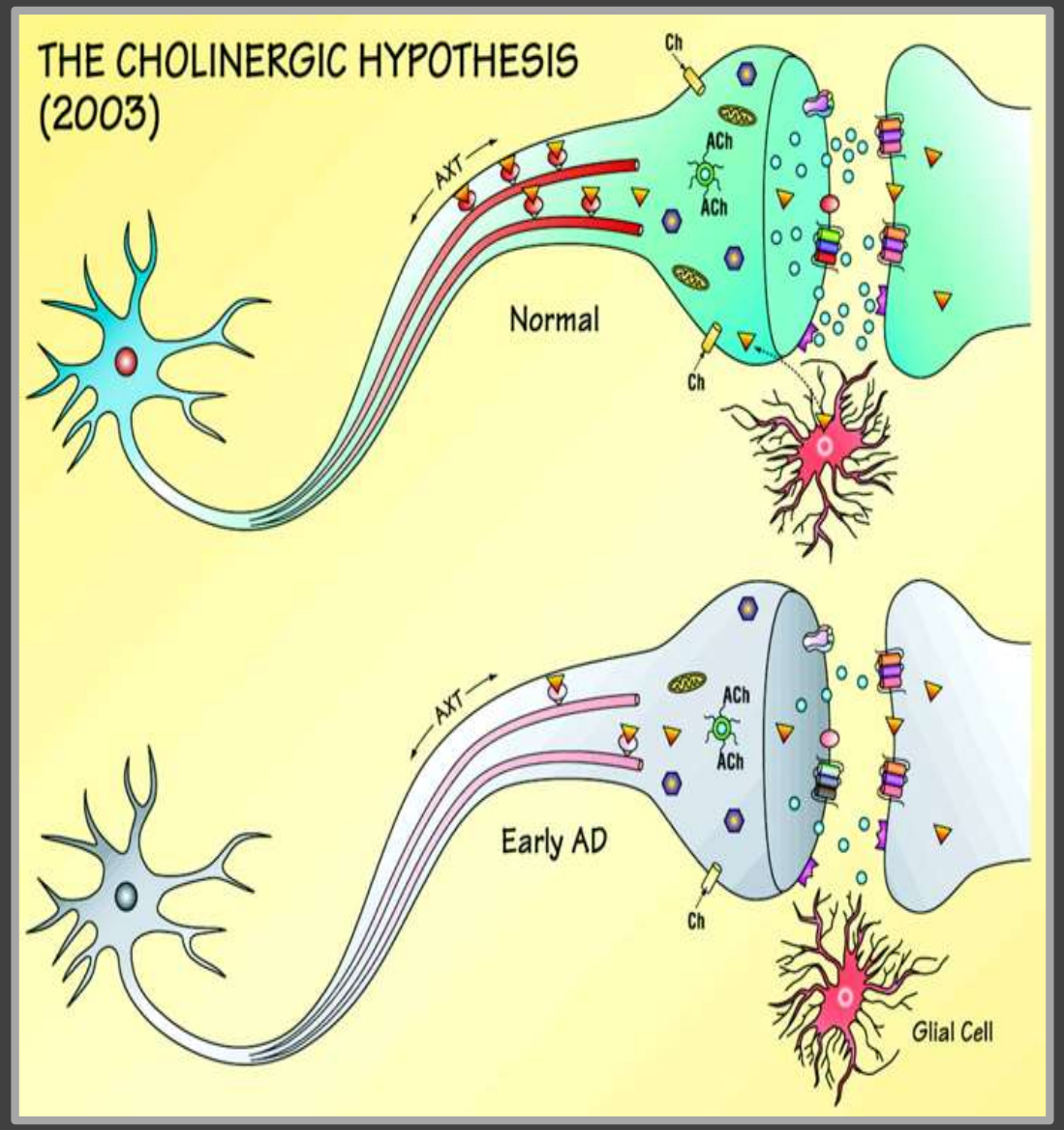

Understanding the treatment of Alzheimer's Disease

Jonathan Drake, MD

Rhode Island Hospital

Associate Director, Alzheimer’s Disease and Memory Disorders Center

April 25, 2024

Lifespan

BROWN
Alpert Medical School

LEARNING OBJECTIVES

- ATTAIN A BASIC FOUNDATION OF PATHOLOGIC BRAIN CHANGES IN ALZHEIMER'S DISEASE

- UNDERSTAND HOW SYMPTOMATIC THERAPIES TARGET CERTAIN ASPECTS OF ALZHEIMER'S DISEASE RELATED BRAIN CHANGES

- FROM THIS PERSPECTIVE, FURTHER UNDERSTAND OF THE RATIONALE BEHIND NEWLY FDA APPROVED DISEASE MODIFYING THERAPIES FOR ALZHEIMER'S DISEASE

OVERVIEW

- 1) Alzheimer's 101
  - Is it Alzheimer's or dementia?
  - Alzheimer's neurobiology basics
- 2) Symptomatic therapies Alzheimer's
  - Synapses and neurotransmitters
  - Not enough neurotransmitter: The case for Aricept
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  - Other neurotransmitters: Treating mood and thought disorders
- 3) The new era of disease modifying therapies

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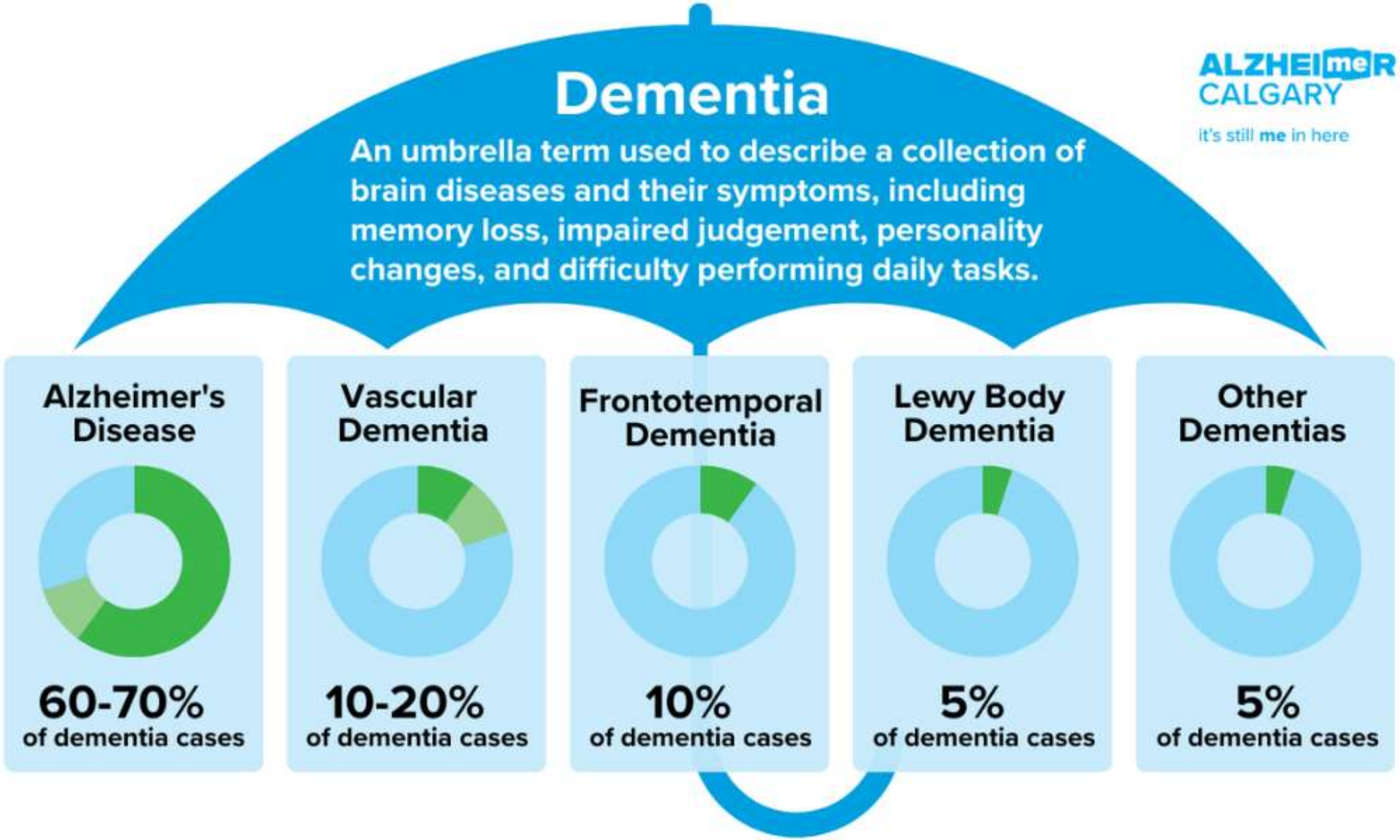
DEMENTIA: A DESCRIPTIVE TERM

