Research in Memory Disorders

Where are we now?

Allan L Bernstein M.D.

How does memory work

- Input
- Coding
- Storage
- Retrieval

Input

- Combination of
  - Hearing
  - Seeing
  - Smelling
  - Tasting
  - Awareness of the environment

Input depends on ATTENTION

- Hearing and listening are different (Paul Simon said it in “The Sounds of Silence”)
- Seeing and registering are different
- Awareness of the environment is the ability to integrate all the input modalities

What interferes with attention?

- Poor sleep
- Depression
- Alcohol
- Medications
- Pain
- PTSD
- Impaired hearing
- Boredom

Medications that interfere with memory

- Antihistamines
- Anti-anxiety medication (I.e. Ativan, Valium)
- Chemotherapy
- Narcotics
- OTC sleep meds, i.e., Benadryl
- Some antidepressants
- Anticholinergics ,i.e., medications for spastic bladders or spastic muscles
- Anti-seasickness patch or pills

Encoding new material

- Moving from short term to long term memory requires “quality” sleep
- Requires non-drug related sleep
- May be impaired by ‘jet lag’

Storage

- Intact brain essential from cross communication
  - Strokes
  - Trauma
  - Scar tissue from infections
  - COVID?

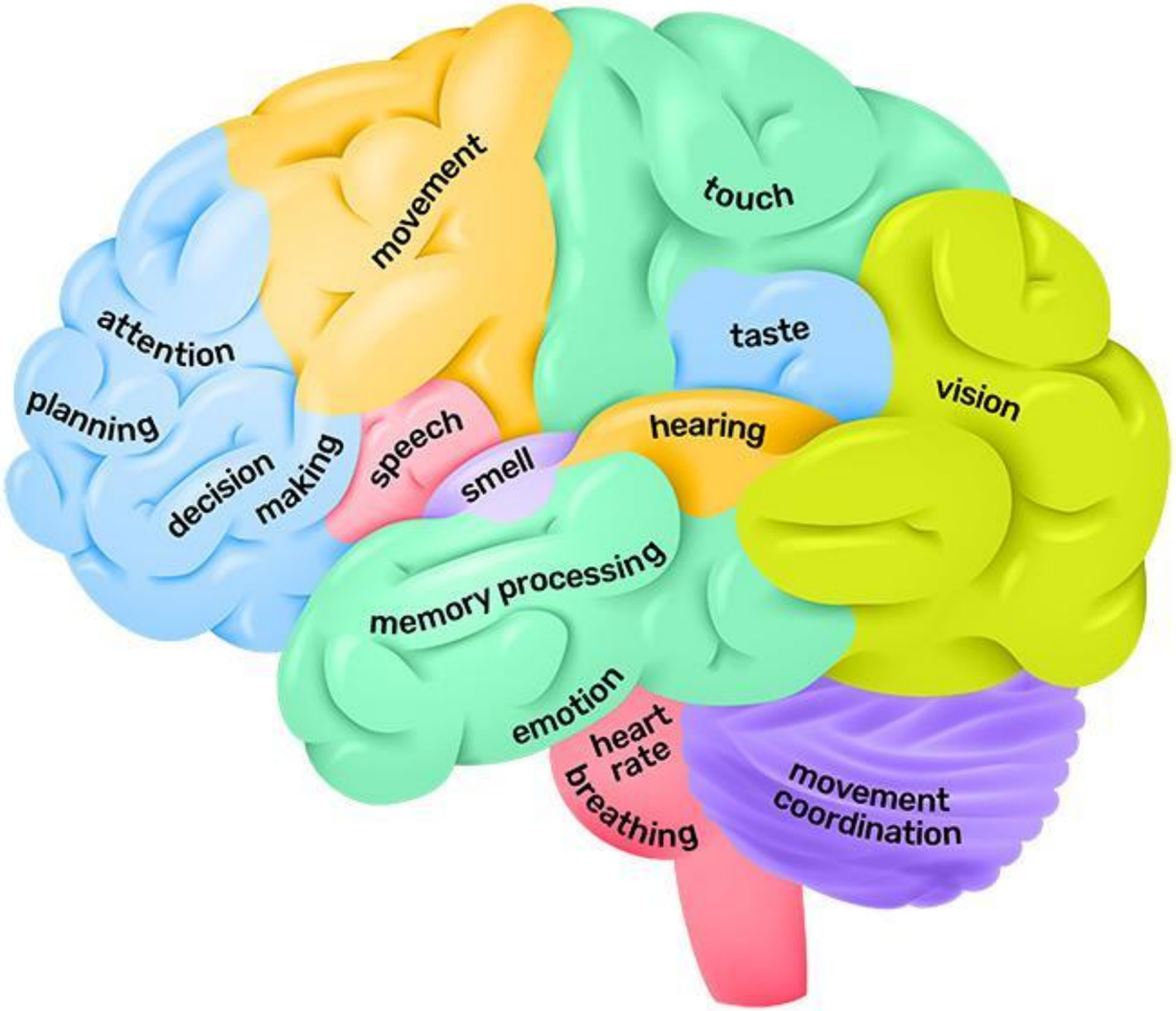
Retrieval

- Comes from multiple parts of the brain simultaneously
  - Smell triggers memory of what/where
  - Sound triggers memory of when/who
  - Vision triggers what/where/how
  - Motor memory - ride a bike, play the piano, throw a ball
  - Speech is the most complicated area to retrieve

