PSYC301: Brain dysfunction affecting memory

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Lecture outline

Amnesia and memory types

Long-term potentiation

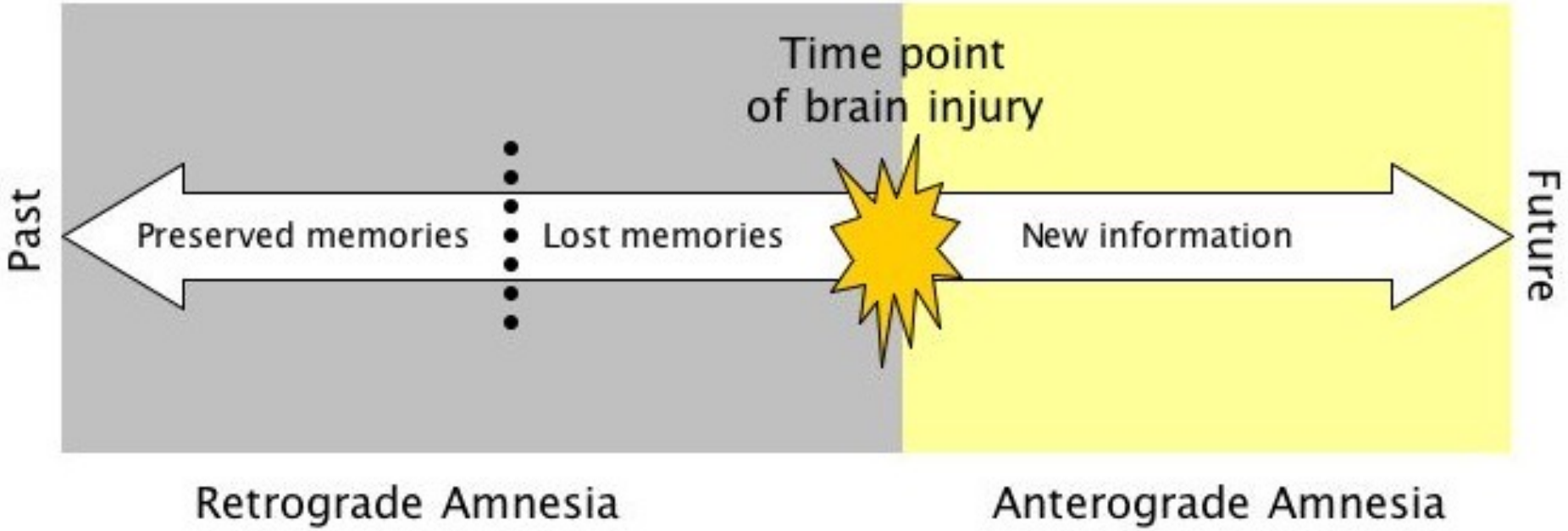
Korsakoff’s syndrome

Alzheimer’s disease

Learning objectives

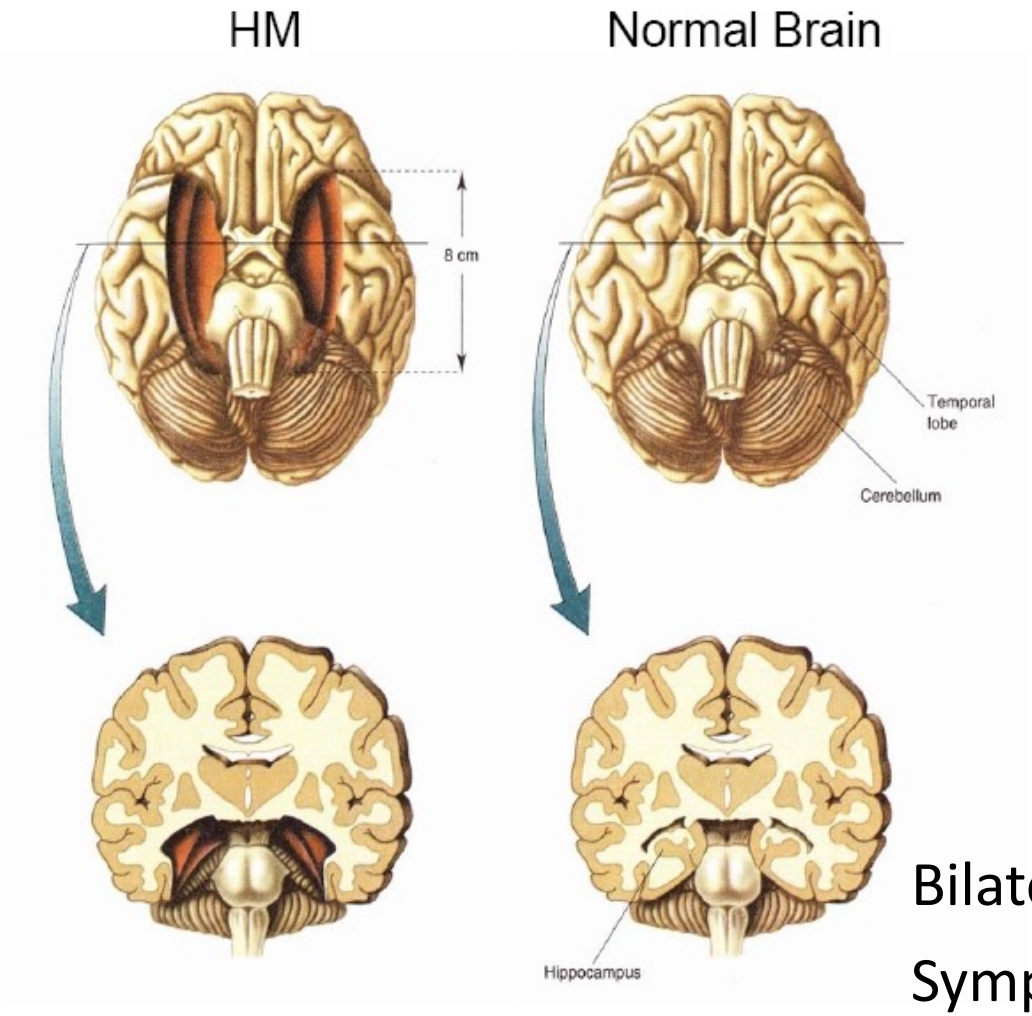
1. Describe the two primary types of amnesia, and how amnesia patients helped us understand the nature of memory in the brain.
2. Describe and define the divisions of memory.
3. What does the hippocampus do? Why might it be necessary for explicit long-term memory formation?
4. What is long-term potentiation? Describe how it works at the synaptic level, including the key receptors. How do these receptors and LTP explain a variety of brain-dysfunction-related phenomena?
5. Explain what Korsakoff's syndrome is, and describe the memory deficits associated with it. What brain structure(s) are implicated in Korsakoff's syndrome?
6. Describe the symptoms and progression of Alzheimer's disease.
7. Identify three major neurological features of Alzheimer's disease.
8. Identify seven biomarkers of Alzheimer's disease.
9. Discuss theories of the pathogenesis of Alzheimer's disease. While none is a perfect fit, which theory currently seems to best describe the disease? How might some of these theories work together to cause the disease?
10. Read the associated paper by Quiroga on concept cells (as discussed with the "Halle Berry neuron" in our previous lecture). How might these concept cells be related to the biological processes of memory, including hippocampal indexing and consolidation?