- GENERAL TERM referring to cognitive impairment that leads to

  LOSS OF ABILITY TO **FUNCTION INDPENDENTLY** IN EVERYDAY LIFE

- Many ***Causes:***
  - Neurodegenerative disorders (i.e., Alzheimer's disease)
  - Cerebrovascular/microvascular disease
  - Medical conditions (B12 deficiency, hypothyroidism, etc.)
  - Brain injury
  - Many others…
- Contrast with **MILD COGNITIVE IMPAIRMENT**, where someone has cognitive impairment that *beyond expected age-related forgetfulness*, but for the most part ***ABLE*** **TO FUNCTION INDEPENDENTLY**

DEMENTIA: IS *CAUSED* BY A NUMBER OF *DISEASES*



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AD… is A PROGRESSIVE NEURODEGENERATIVE DISORDER

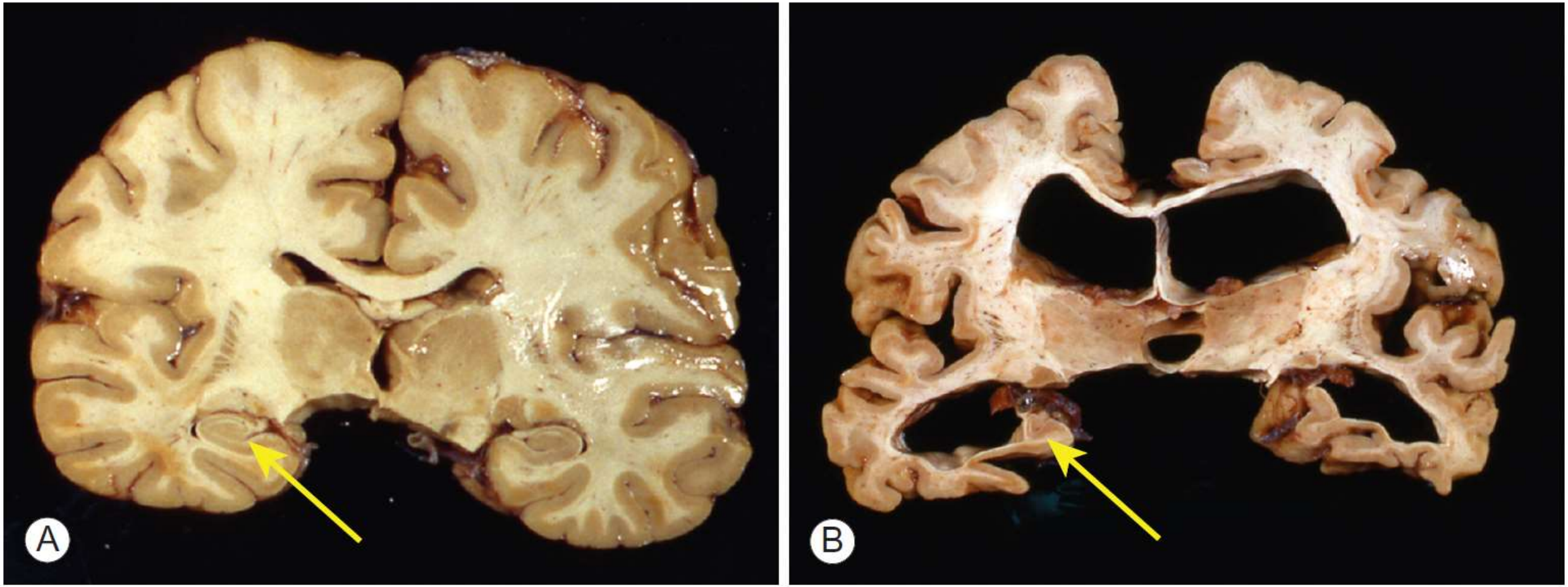
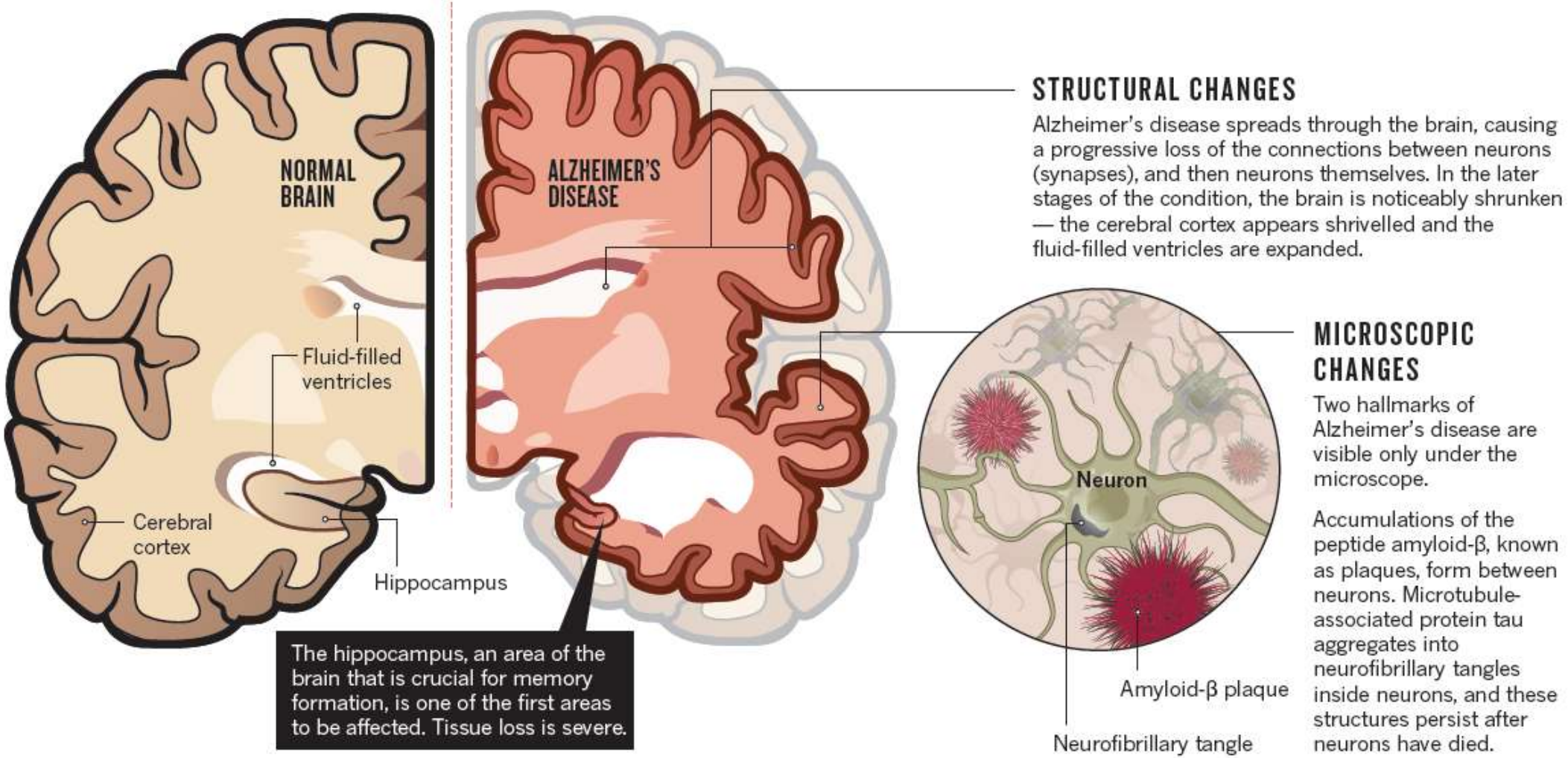