Speech/conversation

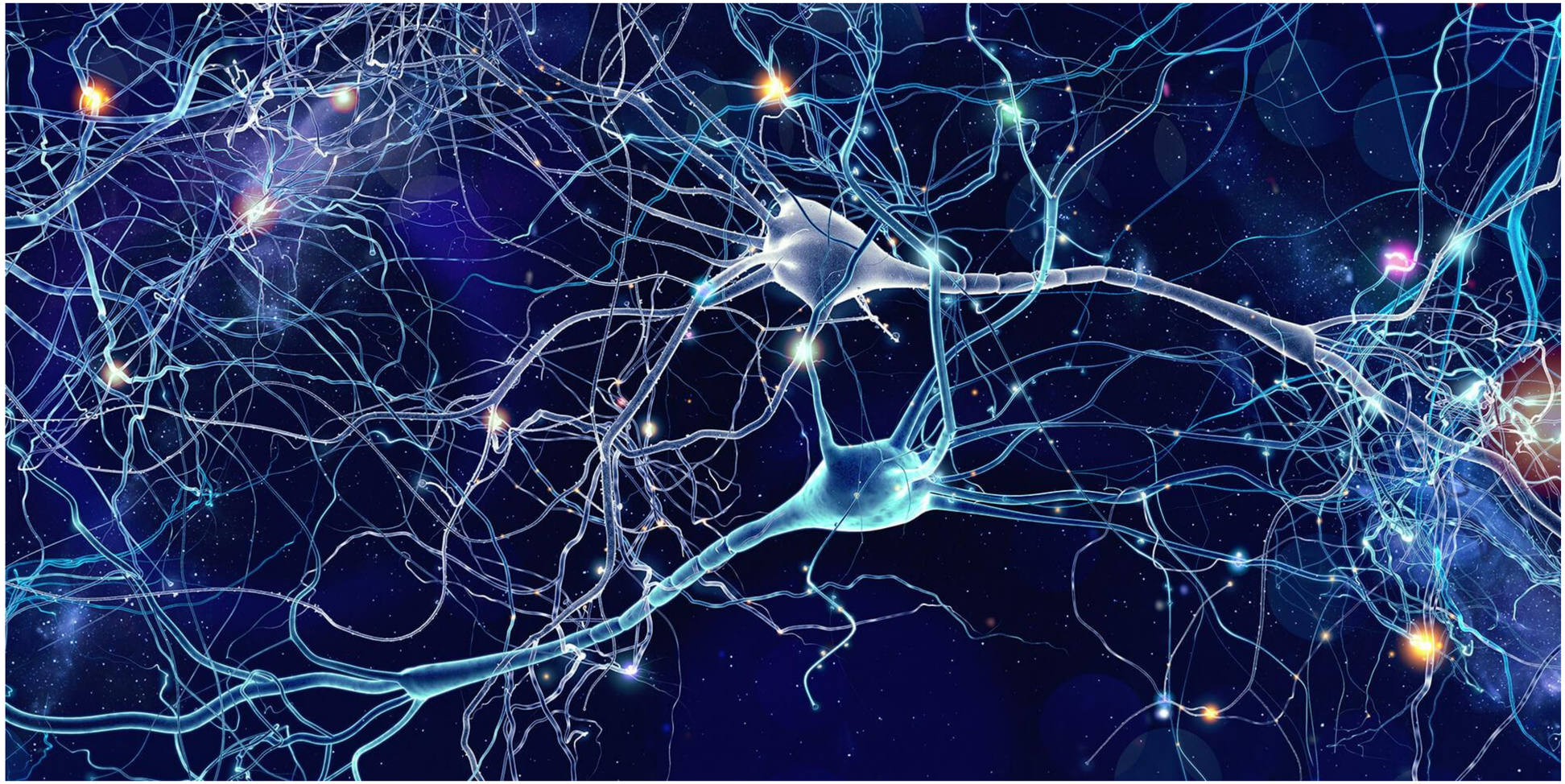
Critical brain activity

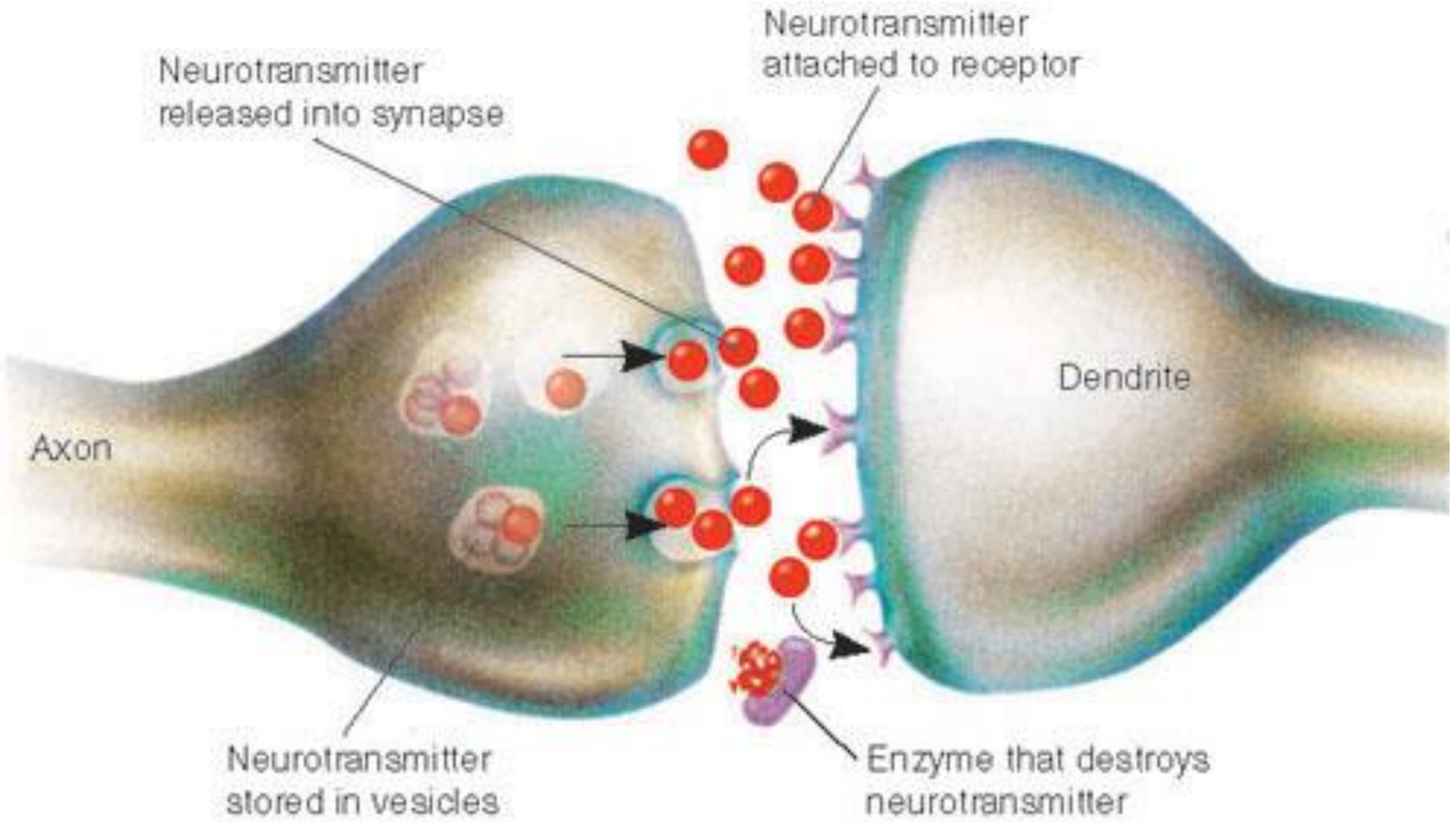
- Hear it
- Interpret it
- ‘Read’ the tone
- Recognize the cadence, accent, emotional content
- Create an answer
- ALL IN A MILLISECOND


movement
touch
attention
taste
vision
planning
hearing
speech
decision
making
smell
memory processing
emotion
heart
rate
breathing
movement
coordination