Types of amnesia



Retrograde amnesia is more common for recent memories than for older memories

Patient HM



Bilateral medial temporal lobectomy to treat epilepsy

Symptoms seem especially (but not solely) related to hippocampus loss

HM's symptoms

Brenda Milner

Profound anterograde amnesia

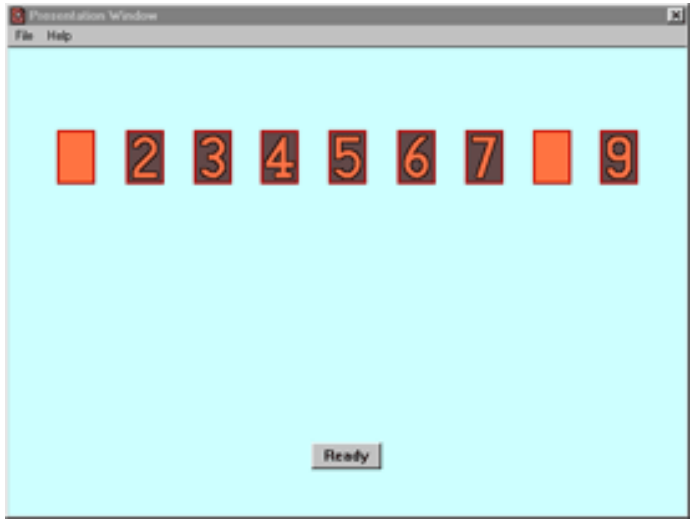
Some retrograde amnesia

BUT not all memory affected…

Memory duration

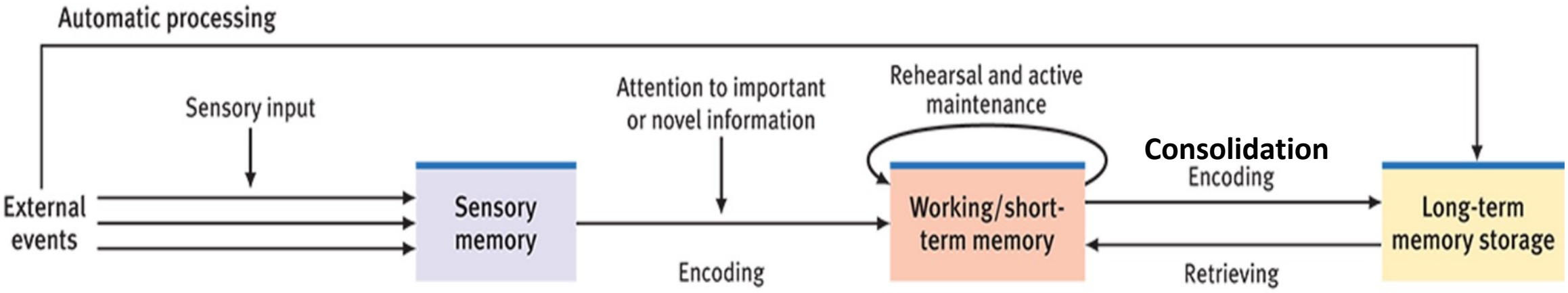
Working (aka short-term) memory

e.g. HM could perform digit task



Long-term memory

HM could not consolidate



Amnesia

Consciousness & memory

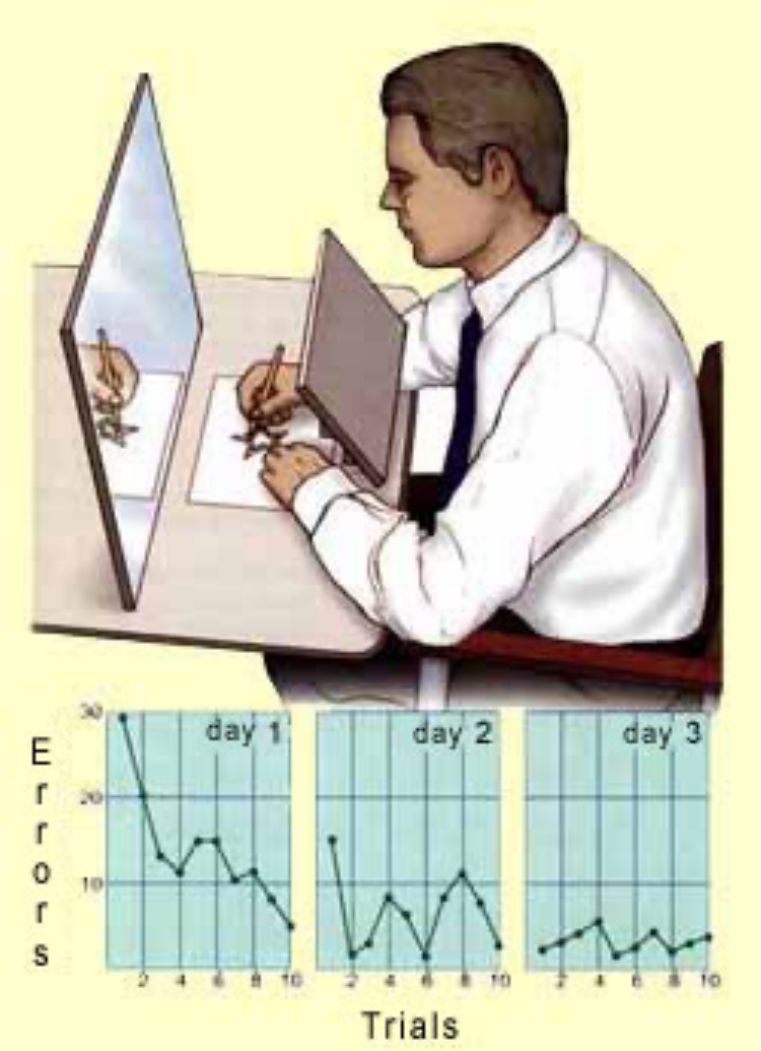
HM's memory was not impaired for:

Mirror drawing test

Pavlovian conditioning

Priming

S _ _ P



Consciousness & memory

Explicit memory

vs.

Implicit memory

Subtypes of explicit memory

Other amnesia patients demonstrated that some types of explicit memory could be lost, while others were intact, which led to separation of:

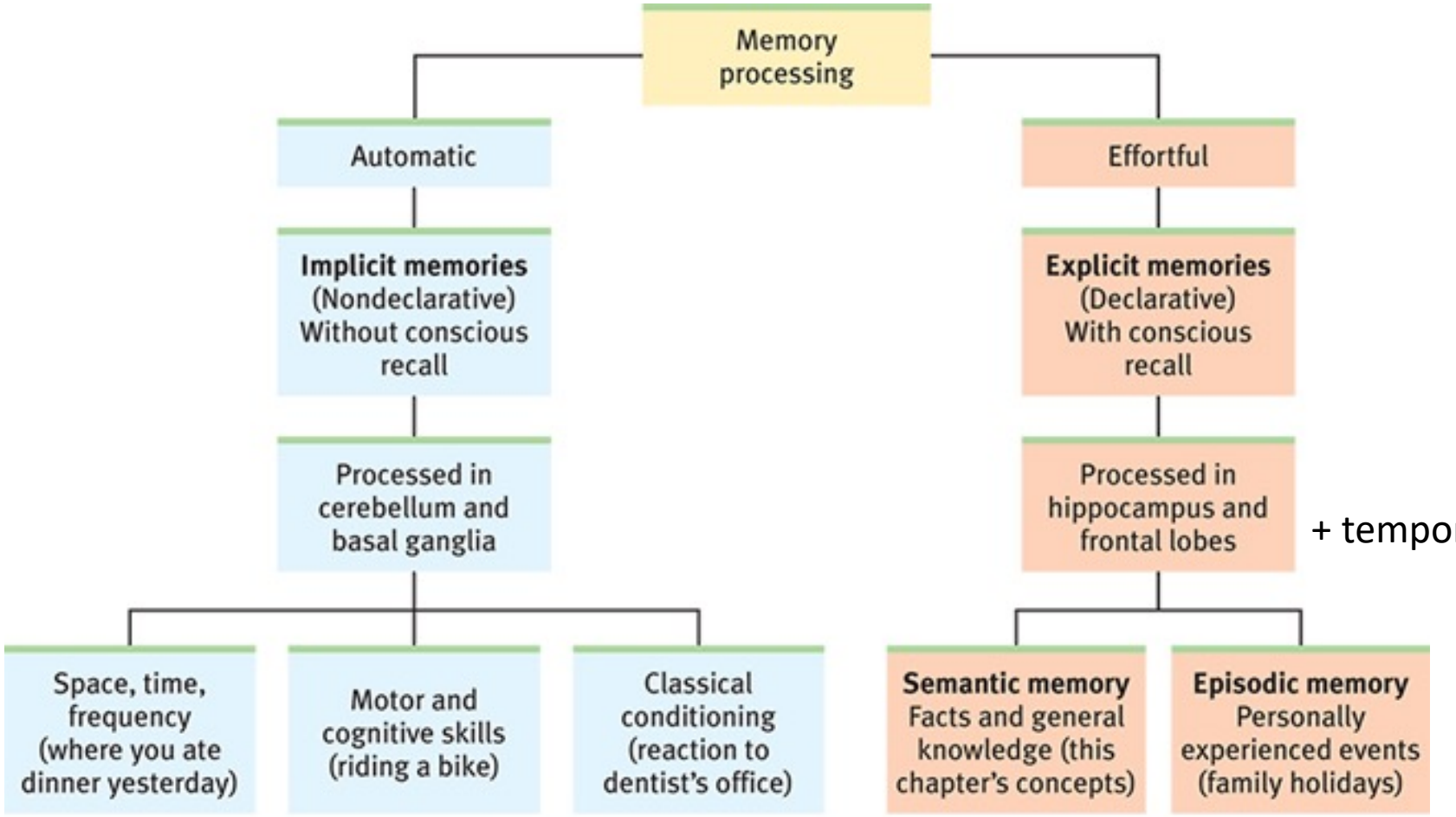
Episodic memory

Semantic memory

https://www.youtube.com/watch?v=tXHk0a3RvLc

Patient KC

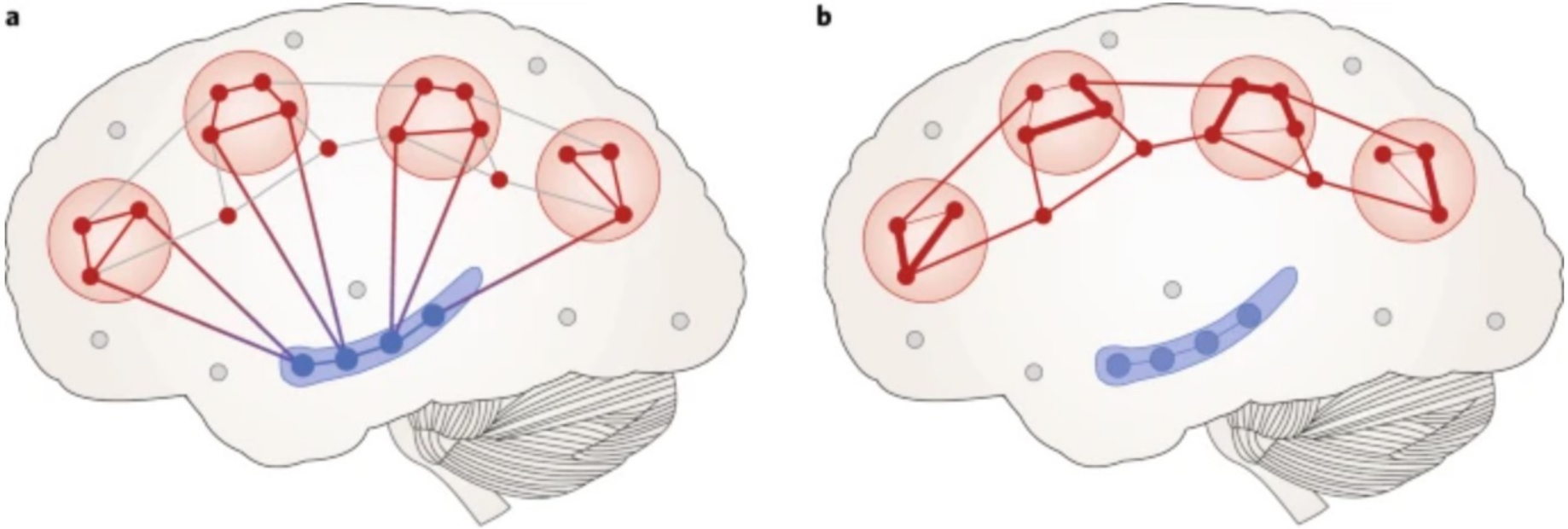
In sum: memory is not a unitary construct



+ temporal lobes

So what's the hippocampus actually doing?