FIGURE 4-5 Coronal view of gross pathology in Alzheimer's disease. Coronal view through a brain with Alzheimer's disease **(B)** compared with a healthy brain **(A)**. Note the hippocampus (arrows), intact in the healthy brain and atrophic in the brain with Alzheimer's disease (note also the enlarged ventricles).

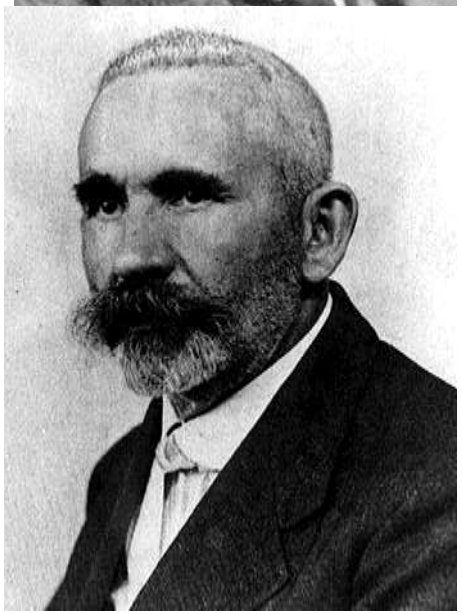
Source: Budson A, 2015

AD… begins with BUILD-UP OF TOXIC PROTEINS IN THE BRAIN



AD… characterized by build-up of AMYLOID AND TAU PROTEINS

- 1906 Alois Alzheimer: Reported "A peculiar severe disease process of the cerebral cortex" at the 37th Meeting of South-West German Psychiatrists
- 1906 + 1911 Alzheimer and Emil Kraepelin: Published reports demonstrating novel pathological findings attributed to this disease
- "Alzheimer's disease" (coined by Kraepelin in 1911) at that point referred to rare form of dementia affecting middle-aged
- "Senile dementia" (SD) referred to more common form of dementia affecting 65+ year-olds



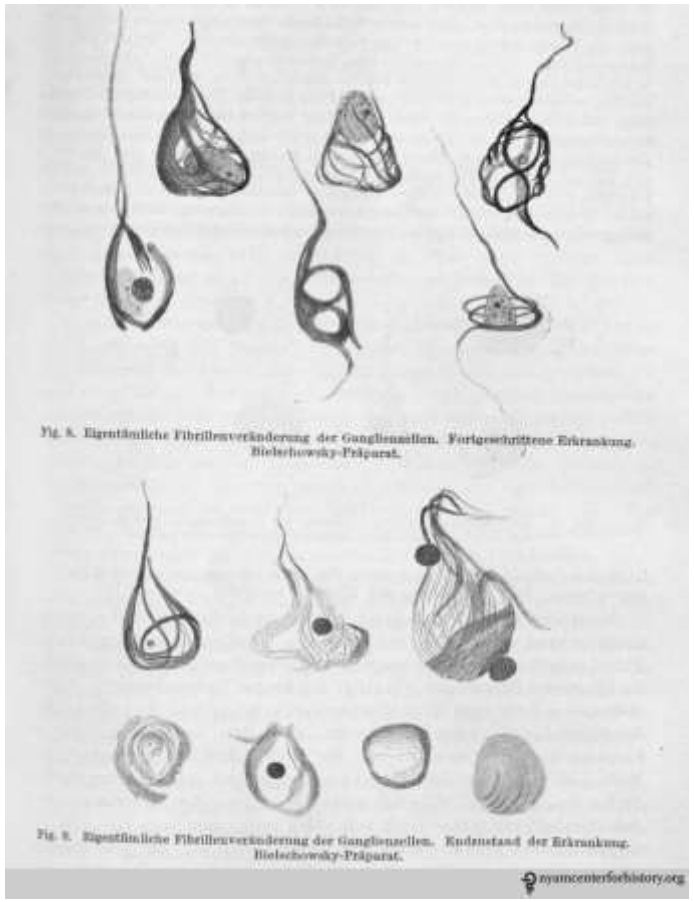
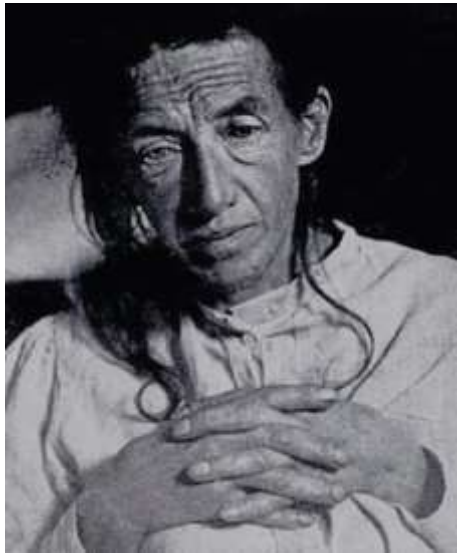


Fig. 8. Eigentümliche Fibrillenveränderung der Ganglienzellen. Fortgeschrittene Erkrankung. Bielschowsky-Präparat.