A hundred billion cells

A hundred trillion contact points




Neurotransmitter
released into synapse
Neurotransmitter
attached to receptor
Dendrite
Axon
Neurotransmitter
stored in vesicles
Enzyme that destroys
neurotransmitter

Synapse

- Electrical stimulation
- Chemical release
  - Every synapse has multiple chemicals in different proportions
- Crosses to the next nerve and starts a new electrical impulse

Neurotransmitters

- Dopamine
- Serotonin
- Acetyl choline
- Norepinephrine
- Glutamate
- Endorphins

A healthy brain needs

- Oxygen
- Glucose , but not too much
- Ketones
- Vitamins
- Minerals
- IT IS RUNNING FULL SPEED 24/7
- IT DOES NOT “SLEEP!”

What can go wrong?

Hint: everything

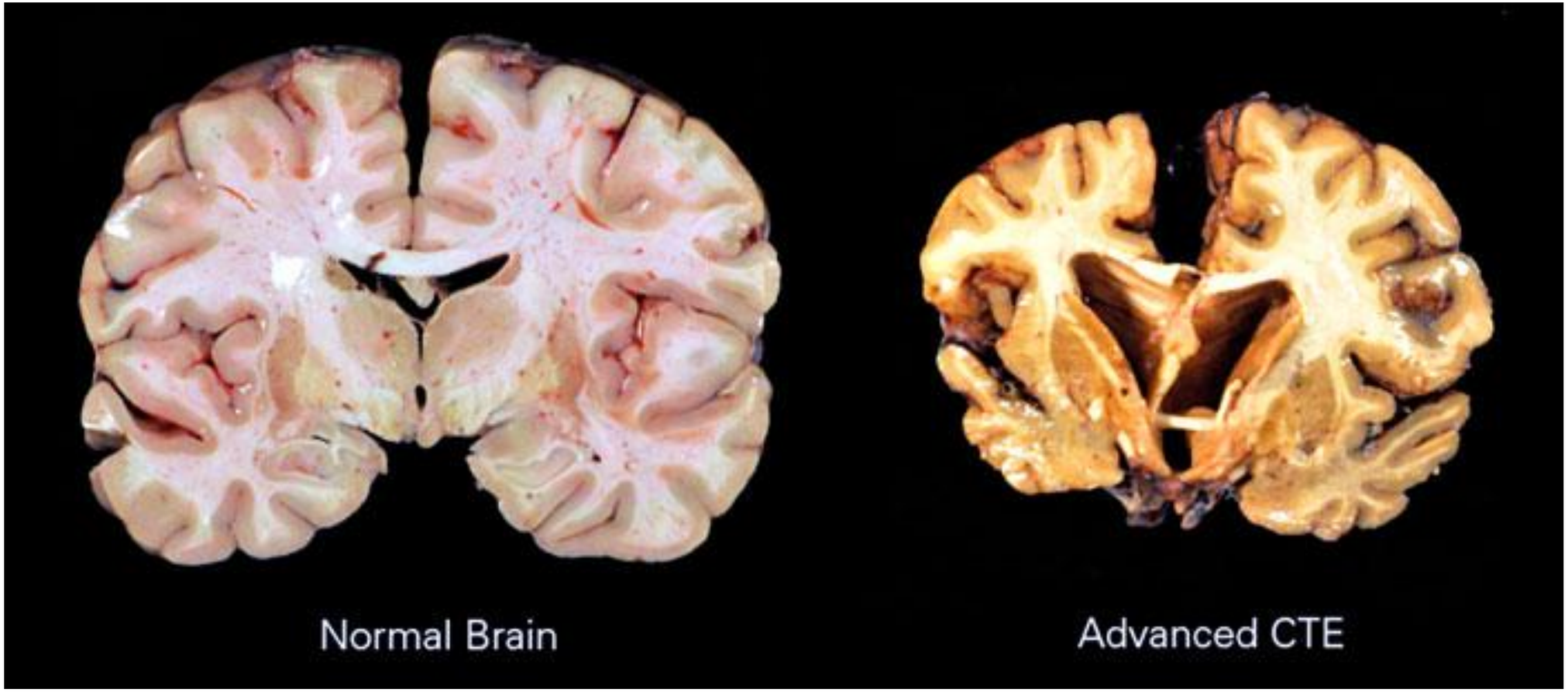
- Strokes
  - Big ones or multiple small ones
- Lack of oxygen
  - Cardiac arrests, drowning
- Toxic chemicals
  - Lead, mercury, herbicides, ?air pollution
- Trauma
  - One big one or multiple small ones

What can go wrong?

- Nutritional deficiencies
  - Mainly children
- Chronic alcohol abuse
- Degenerative disease
  - Alzheimer’s
  - Parkinson’s

Chronic traumatic encephalopathy

Football players, boxers , possibly soccer players



Dementia

- A gradual, progressive loss of previously learned cognitive activities.
  - The key is the progressive nature of the problem. There are multiple etiologies, and Alzheimer's is one specific type
- It effects multiple systems including memory, judgement, orientation, mood, executive function, speech and language

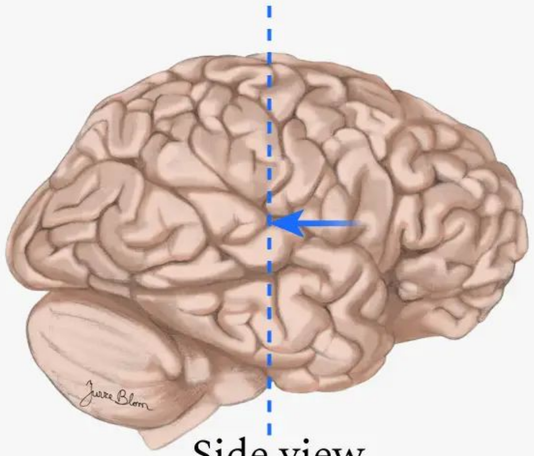
Alzheimer’s disease

- Described in 1907
- Findings include
  - Amyloid plaque
  - Neurofibrillary tangles (tau)
  - Other degenerative changes, not as prominent, including Lewy bodies, and arteriosclerotic changes