- Hippocampal indexing theory
  (Teyler and DiScenna, 1986; Teyler and Rudy, 2007)
- Indexing required (at first) to generate recall from other areas



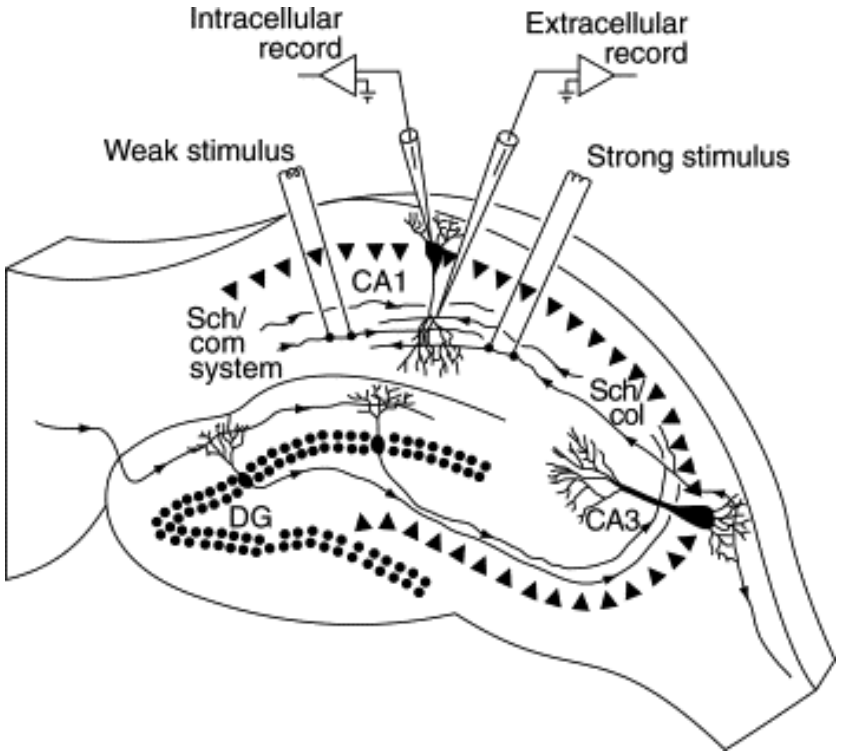
Amnesia

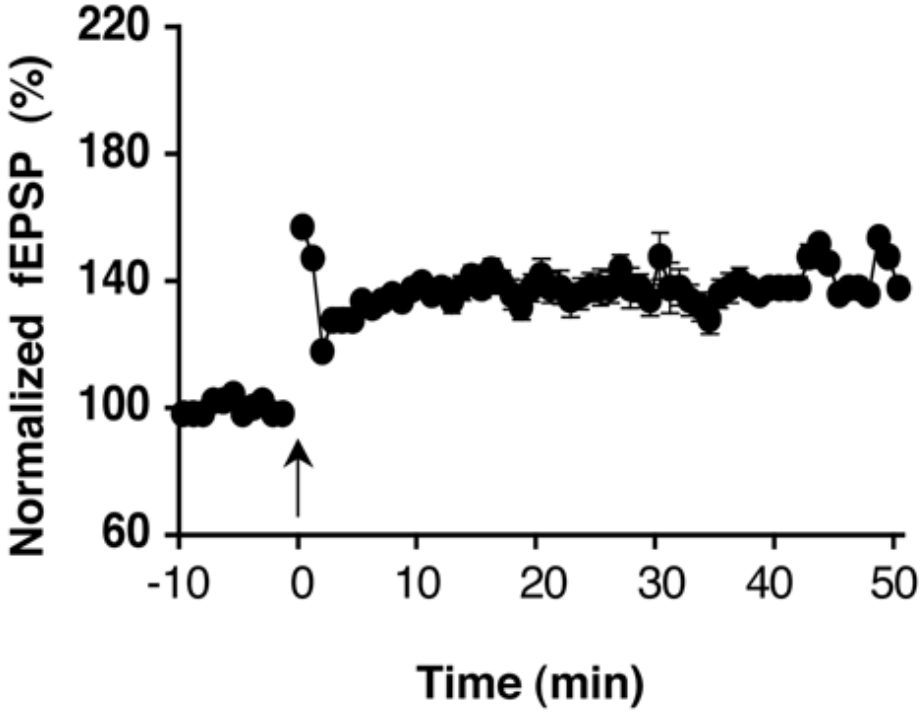
A cellular basis for memory: Long-term potentiation (LTP)