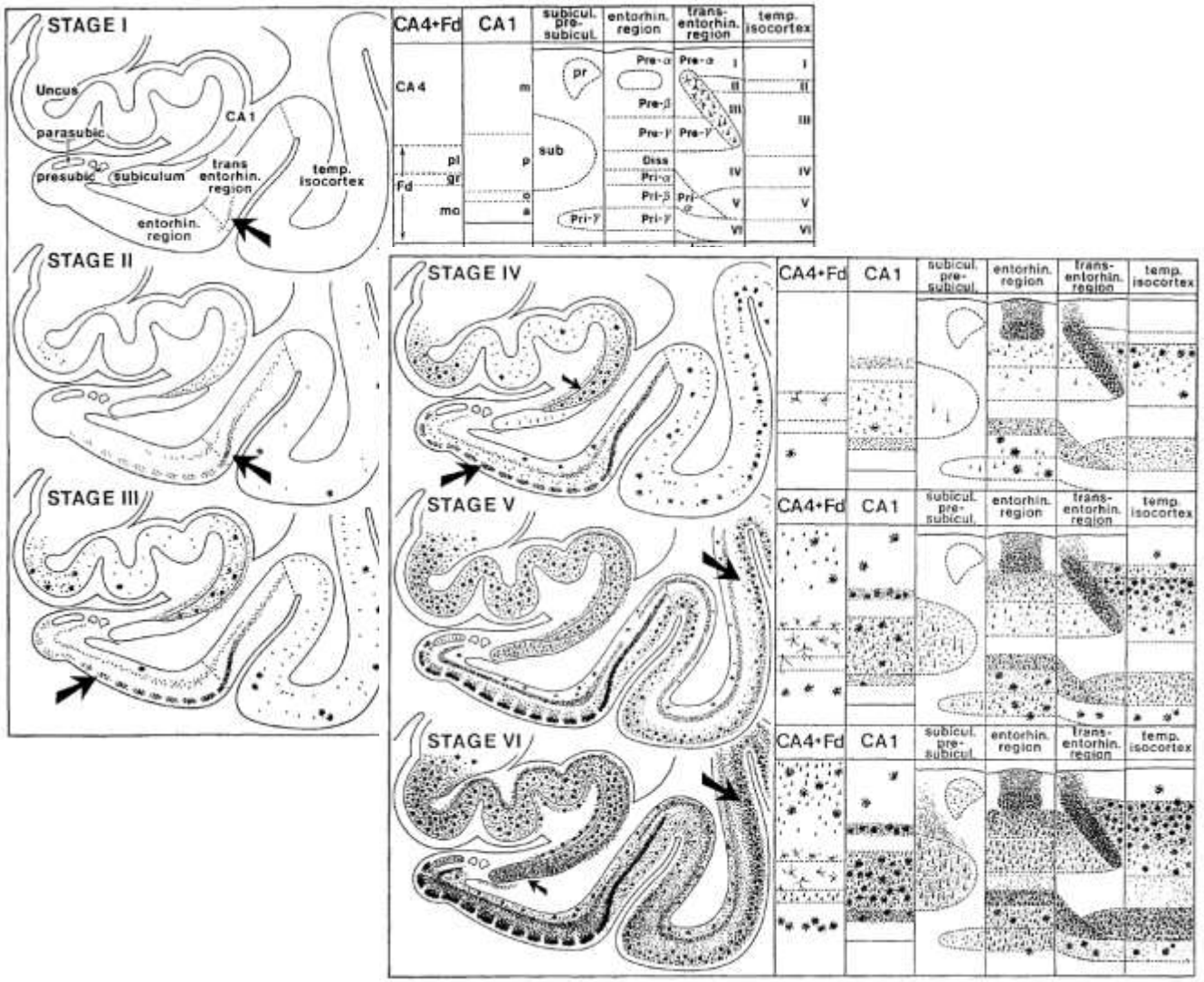
Fig. 9. Eigentümliche Fibrillenveränderung der Ganglienzellen. Endstadt der Erkrankung. Bielschowsky-Präparat.