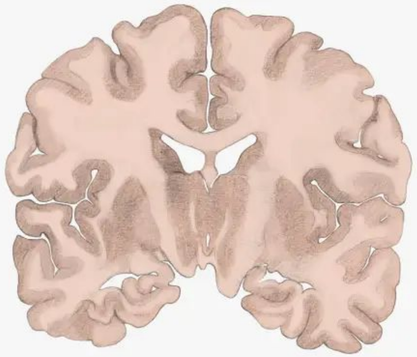
Alzheimer’s disease

Making a diagnosis

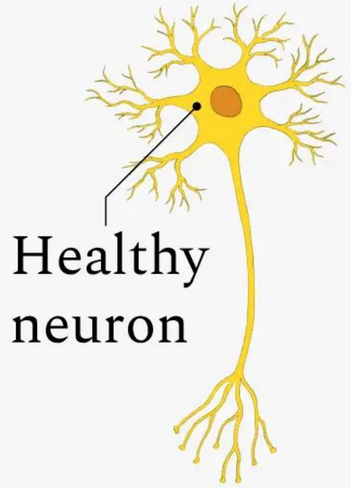
- Diagnosis-previously only at autopsy
- Currently we can identify amyloid and tau
  - PET imaging
  - CSF
  - Blood test
- These are all very expensive, not covered by insurance and available in research studies only!



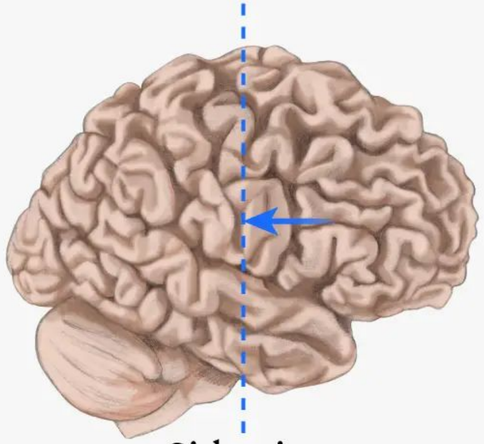
Side view



Cross-section



Healthy brain



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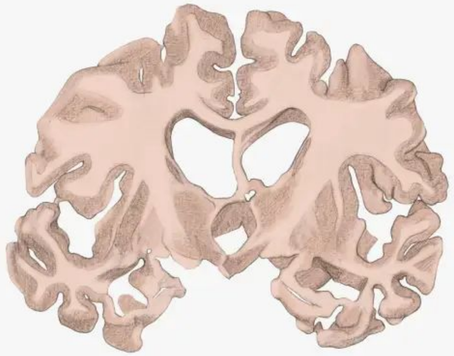

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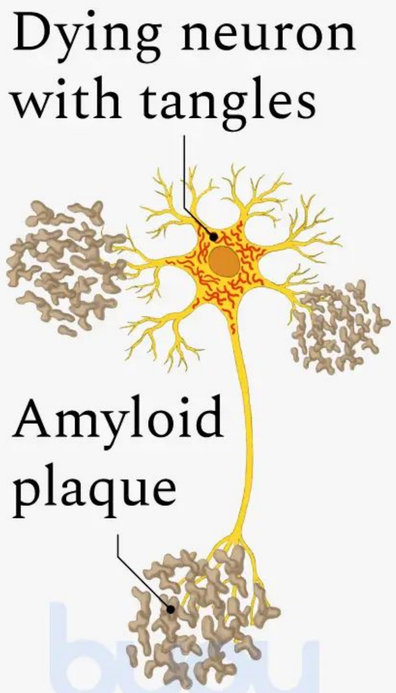