Performed in rats, in the hippocampus

Artificial stimulus (tetanus), but likely mimics natural pattern

Measure via electrodes





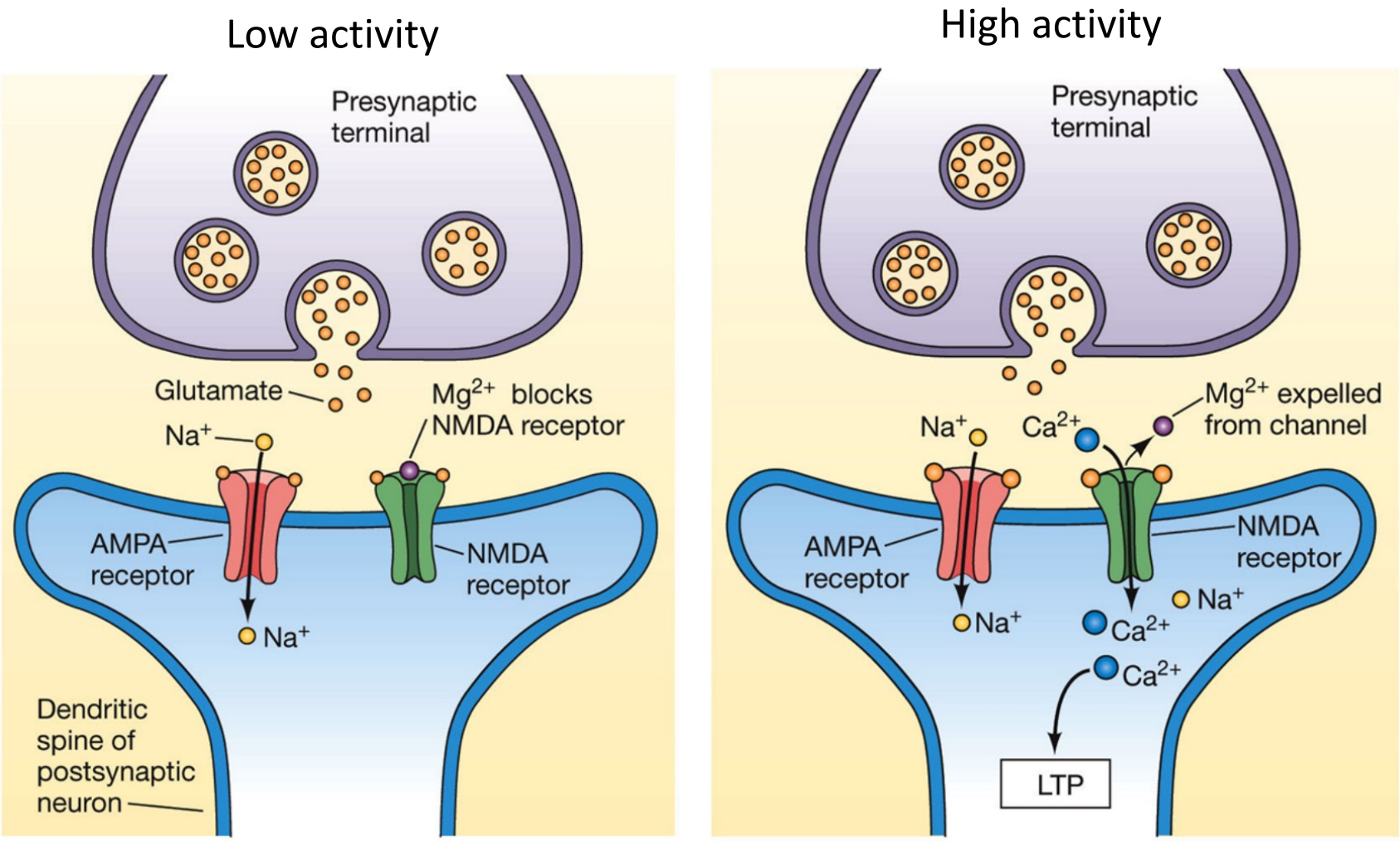
How LTP works

As previously discussed

AMPARs

NMDARs

Magnesium block

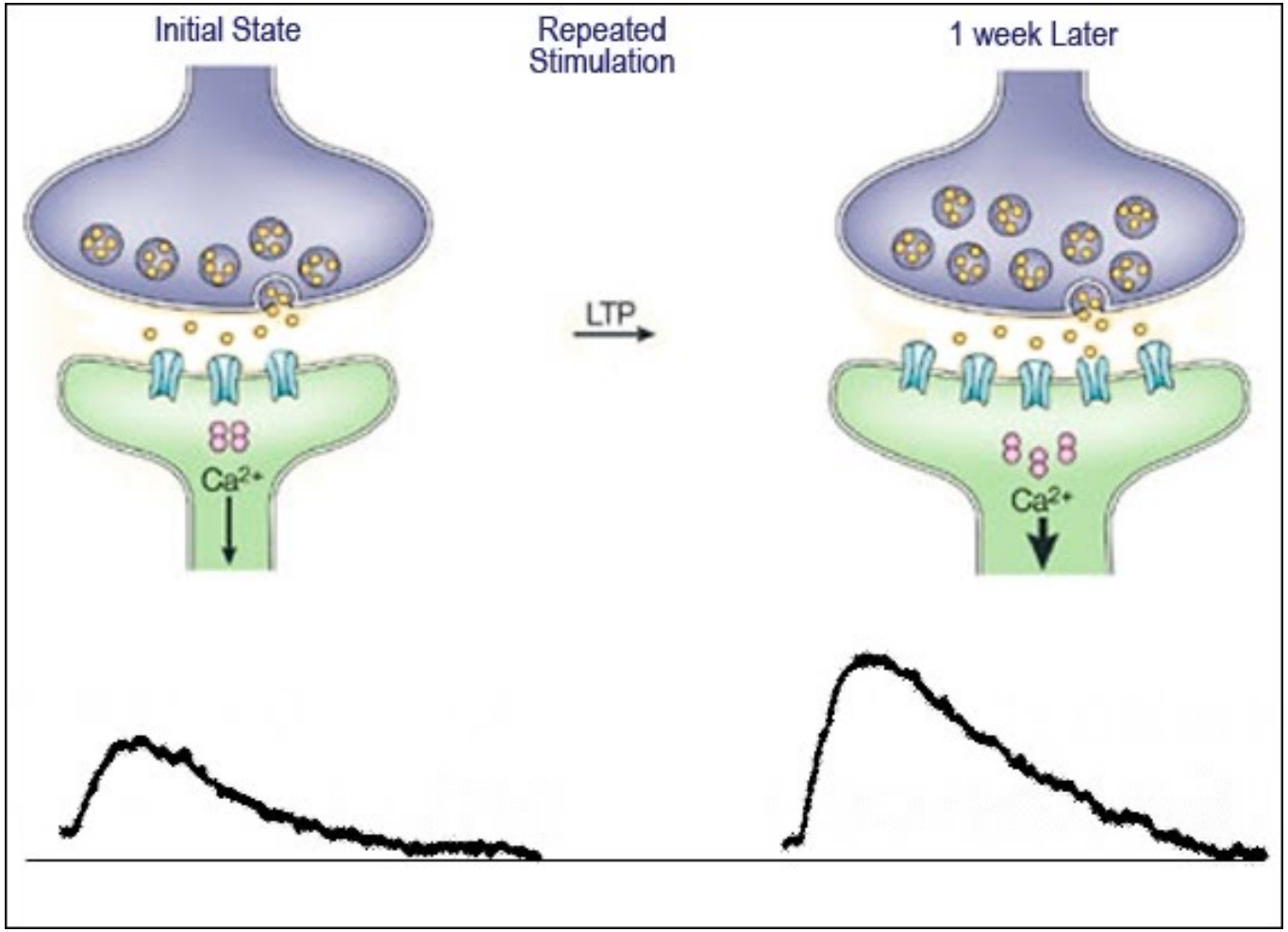


https://www.youtube.com/watch?v=vso9jgfpI_c

Changes during LTP

Functional (immediate)

Structural (slower, long-lasting)



NMDARs are implicated in a number of brain dysfunctions

LTP is more prominent in memory-related areas

So is epilepsy!

NMDAR activity allows Ca++ into the cell

Ca++ is a potent signalling molecule

Too much Ca++ triggers apoptosis

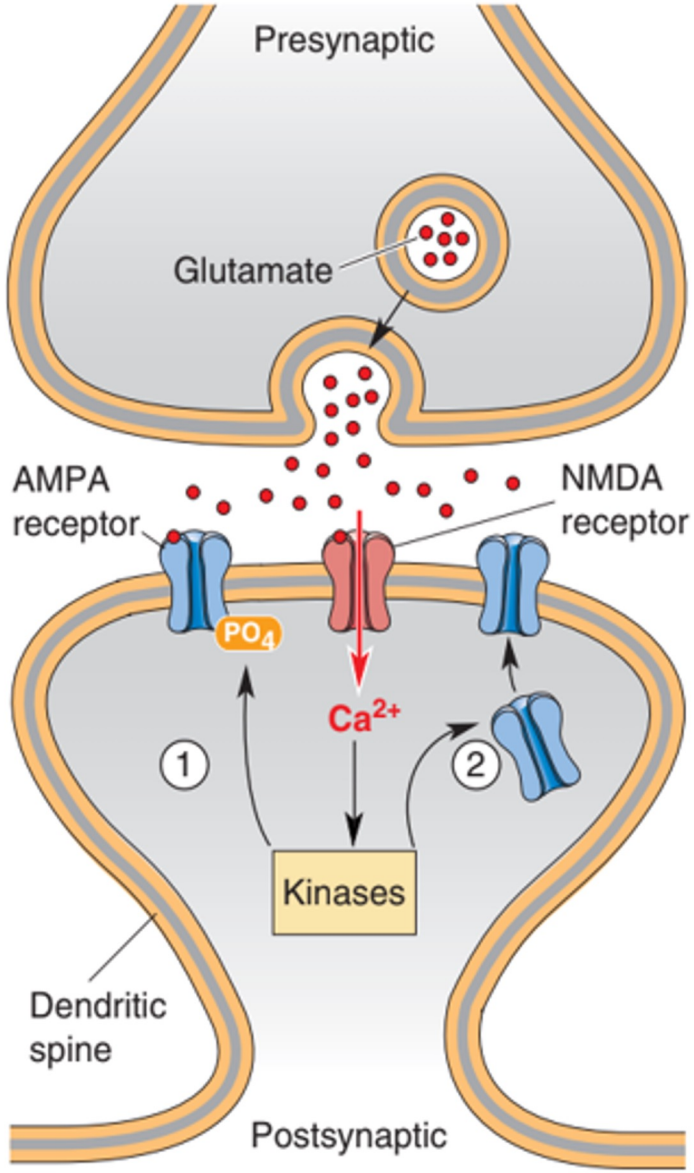
As in stroke penumbra

As in excitotoxicity in general

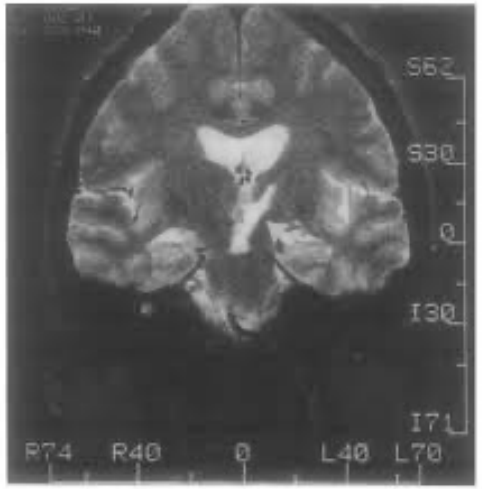
As in tonic-clonic seizures

Alcohol, PCP, ketamine are NMDAR antagonists

Effect on memory?