nyamcenterforhistory.org



Auguste Deter

AD… is SPREAD OF PATHOLOGY



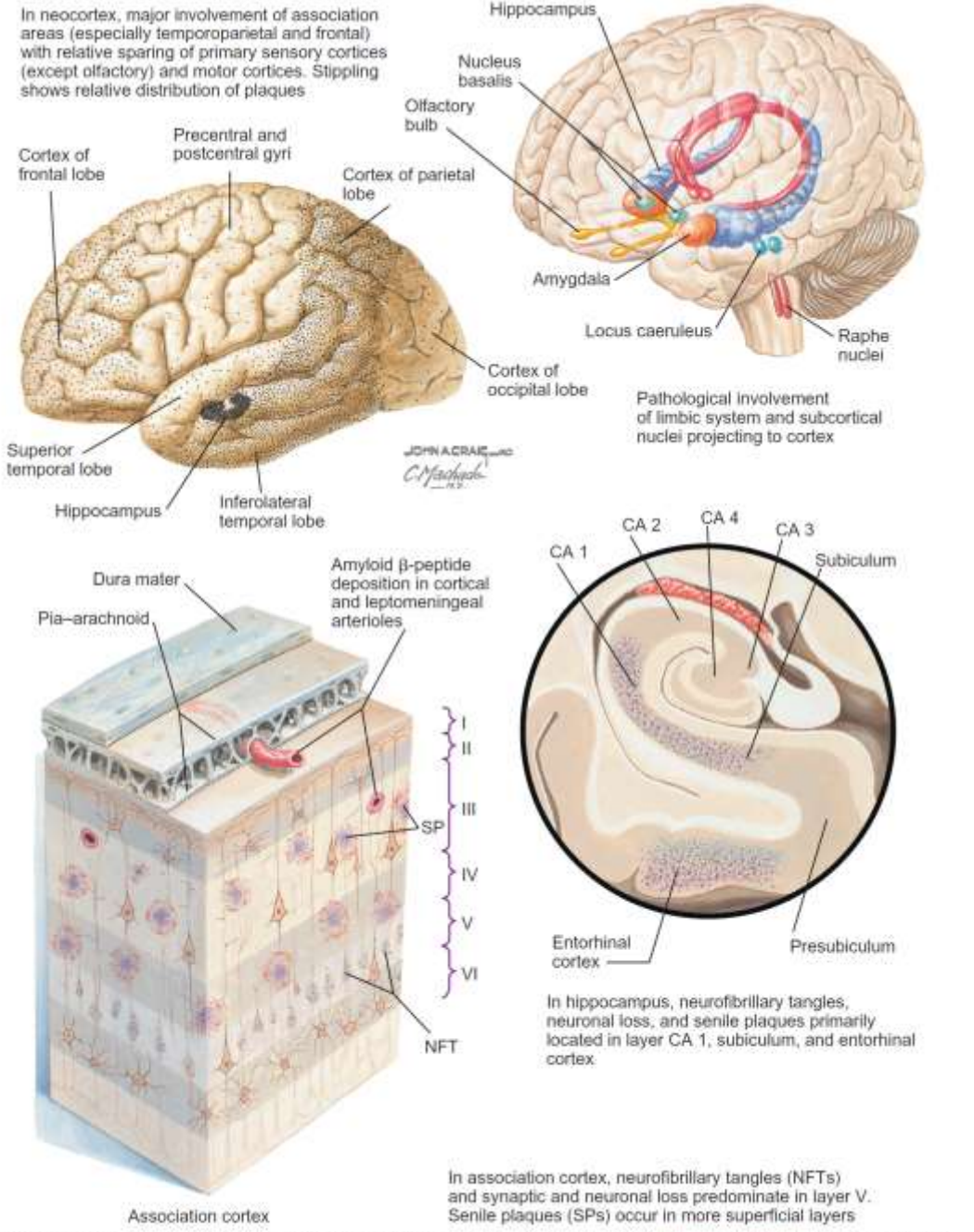
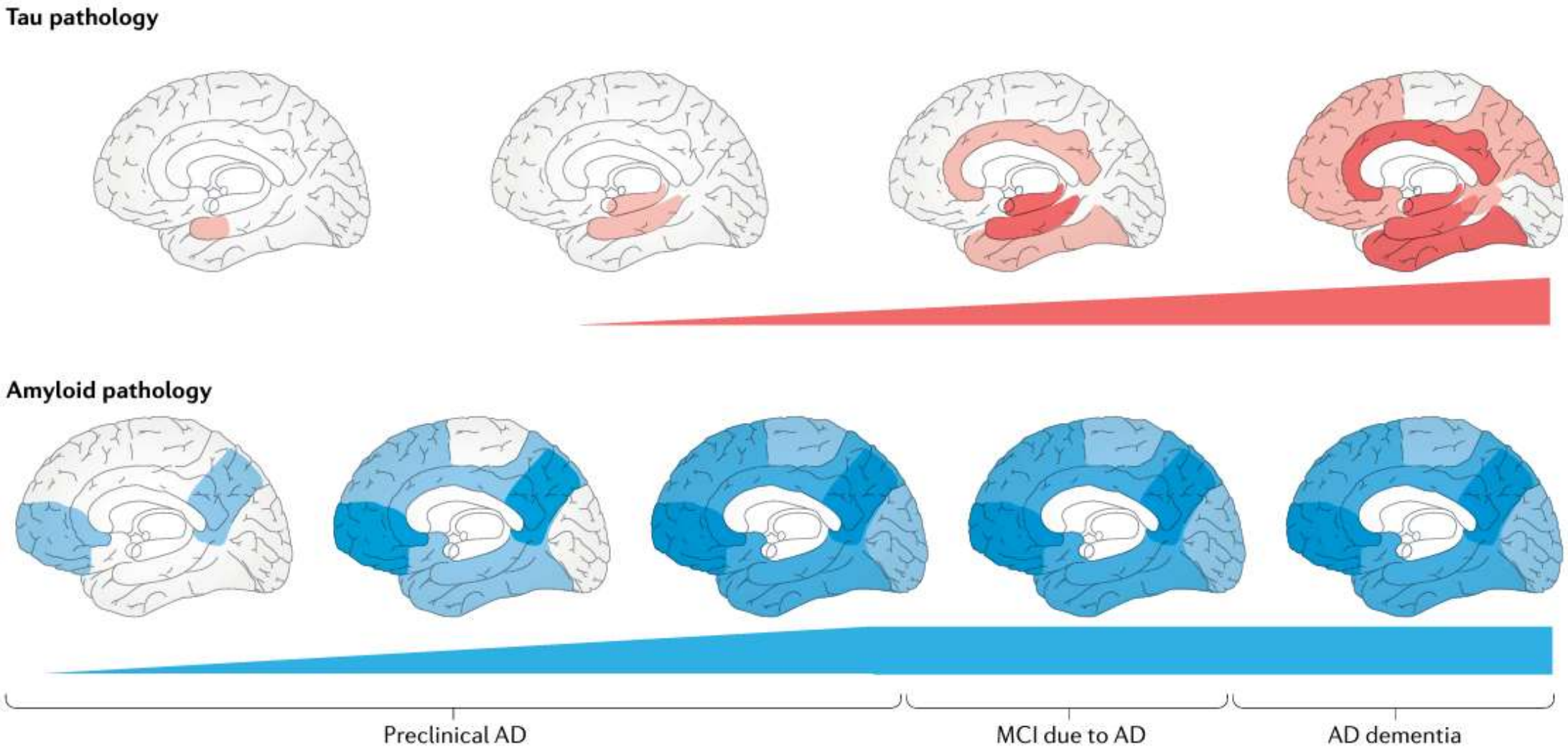


FIGURE 2-1 The relative distribution of Alzheimer's pathology in the brain. (Netter illustration from www.netterimages.com. Copyright Elsevier Inc. All rights reserved.)

Source: Budson A, 2015; Braak H, 1991

AD… is SPREAD OF PATHOLOGY

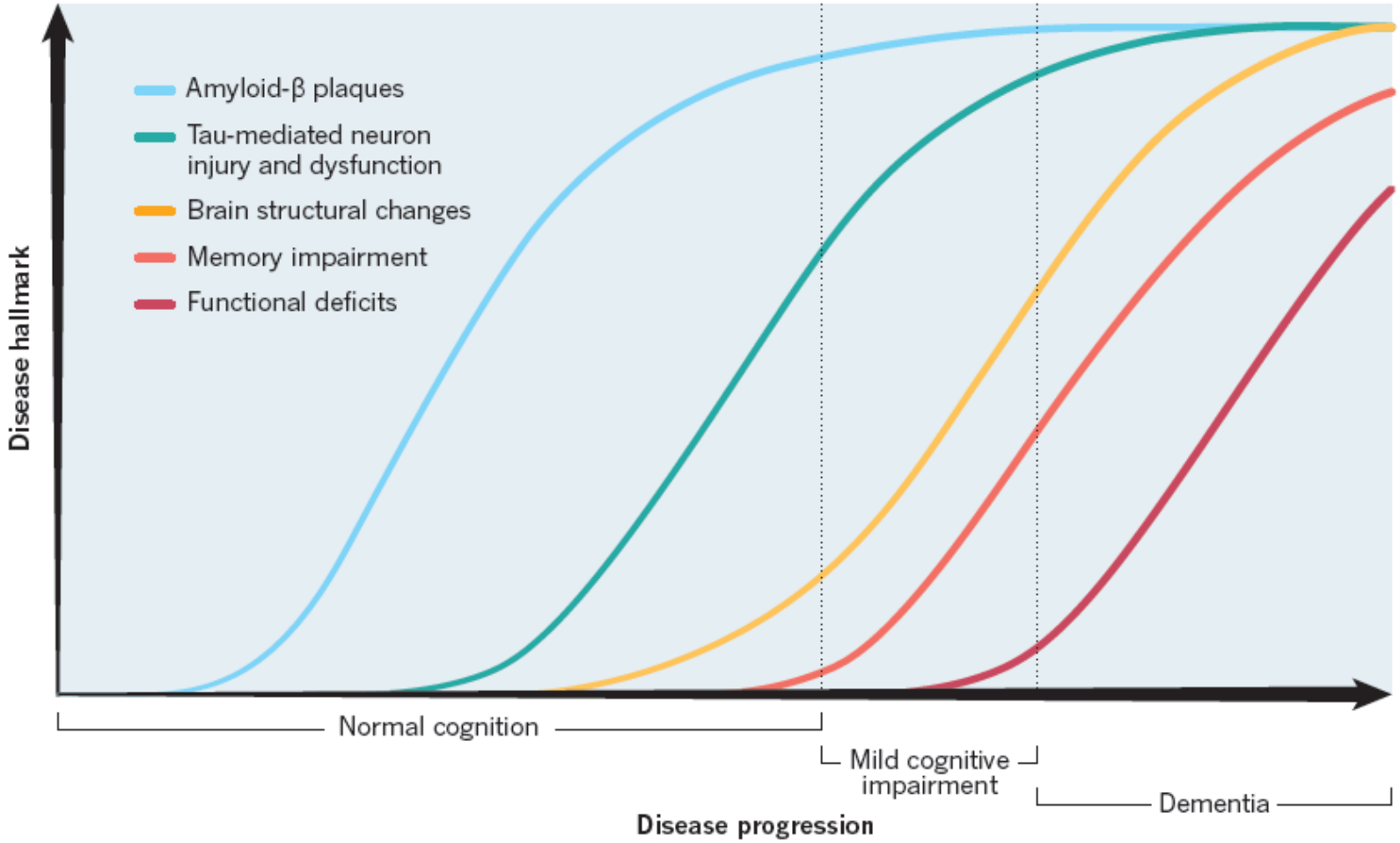


Source: van der Kant et al 2019

AD… causes PROGRESSIVE DECLINE IN FUNCTION

A SLOW MARCH

By the time that a person begins to experience the symptoms of Alzheimer's disease, the condition is already well-established in the brain. The accumulation of amyloid-β, generally thought to be the first step in disease progression, could precede symptoms by 10–15 years. Tau accumulation occurs later, much closer to the onset of neurodegeneration.