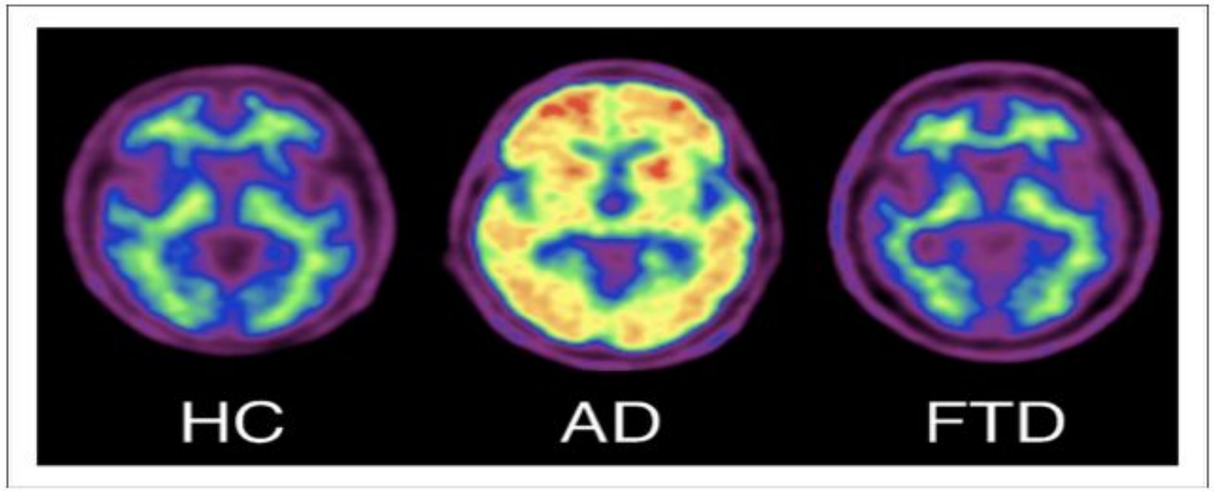
Alzheimer's disease

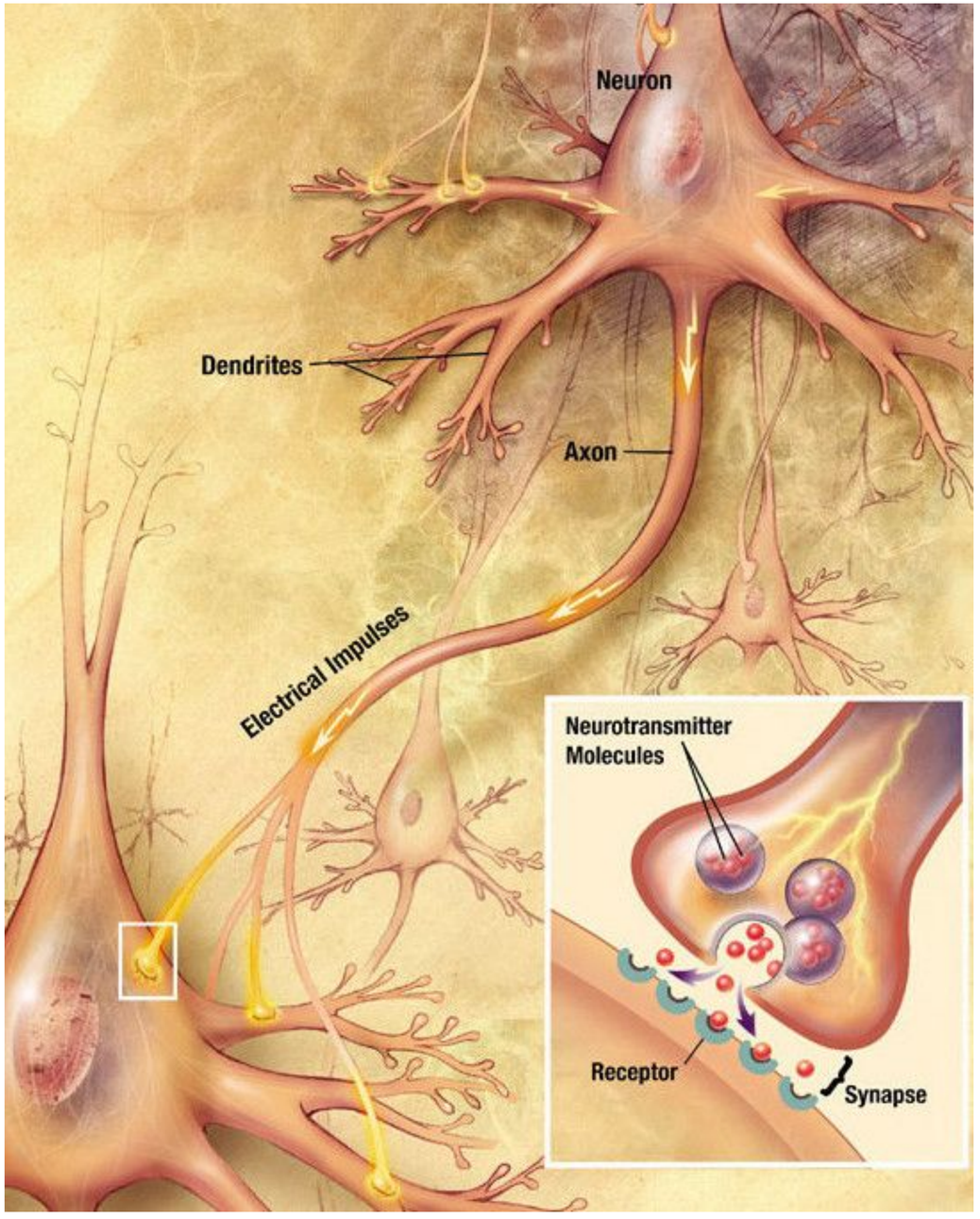
What is amyloid

- A lipid-like material essential to many functions in the body and the brain
- Three forms, all starting with APP (amyloid precursor protein)
  - Various enzymes cleave the protein into amino acid units, 38 units long, 40 units long and 42.
  - The 42 is the one that ‘clumps’ and precipitates into the brain tissue

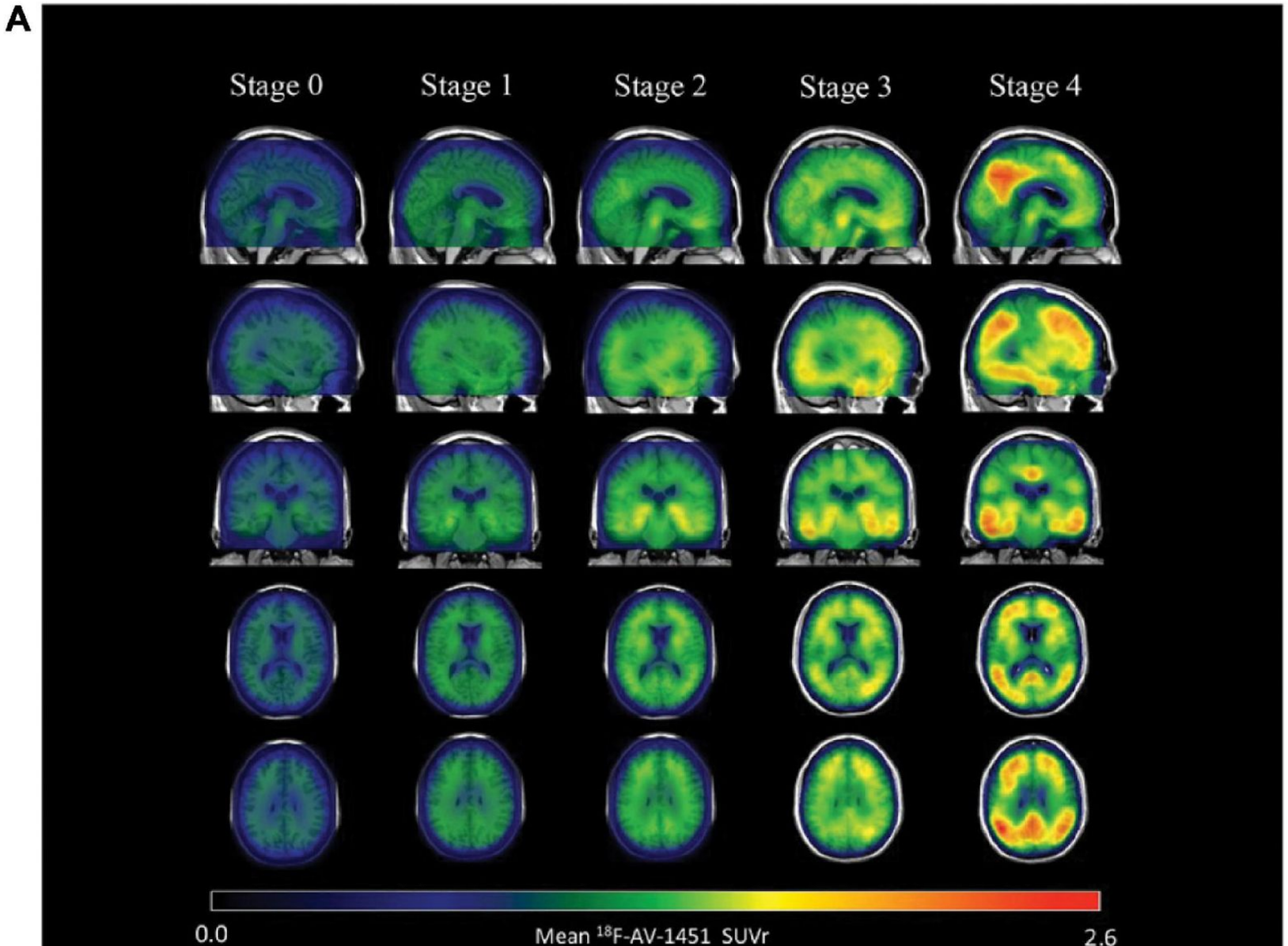
We can identify Alzheimer's disease in real time using PET imaging