Korsakoff’s syndrome



Patient NA

Without memory
https://www.facebook.com/watch/?v=2914043962216

aka Wernicke-Korsakoff’s syndrome

A medial diencephalic amnesia

c.f. Patient NA

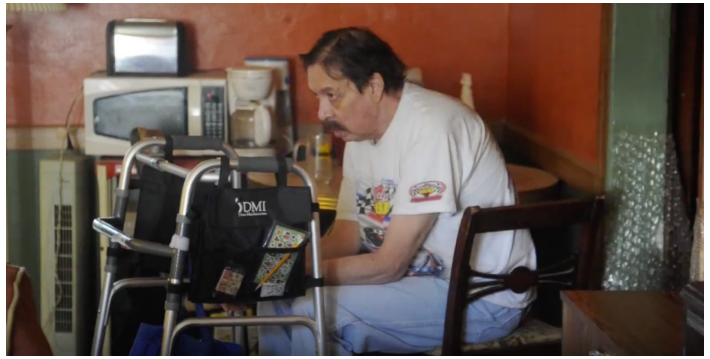
Caused by brain damage due to thiamine (vitamin B1) deficiency

Severe anterograde amnesia, mild retrograde amnesia

Commonly seen in prolonged, heavy alcohol consumption

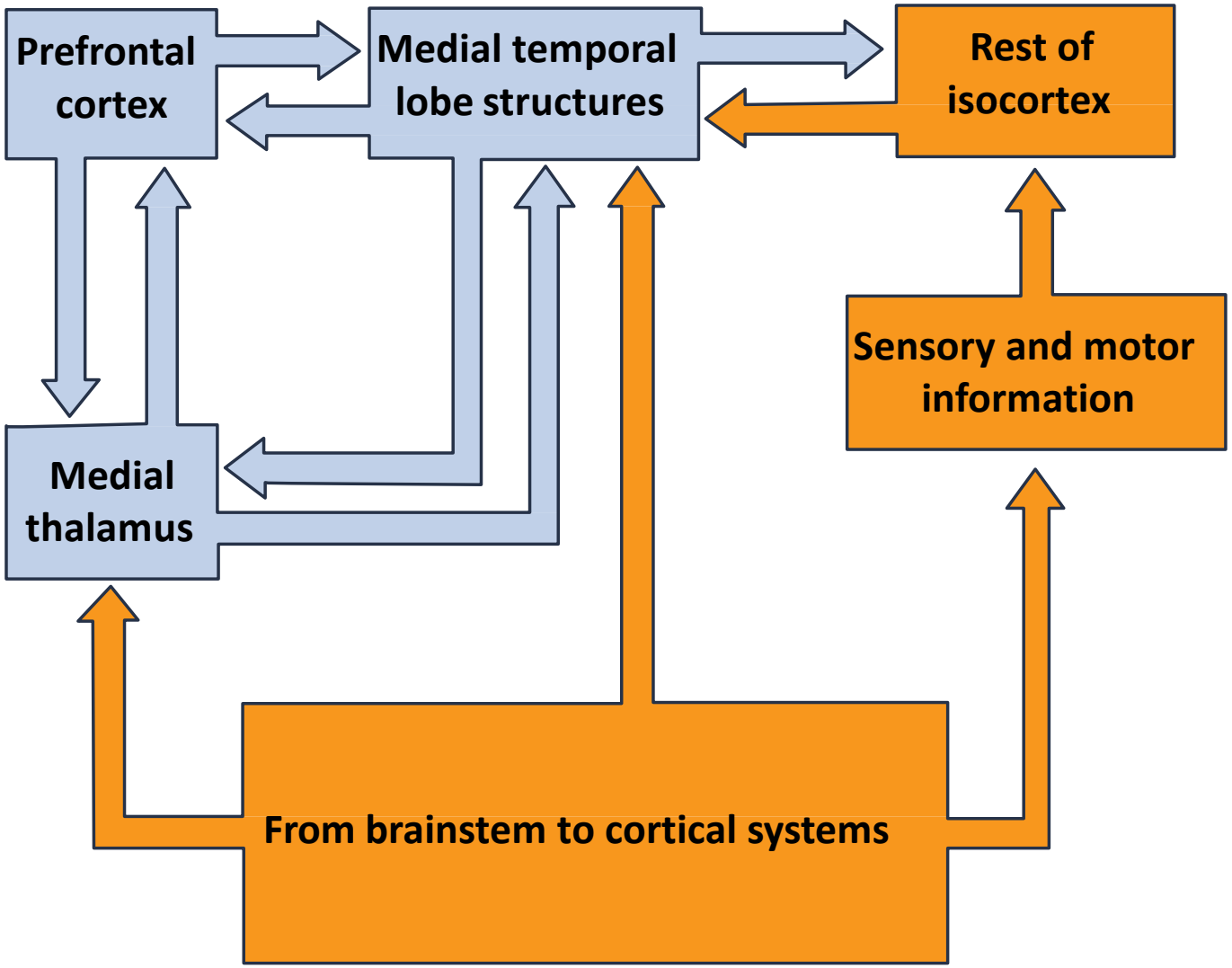
Why? (2)

Amnesia + sensorimotor problems, confusion, personality changes (i.e. dementia)



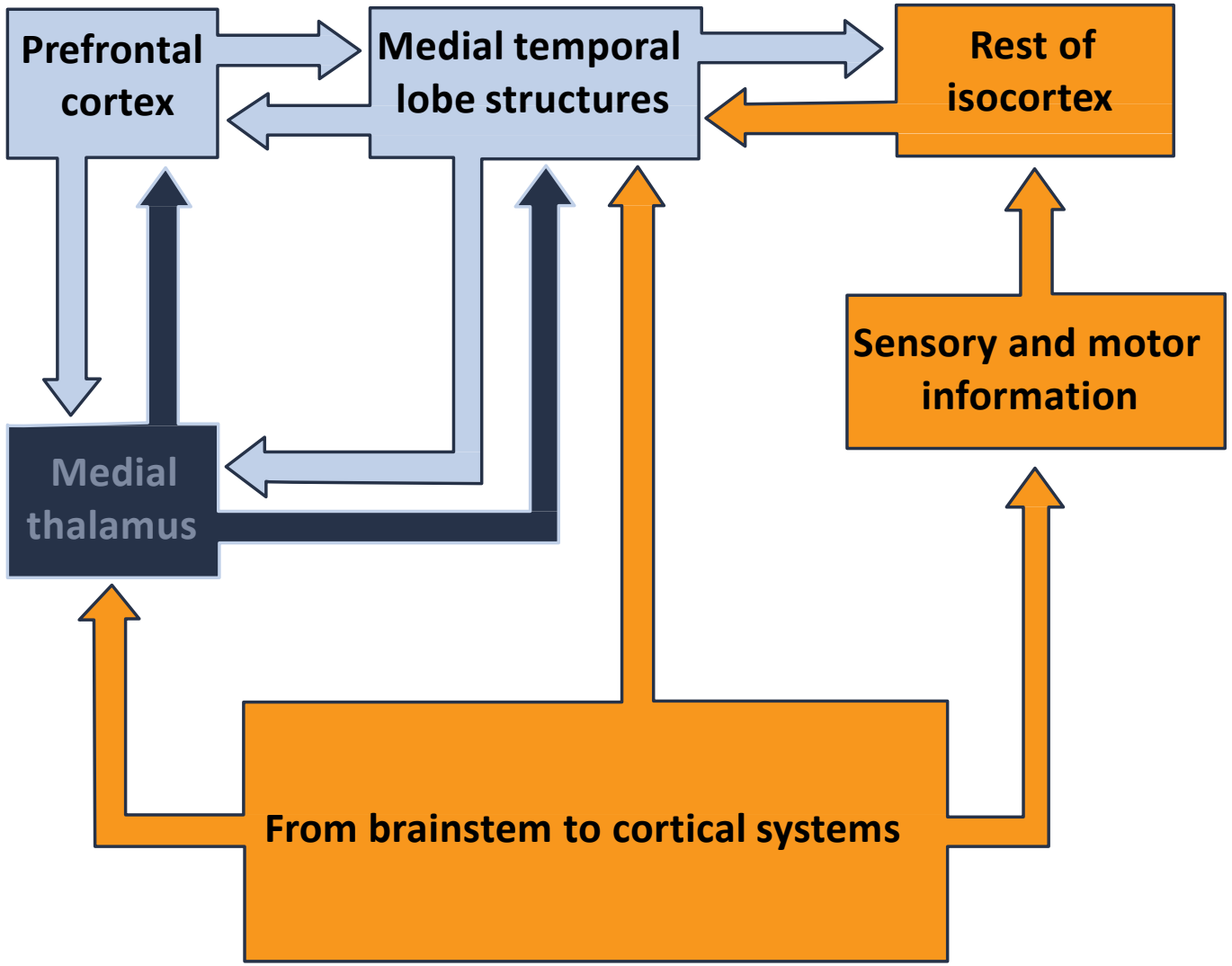
https://www.youtube.com/watch?v=AZ1Rc22MKu4

Proposed neural circuit for explicit memory



adapted from Kolb & Wishaw, 2009

Proposed neural circuit for explicit memory



adapted from Kolb & Wishaw, 2009

Alzheimer’s disease

Most common cause of dementia

Early symptoms sometimes referred to as mild cognitive impairment (MCI)

Early symptoms: selective declines in memory

Later symptoms: confusion, irritability, anxiety, deterioration of speech

Advanced stages: difficulties with even simple responses or behaviours (e.g. swallowing, bladder control)

Alzheimer’s disease

Tremendous incidence in older adults

Occasional early onset from genetics, but otherwise no single gene associated with AD

