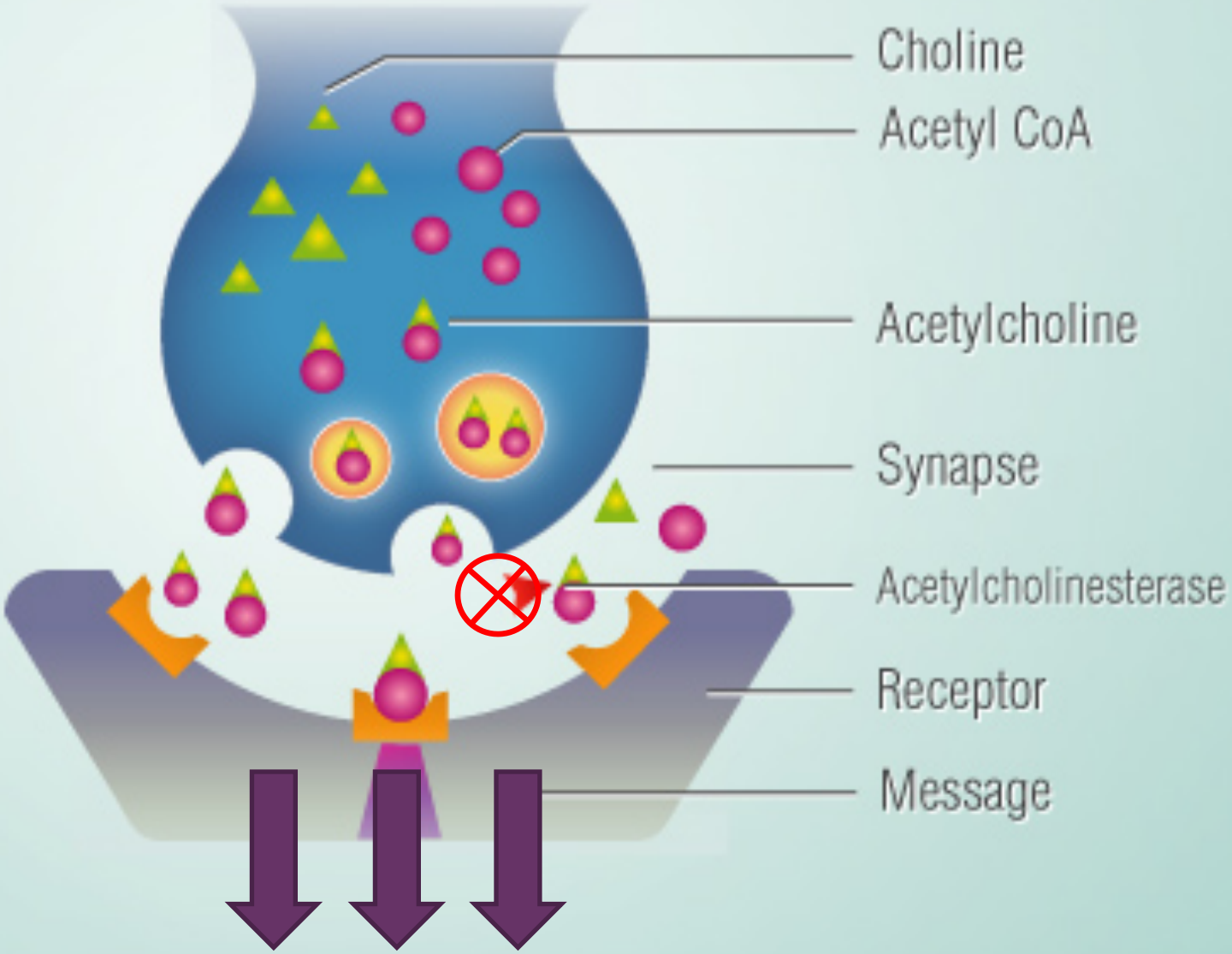
Acetylcholine