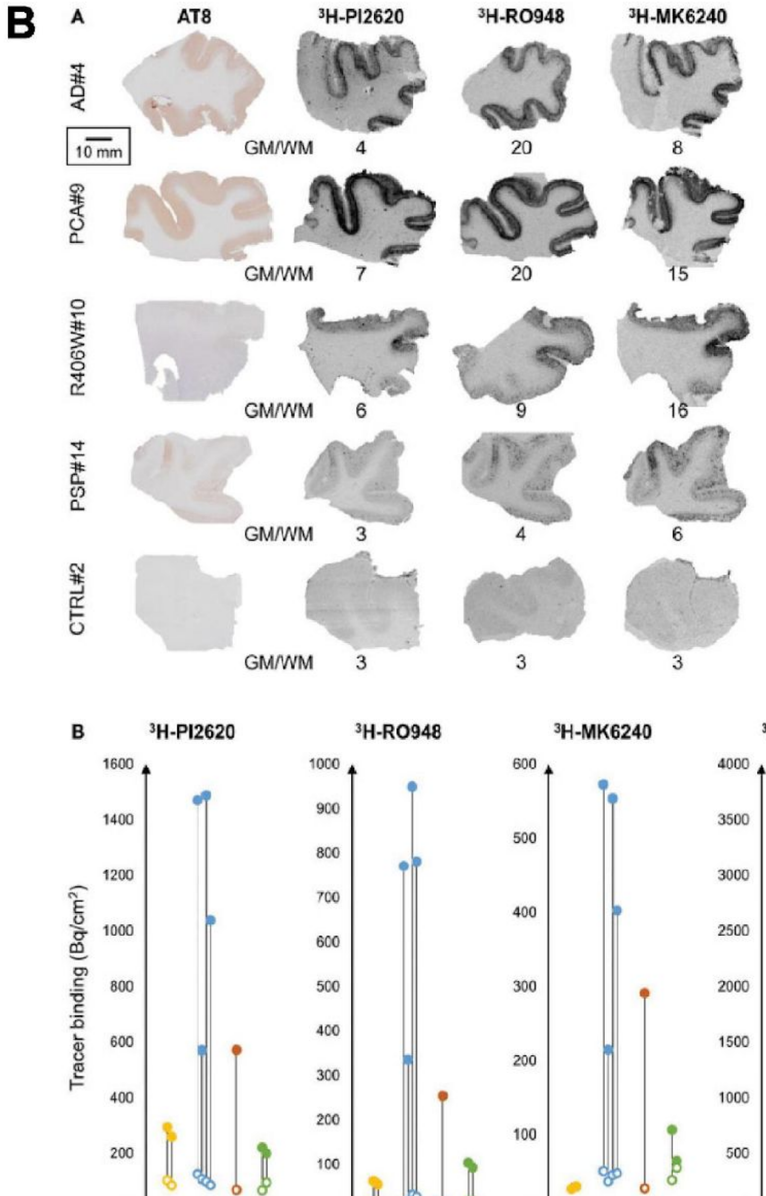
Amyloid specific imaging




Neuron
Dendrites
Axon
Electrical Impulses
Neurotransmitter Molecules
Receptor
Synapse