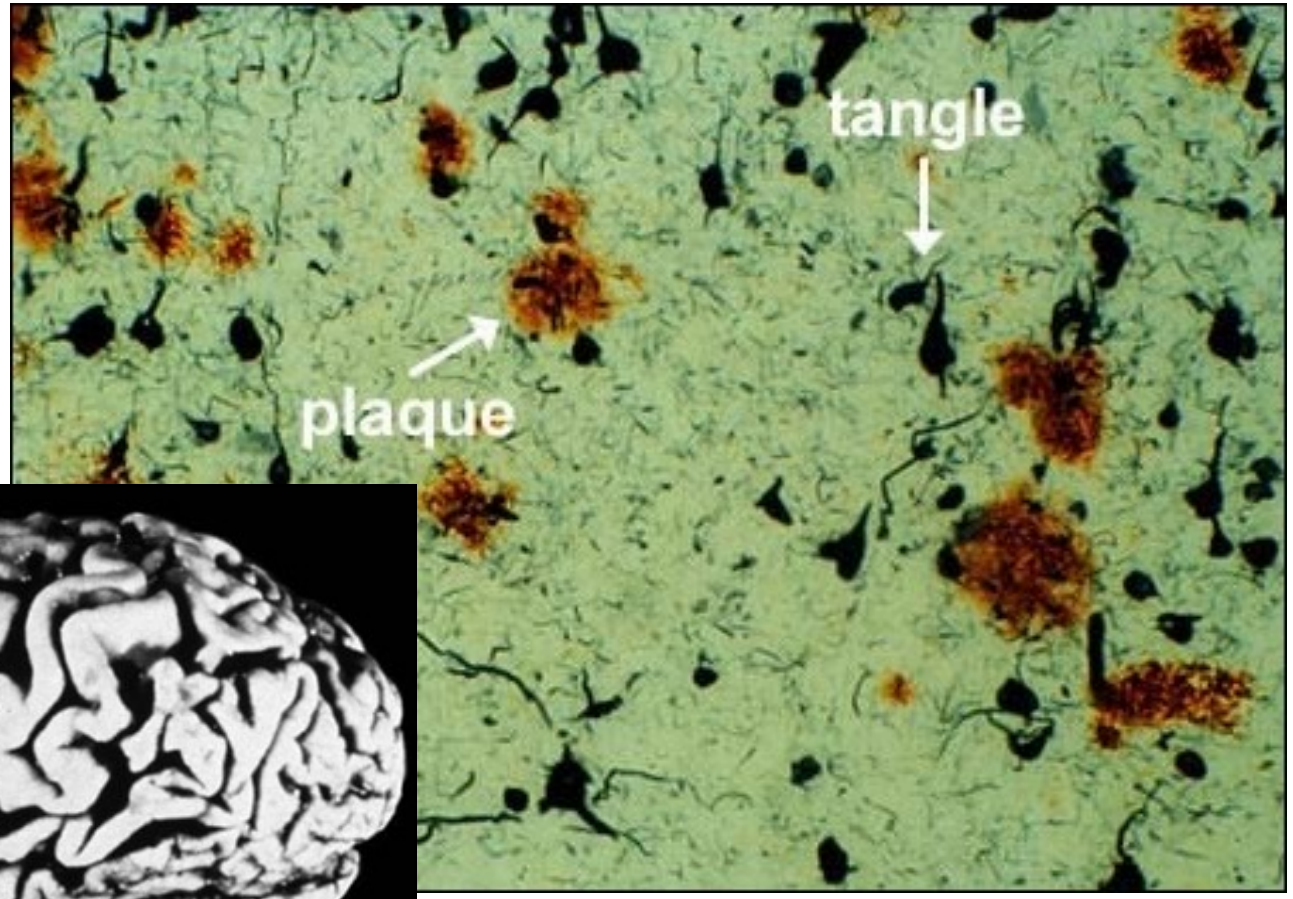
Appears first in the medial temporal lobe structures, then to cortex

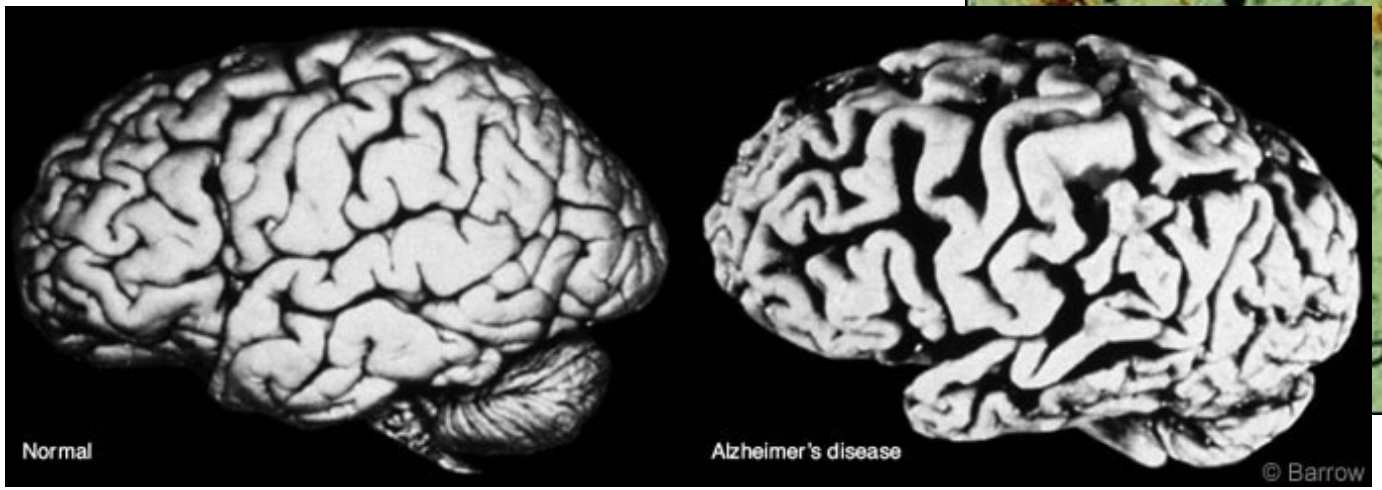
No cure

Diagnosis traditionally “probable” until post-mortem

The defining characteristics of AD

1. Brain volume decrease
2. Neurofibrillary tangles
3. Amyloid plaques

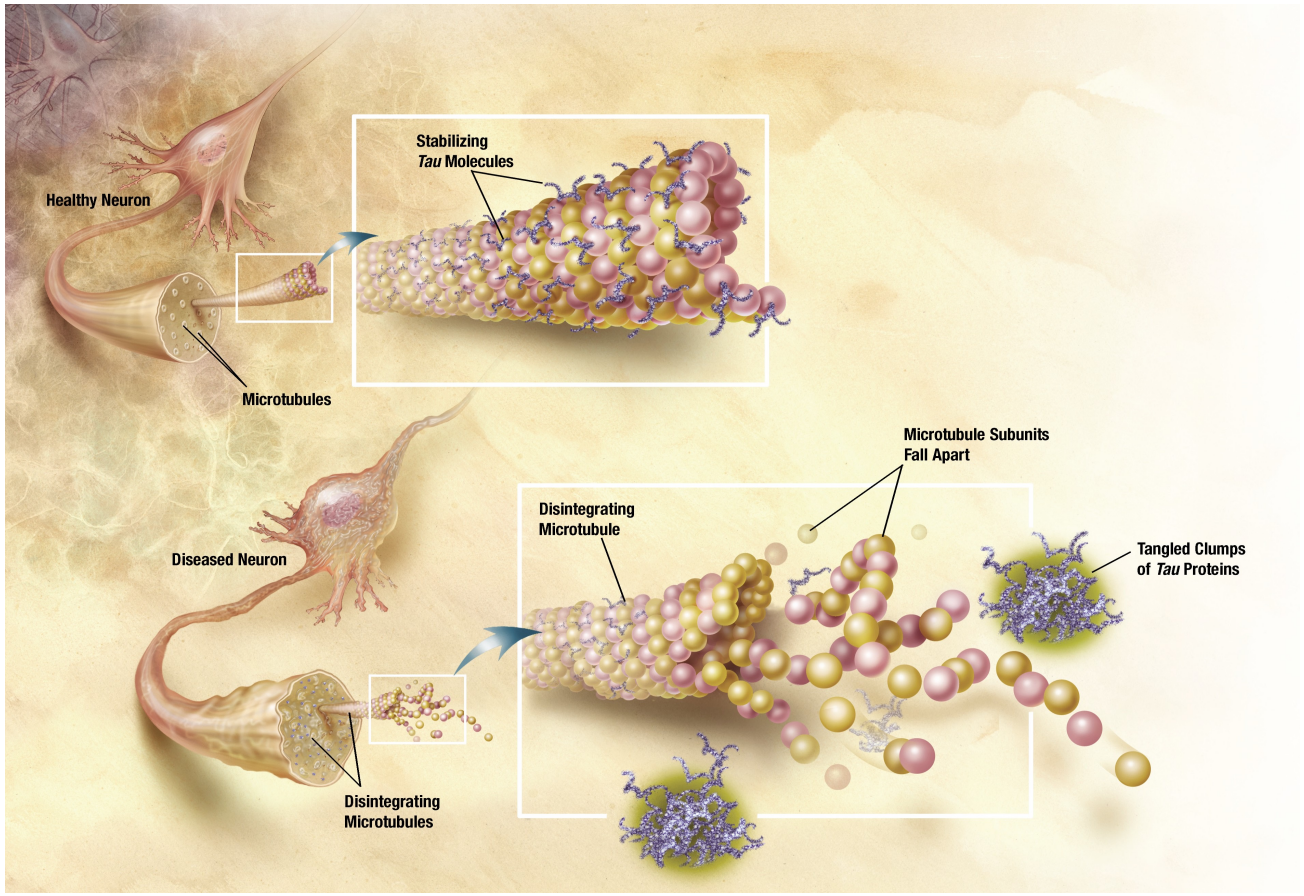




Neurofibrillary tangles (again)