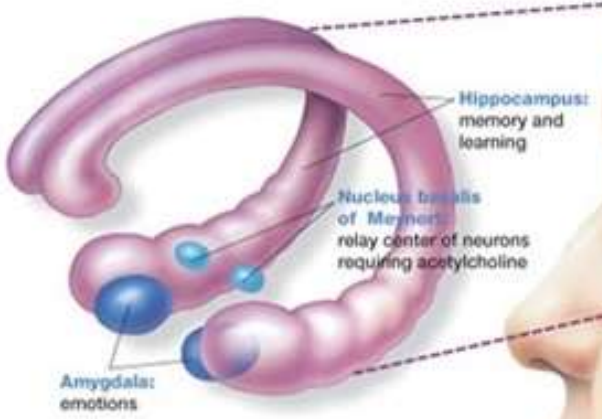
Source: Drew L, 2018

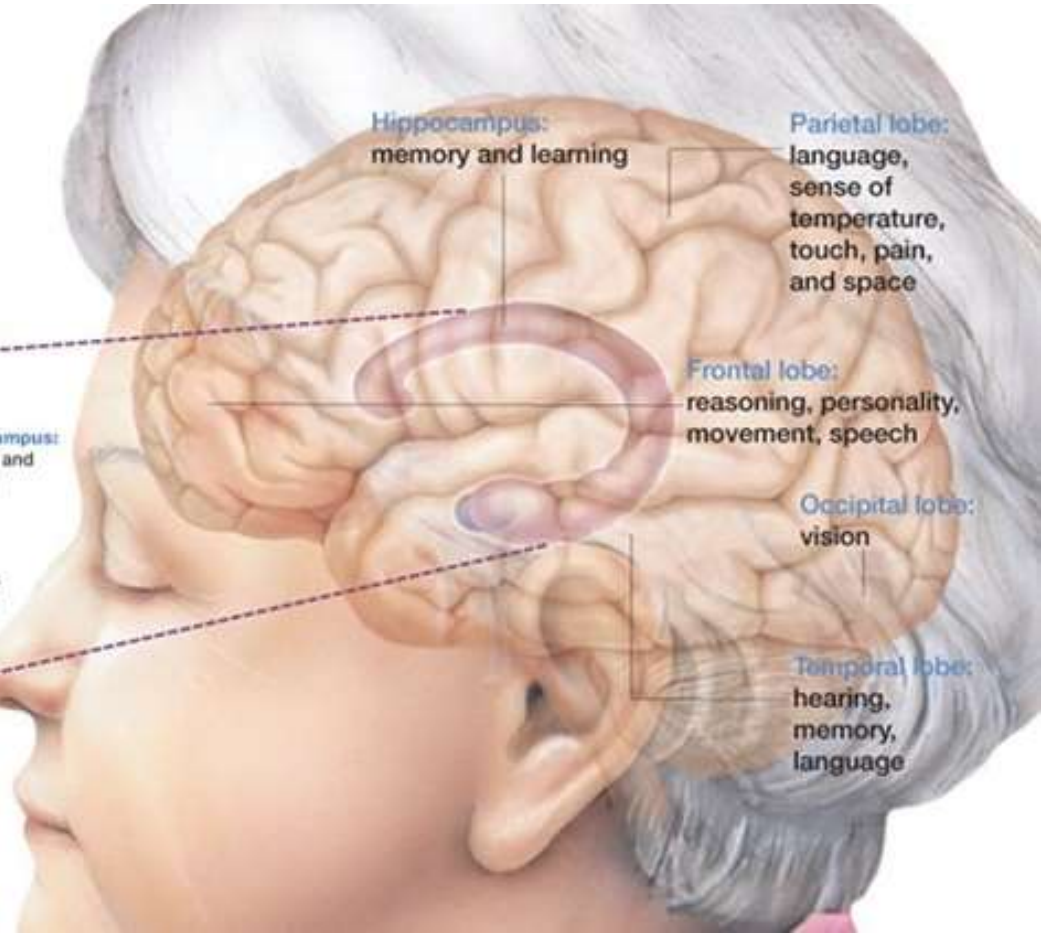
AD… causes PROGRESSIVE MEMORY LOSS (and more)

Understanding

Alzheimer's Disease

The most common form of dementia is Alzheimer's Disease (AD), a slowly progressive disorder that destroys the neurons and communication pathways of the brain. It is the seventh leading cause of death in adults in the U.S. and it is perhaps the most devastating chronic disease for patients and their families.