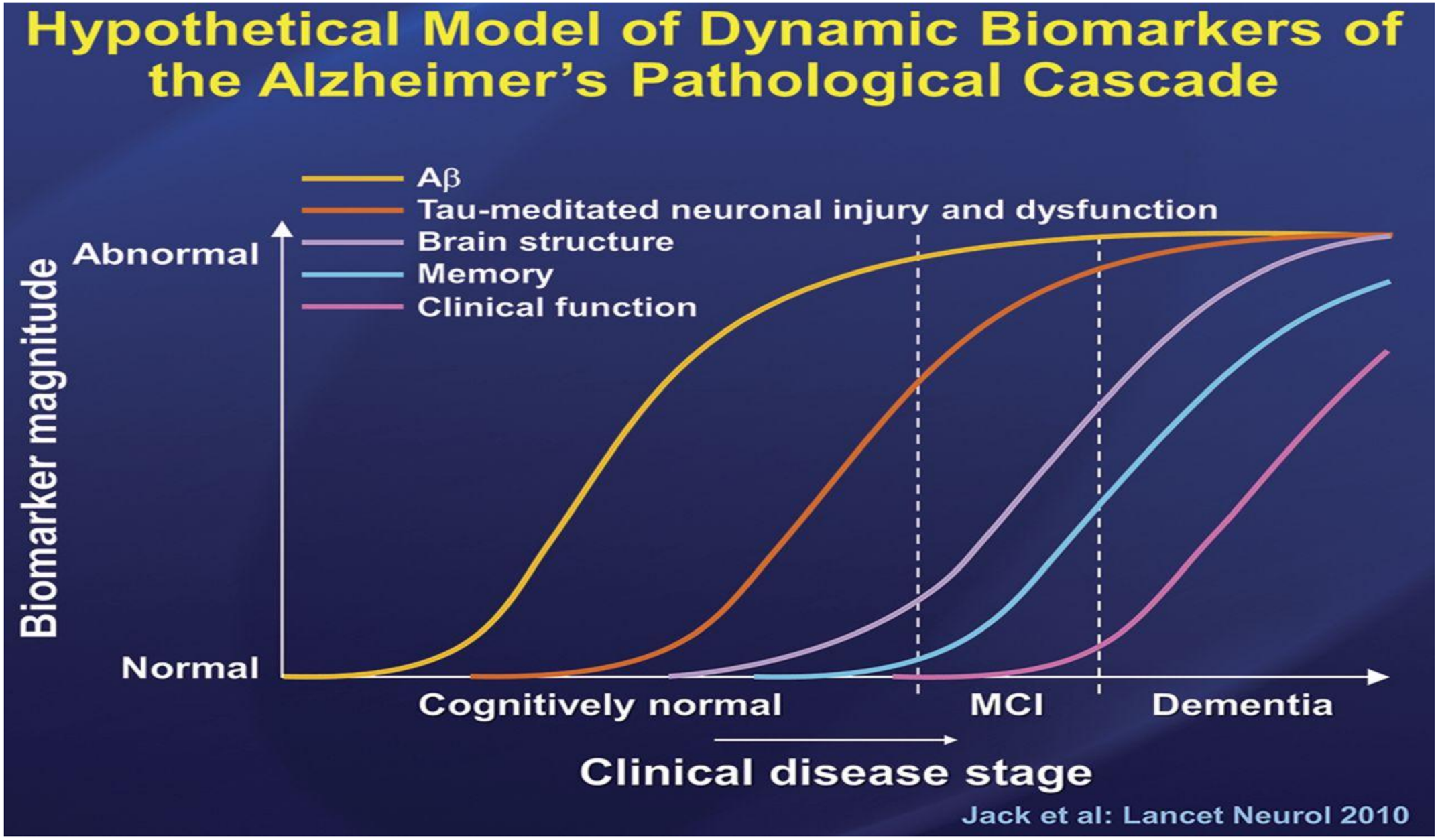
Tau imaging with PET





APOE genes and risk of Alzheimer's Disease

Genotype	E2/E2	E2/E3	E2/E4	E3/E3	E3/E4	E4/E4
Disease Risk	40% less likely	40% less likely	2.6 times more likely	Average risk	3.2 times more likely	14.9 times more likely


Hypothetical Model of Dynamic Biomarkers of the Alzheimer's Pathological Cascade
Aβ
Tau-meditated neuronal injury and dysfunction
Brain structure
Memory
Clinical function
Abnormal
Normal
Biomarker magnitude
Cognitively normal
MCI
Dementia
Clinical disease stage
Jack et al: Lancet Neurol 2010

Research studies in Alzheimer’s

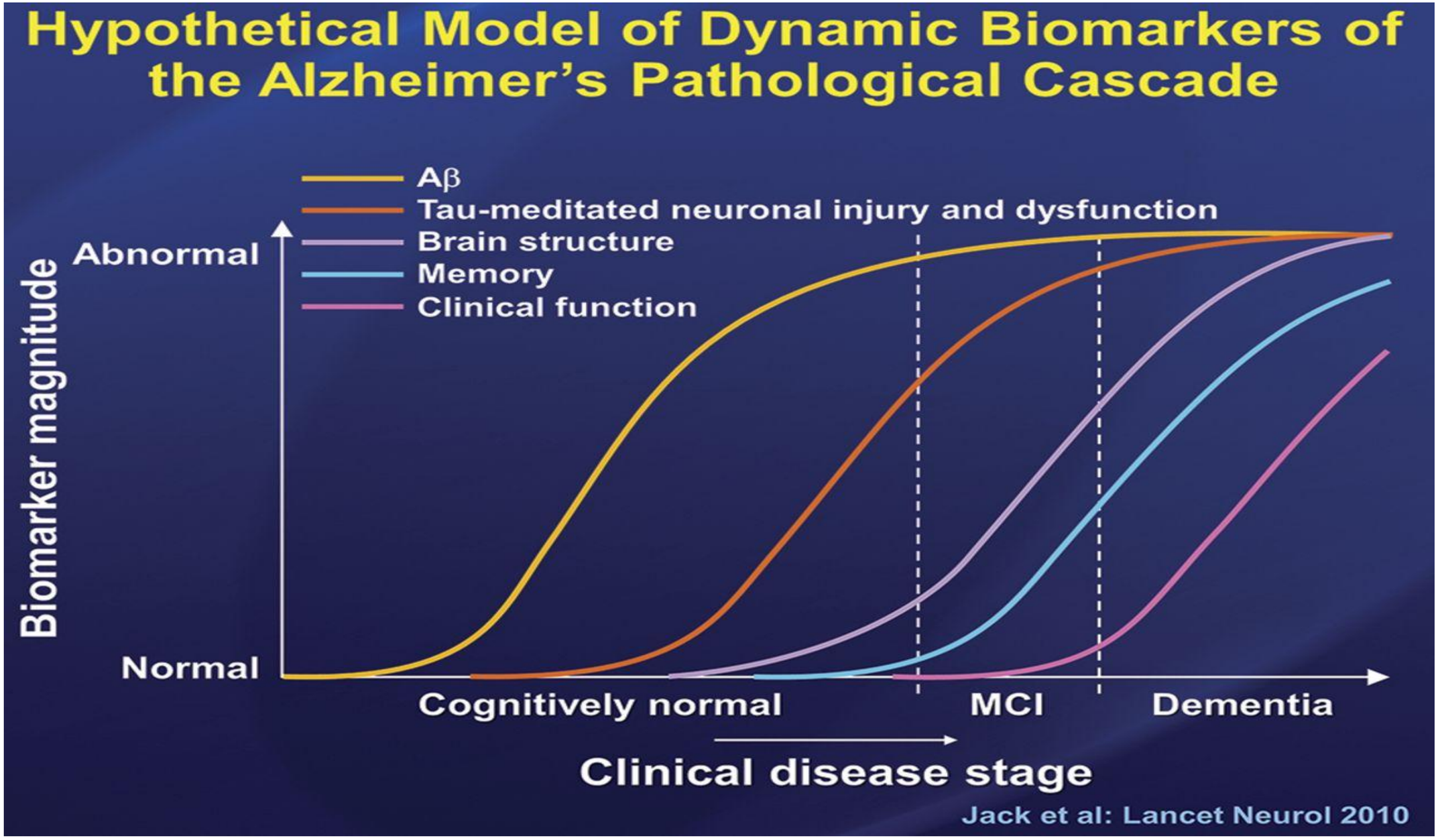
- Anti-amyloid
  - 10, or more trials using anti-amyloid antibodies
  - NONE showed any benefit in slowing down the decline
- Anti-tau
  - Five recent studies using anti-tau antibodies
  - NONE showed and benefit in slowing the decline
- Blocking the enzyme that creates amyloid 42 from APP
  - Toxic to the liver. (It didn’t do it to rats!) Never got to find out if it actually helps
- Drugs designed to add growth factor to the brain
  - No benefit