i.e. Hyperphosporylated tau aggregates

Intracellular

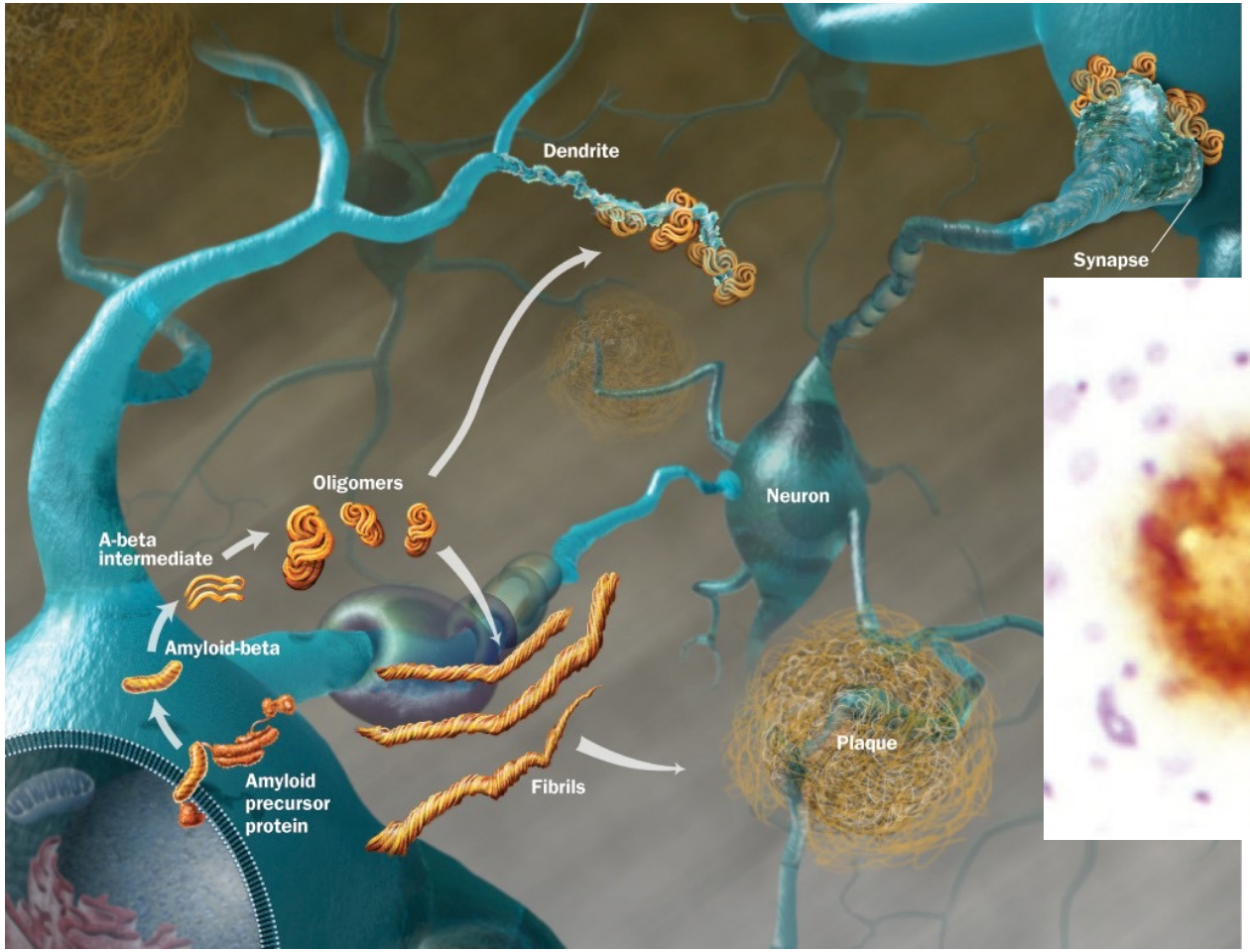


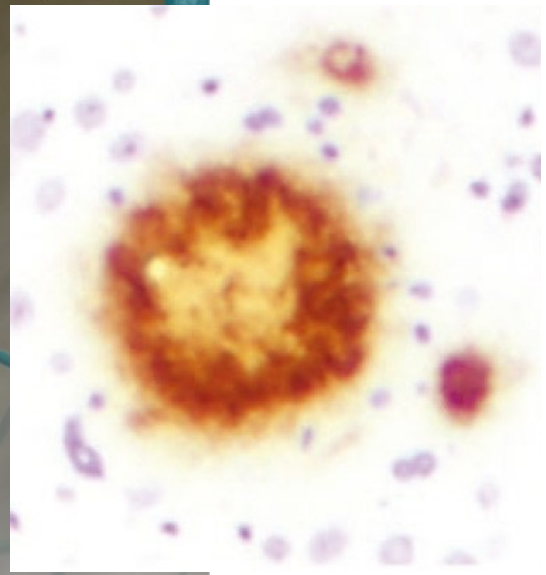
Amyloid plaques

Comprised of beta-amyloid protein, aka A-beta

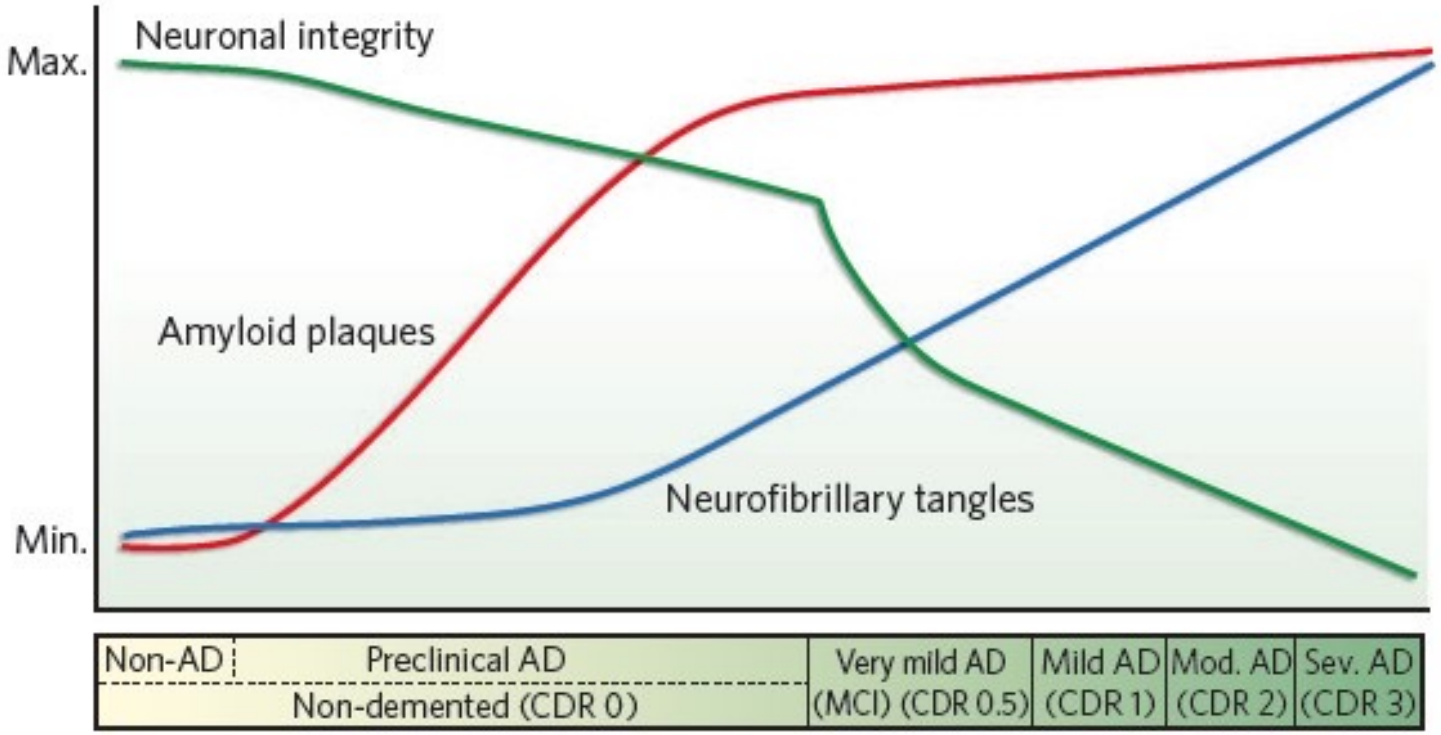
Beta-amyloid comes from amyloid precursor protein (APP)