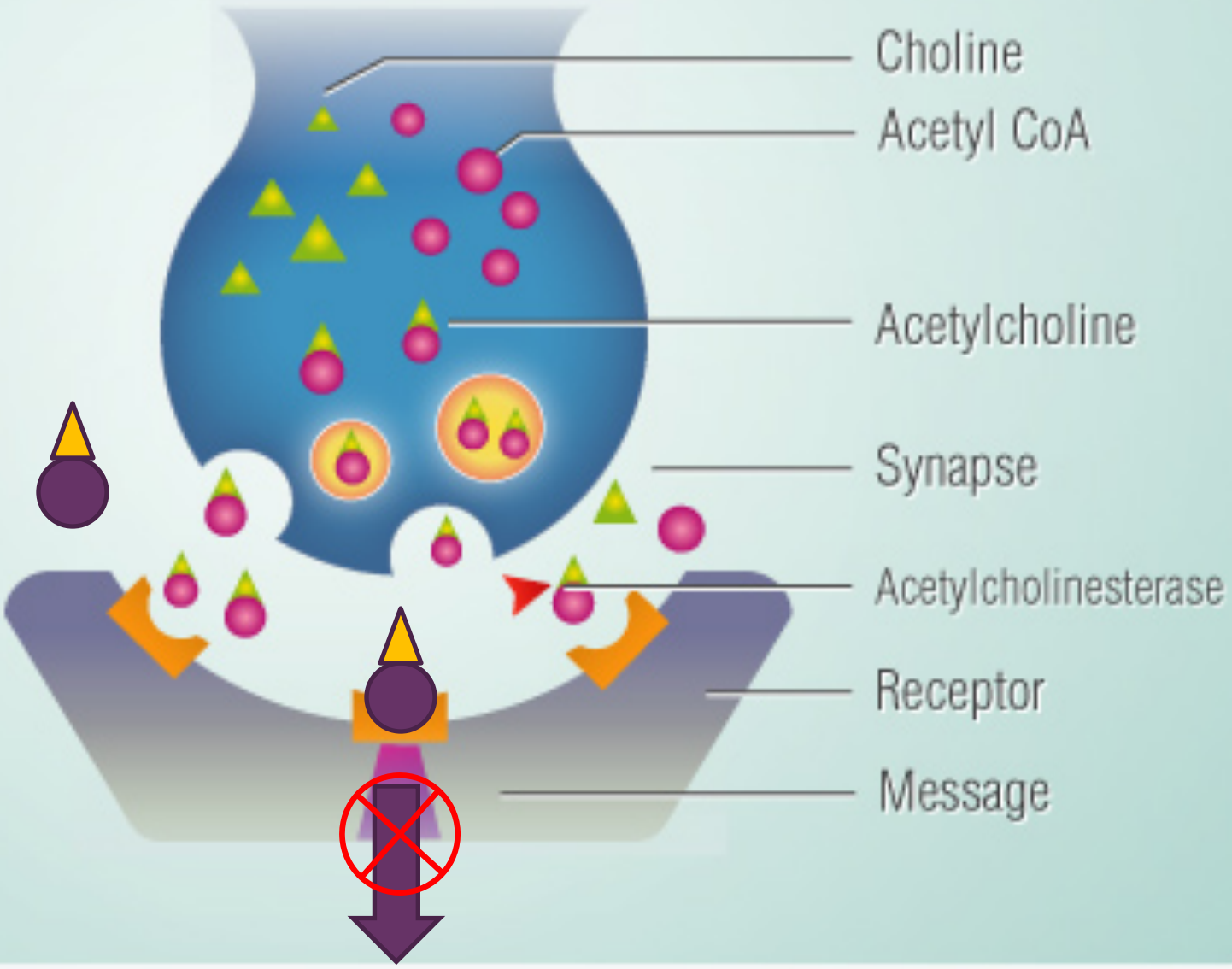
PRO CHOLINE:

Acetylcholinesterase inhibitor e.g. donepezil for AD:

Inhibits breakdown of acetylcholine, improving neurotransmission



Anticholinergic: i.e. benadryl, Detrol, amitryptyline: competitive inhibitor of acetylcholine, blocking neurotransmission



Anticholinergics and Cog Impairment

- Multiple studies now show a fairly strong positive association with these drugs and the following:
  - Development of cognitive impairment/MCI
  - Risk factor for actually developing dementia

- Recommendations:
  - Reduce or stop as many definite anticholinergics as you can
  - Remember that new drugs won't be on these lists

Ancelin ML. BMJ 2006; 25:455

FDA Approved Meds for AD

- Acetylcholinesterase inhibitors
  - Donepezil (Aricept)
  - Galantamine (Razadyne)
  - Rivastigmine (Exelon) comes in a patch form
- Side effects
  - Nausea, diarrhea, vivid dreams. May stop if unexplained weight loss
  - Bradycardia, syncope, falls (HR 1.5-1.7): If unexplained syncope, consider stopping
- Memantine (Namenda): NMDA receptor antagonist
  - Common: N/V, diarrhea, dizziness, Hypo- or Hypertension
- Probably ok to continue in hospital??
  - Minimal drug:drug interactions, but…
  - Little to no data on how to stop these meds

Gill SS et al. Arch Intern Med. 2009;169:867

Resources

- Alz.org
- lbda.org
- Aftd.org
- Memory Brain Wellness Center website:
  - http://depts.washington.edu/mbwc/
- HRSA dementia curriculum:
  - https://bhw.hrsa.gov/grants/geriatrics/alzheimers-curriculum
- Area agency on aging in your county

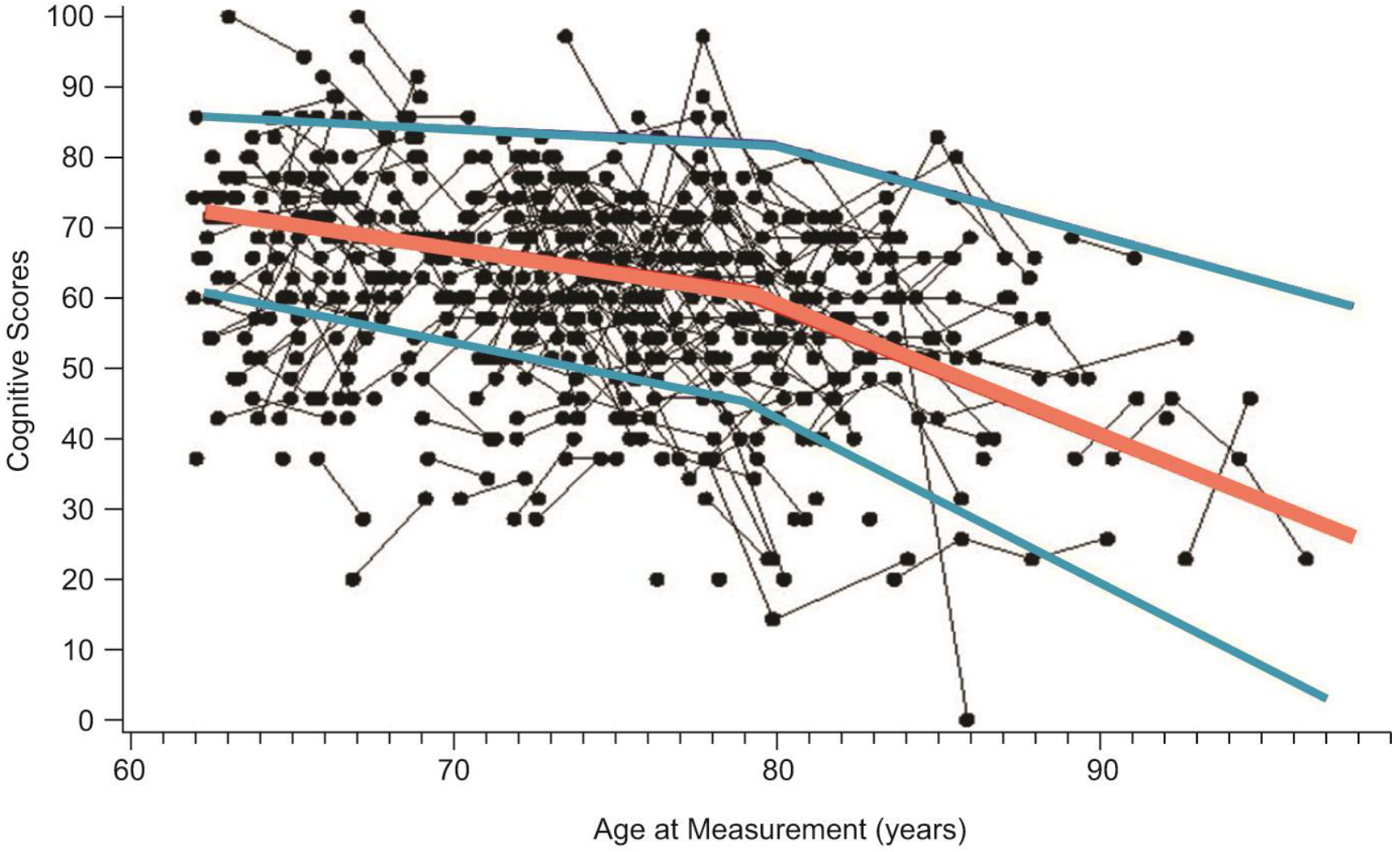
Questions?