Research studies in Alzheimer’s

- Changing diets in people with cognitive decline
  - Minimal slowing of decline- not significant
- Stimulating the brain with magnets and/or low current electrodes
  - Early studies show ‘possible’ effect
- Using nasal insulin or other anti-diabetes medications
  - No effect

Research studies in Alzheimer’s

- Why have all the trials, billions of dollars, failed?
- EVERY TRIAL STARTED WITH PEOPLE ALREADY IN COGNITIVE DECLINE
- Dementia may be a PREVENTABLE condition, but not a treatable one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Prevention Strategies

Epidemiology studies-large databases

- Increased risk of dementia
  - Low education
  - Social isolation
  - Depression
  - Excess alcohol
  - Smoking
  - PTSD

Prevention Strategies

- Increased risk of dementia
  - Physical inactivity
  - Hypertension
  - Hearing loss
  - Visual loss
  - Diabetes
  - Chronic pain

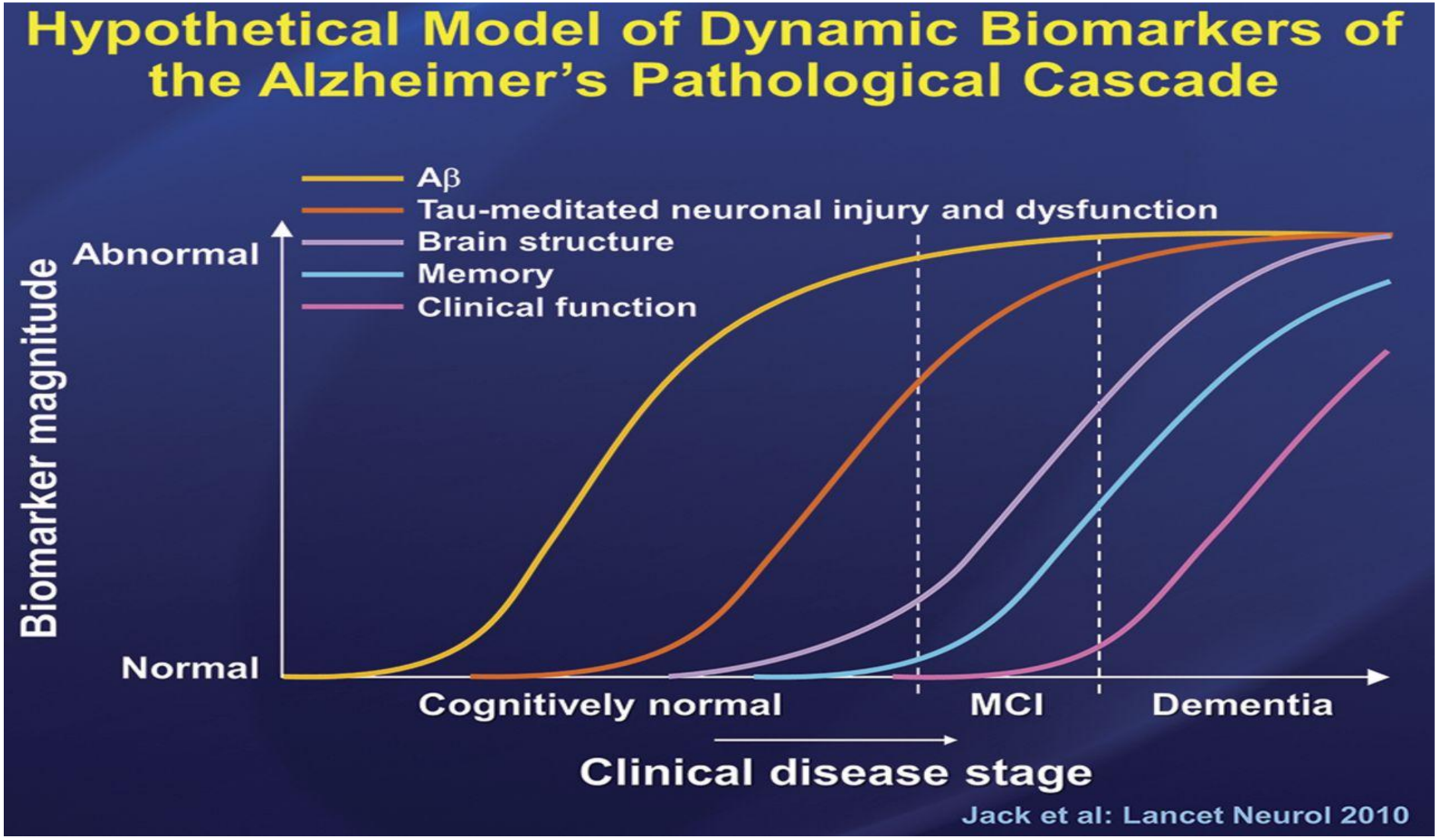
Prevention Strategies

- Increased risk of dementia
  - Air pollution
  - Traumatic brain injuries
  - Poor dental care

Prevention Strategies

- Those item, taken in total, can reduce risk of dementia by 40%
- Adding a DASH diet, Mediterranean diet add another 10% risk reduction

- We can’t change AGE, or GENETICS but we can MOVE THE CURVE
- Recent studies show that people using the behavior modification items listed, have moved the curve between 5 and 10 years, in spite of having amyloid and tau in their brains at autopsy.
- Nobody follow all the items, but even a few can make a difference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New studies

- Finally industry is investigating PREVENTION strategy rather than slowing a disease long after it started
- One study is enrolling people with positive BIOMARKERS (amyloid/tau) on a blood test and who are cognitively normal but high risk due to the biomarkers in a prevention study
- It is designed to remove excess amyloid from the brain over a nine month period and then track people for possible cognitive decline over the next 3-4 years, with all testing done via computers.
- Other studies are likely to follow, since we know we can reduce amyloid.

Questions???