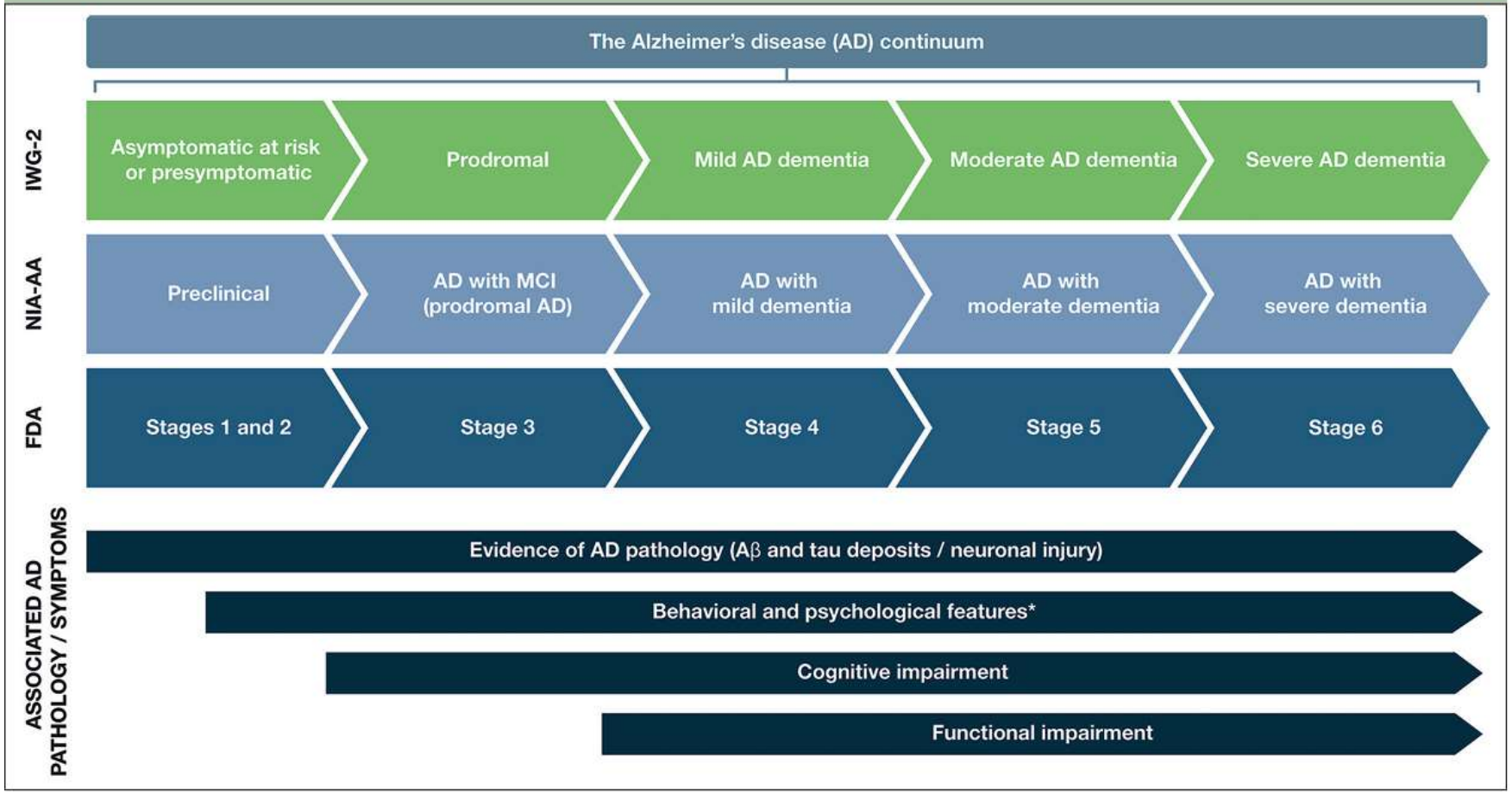


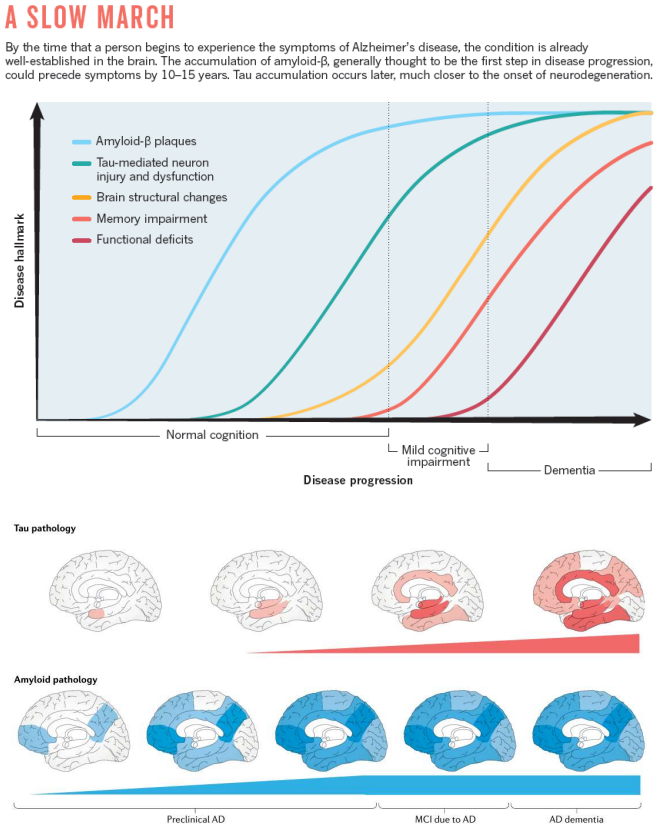
The Aging Brain and Dementia

At birth, the brain contains as many nerve cells called neurons as it will ever have — many billions of neurons! Unlike other cells of our body, such as skin or bone, neurons cannot reproduce themselves. Therefore, as we age, neurons that die from normal wear and tear and injury are not replaced. The normal effects of aging can cause mild forgetfulness and reduced reflexes. However, there are diseases known as dementias that mimic these age-related changes in their early stages. Dementia is characterized by the progressive, yet dramatic, decline of cognitive function.

AD… causes PROGRESSIVE DECLINE IN FUNCTION

Figure 1. Stages within the Alzheimer's disease continuum





Source: Porsteinsson et al 2021

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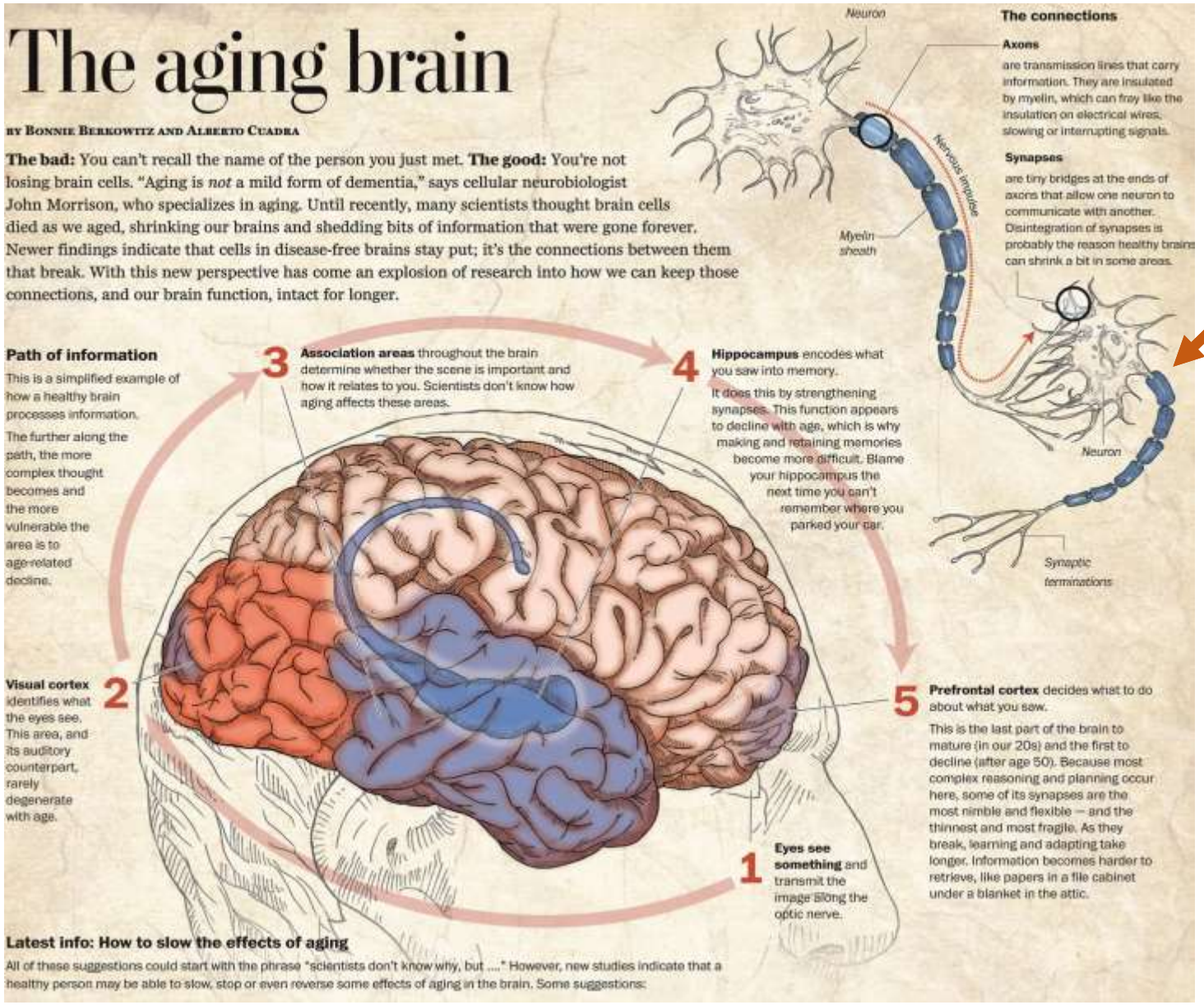
FIXING FAULTY BRAIN WIRING: SYNAPSES AND NEUROTRANSMITTERS