Extracellular





Time course of AD



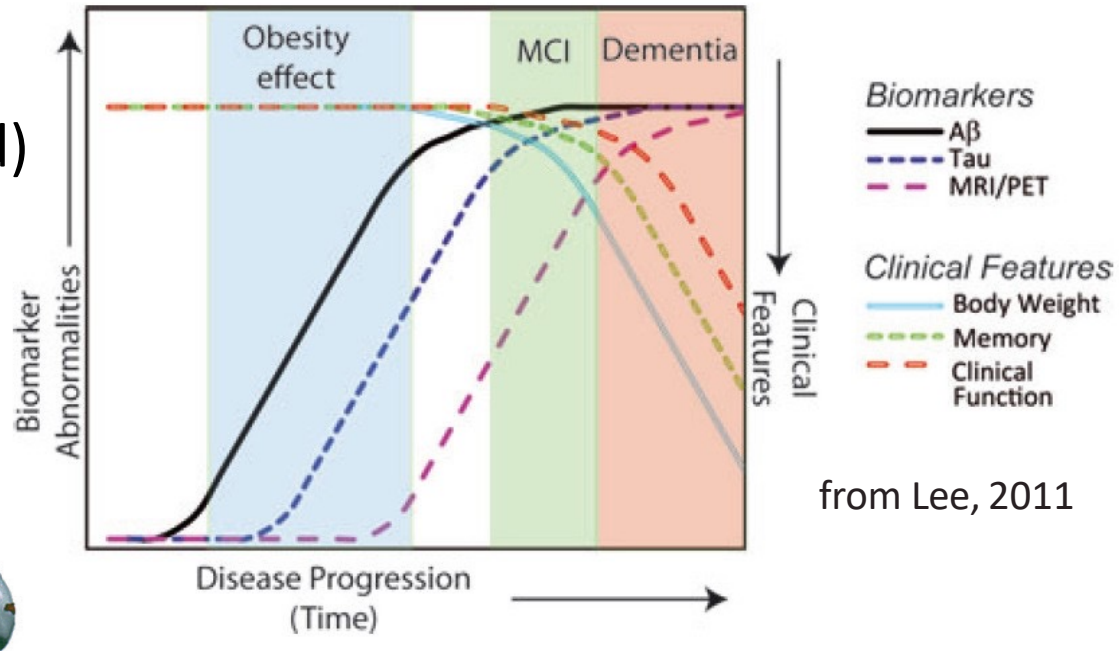
from Perrin, Fagan, & Holtzman, 2009

Likely the end result of processes long progressing in silence

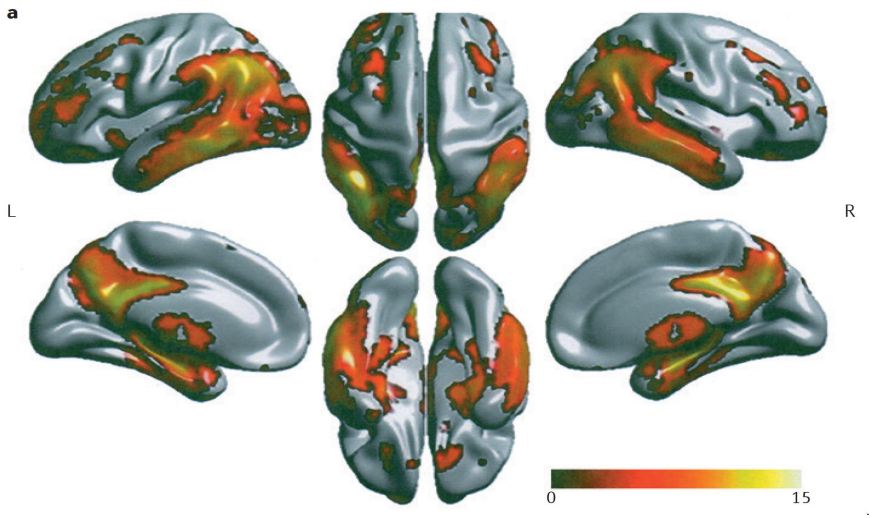
(sound familiar?)

Biomarkers for AD

1. Low beta-amyloid levels in cerebrospinal fluid
2. High tau levels in cerebrospinal fluid
3. PET imaging of beta-amyloid levels (e.g. Amyvid)
4. PET imaging of tau / hyperphosphorylated tau
5. Decreases in hippocampal volume (MRI)
6. Decreases in brain metabolism (FDG-PET)
7. Body weight



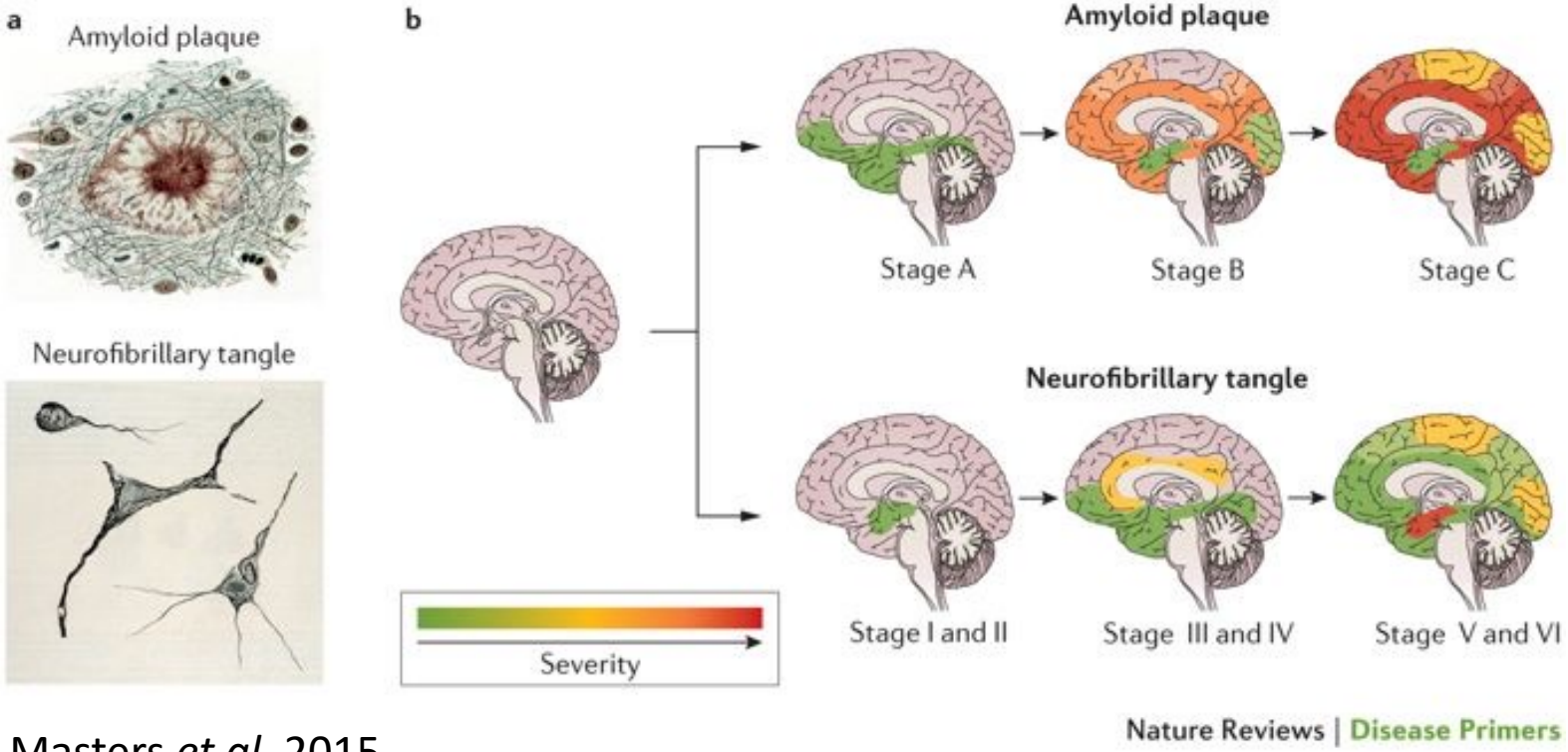
from Lee, 2011



from Jack et al. (2016)

Theories of pathogenesis of AD

1. Amyloid cascade hypothesis
2. Neurofibrillary (or tau) hypothesis
3. Vascular hypothesis
4. Pathogenic spread hypothesis
5. Bacterial hypothesis
   Gum disease & AD?
   e.g. Beydoun *et al*. 2021
6. Fungal hypothesis
   e.g. *Candida albicans*
   e.g. Wu *et al*. 2023
7. Autoimmune hypothesis

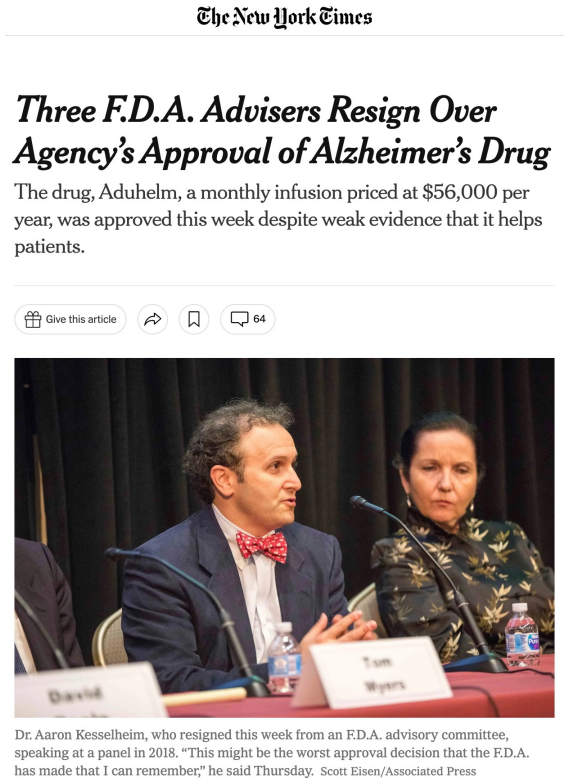


Masters *et al*. 2015

Treatments for AD?

1. Cholinergic (ACh) agonists, e.g. acetylcholinesterase inhibitors
2. NMDAR antagonist (memantine)
3. Lithium
4. Aducanumab (Aduhelm), antibodies for beta-amyloid, discontinued!
5. Lecanemab (Leqembi), recently approved
6. Physical exercise, environmental enrichment

   Also seem to be preventative!



The New York Times

Three F.D.A. Advisers Resign Over Agency's Approval of Alzheimer's Drug

The drug, Aduhelm, a monthly infusion priced at $56,000 per year, was approved this week despite weak evidence that it helps patients.

Give this article 64

Dr. Aaron Kesselheim, who resigned this week from an F.D.A. advisory committee, speaking at a panel in 2018. "This might be the worst approval decision that the F.D.A. has made that I can remember," he said Thursday. Scott Eisen/Associated Press