Supplemental slides

What is normal aging?

- Wide variability in this!
  - A general slowing of cognitive performance
  - A decrease in mental flexibility
  - Some difficulties finding the right word
  - A mild decrease in short-term (working) memory
  - Intact memory for current events
  - Independence in ADL and IADL
  - Retention of verbal abilities and vocabulary
- Changes in perceptual systems or speed of processing associated with normal aging can influence cognitive processes such as attention and memory

Dumas, 2015; Emory Alzheimer's Disease Research Center, 2017; UCSF Memory and Aging Center, 2018d



Blazer DG, Yaffe K, Liverman, CT
IOM Cognitive Aging 2015

Normal Aging or Dementia?

Normal Aging:

- Making a bad decision once in a while
- Missing a monthly payment
- Forgetting which day it is, and remembering later
- Sometimes forgetting which word to use
- Losing things from time to time
- Sometimes needing help using electronic devices
- More time/energy needed to encode new information

Dementia:

- Poor judgment and decision making
- Can no longer manage a budget
- Losing track of the season or year
- Difficulty having a conversation
- Misplacing things and unable to retrace steps
- Difficulty with familiar tasks
- Very difficult to encode new information

Alzheimer's Association (alz.org)

Domains Impaired in Dementia 1/2

- Attention:
  - Sustained and divided attention, processing speed
- Learning and memory:
  - Amnestic: difficultly remembering new info
  - Repeat questions, misplace things, forget appts
- Executive function:
  - Inability to manage finances, plan complex activities, poor judgment
- Language:
  - Word finding trouble, speech and spelling errors

Alzheimer's & Dementia 7 (2011) 263–269, CME Course 2016

Domains Impaired in Dementia 2/2

- Visuospatial:
  - Difficulty recognize faces, objects in direct view, orienting clothes to body
- Personality and behavior:
  - Apathy, social withdrawal, socially unacceptable behaviors
- Social cognition:
  - Difficulty regulating emotion and behavior

- Different dementias show different patterns

Alzheimer's & Dementia 7 (2011) 263–269, CME Course 2016

Angela Hanson, MD
UW Medicine, Harborview Medical Center

uwadrc.org

UW Medicine
UW ALZHEIMER'S DISEASE RESEARCH CENTER