The aging brain

BY BONNIE BERKOWITZ AND ALBERTO CUADRA

The bad: You can't recall the name of the person you just met. **The good:** You're not losing brain cells. "Aging is *not* a mild form of dementia," says cellular neurobiologist John Morrison, who specializes in aging. Until recently, many scientists thought brain cells died as we aged, shrinking our brains and shedding bits of information that were gone forever. Newer findings indicate that cells in disease-free brains stay put; it's the connections between them that break. With this new perspective has come an explosion of research into how we can keep those connections, and our brain function, intact for longer.

Path of information

This is a simplified example of how a healthy brain processes information.

The further along the path, the more complex thought becomes and the more vulnerable the area is to age-related decline.

3 **Association areas** throughout the brain determine whether the scene is important and how it relates to you. Scientists don't know how aging affects these areas.

4 **Hippocampus** encodes what you saw into memory.

It does this by strengthening synapses. This function appears to decline with age, which is why making and retaining memories become more difficult. Blame your hippocampus the next time you can't remember where you parked your car.

2 **Visual cortex** identifies what the eyes see. This area, and its auditory counterpart, rarely degenerate with age.

5 **Prefrontal cortex** decides what to do about what you saw.

This is the last part of the brain to mature (in our 20s) and the first to decline (after age 50). Because most complex reasoning and planning occur here, some of its synapses are the most nimble and flexible — and the thinnest and most fragile. As they break, learning and adapting take longer. Information becomes harder to retrieve, like papers in a file cabinet under a blanket in the attic.

1 **Eyes see something** and transmit the image along the optic nerve.

Latest info: How to slow the effects of aging

All of these suggestions could start with the phrase "scientists don't know why, but ...." However, new studies indicate that a healthy person may be able to slow, stop or even reverse some effects of aging in the brain. Some suggestions:

The connections

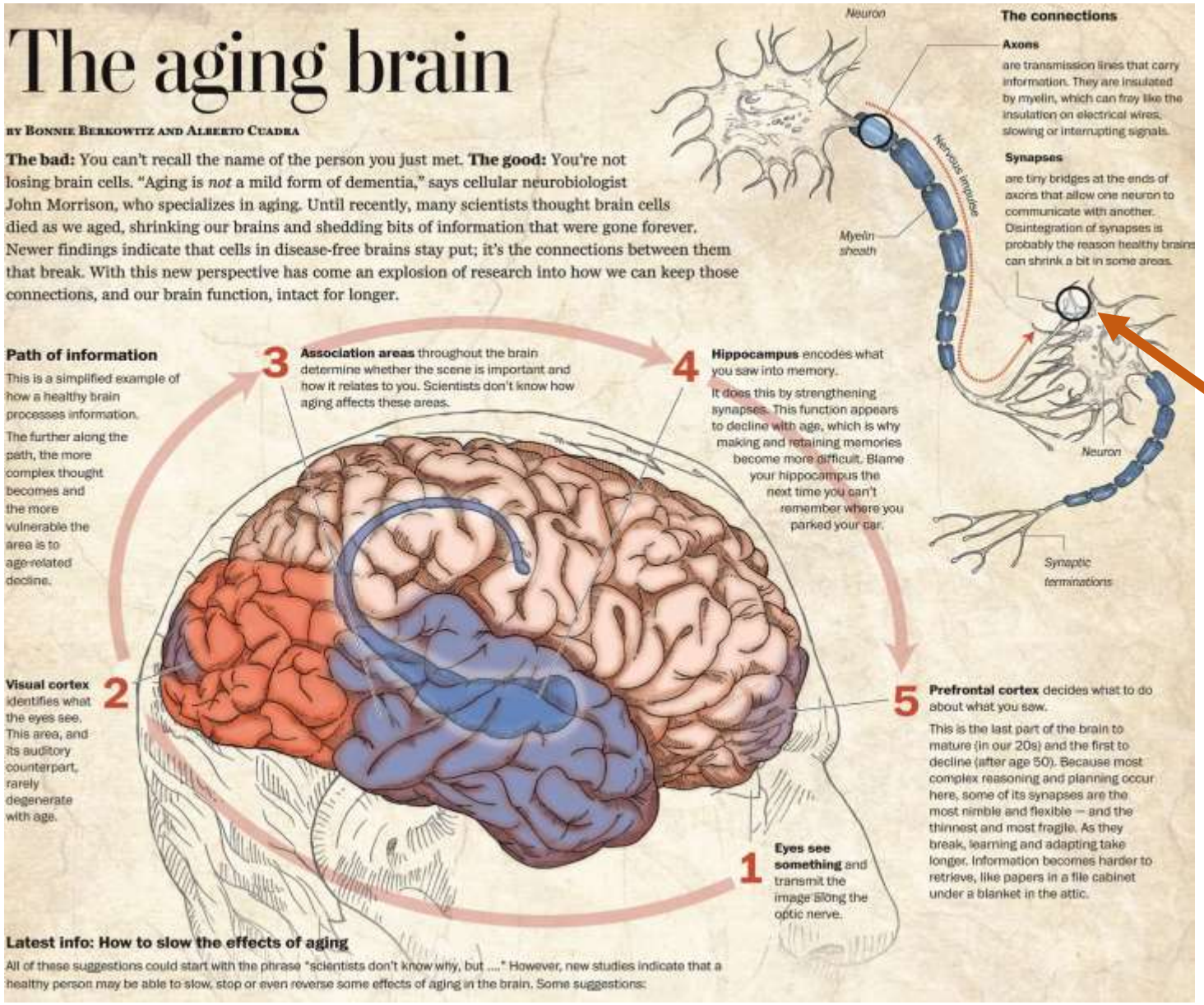
Axons are transmission lines that carry information. They are insulated by myelin, which can fray like the insulation on electrical wires, slowing or interrupting signals.

Synapses are tiny bridges at the ends of axons that allow one neuron to communicate with another. Disintegration of synapses is probably the reason healthy brains can shrink a bit in some areas.

Neuron
Nervous impulse
Myelin sheath
Neuron
Synaptic terminations

- There are about 100 *BILLION* neurons in the brain

FIXING FAULTY BRAIN WIRING: SYNAPSES AND NEUROTRANSMITTERS



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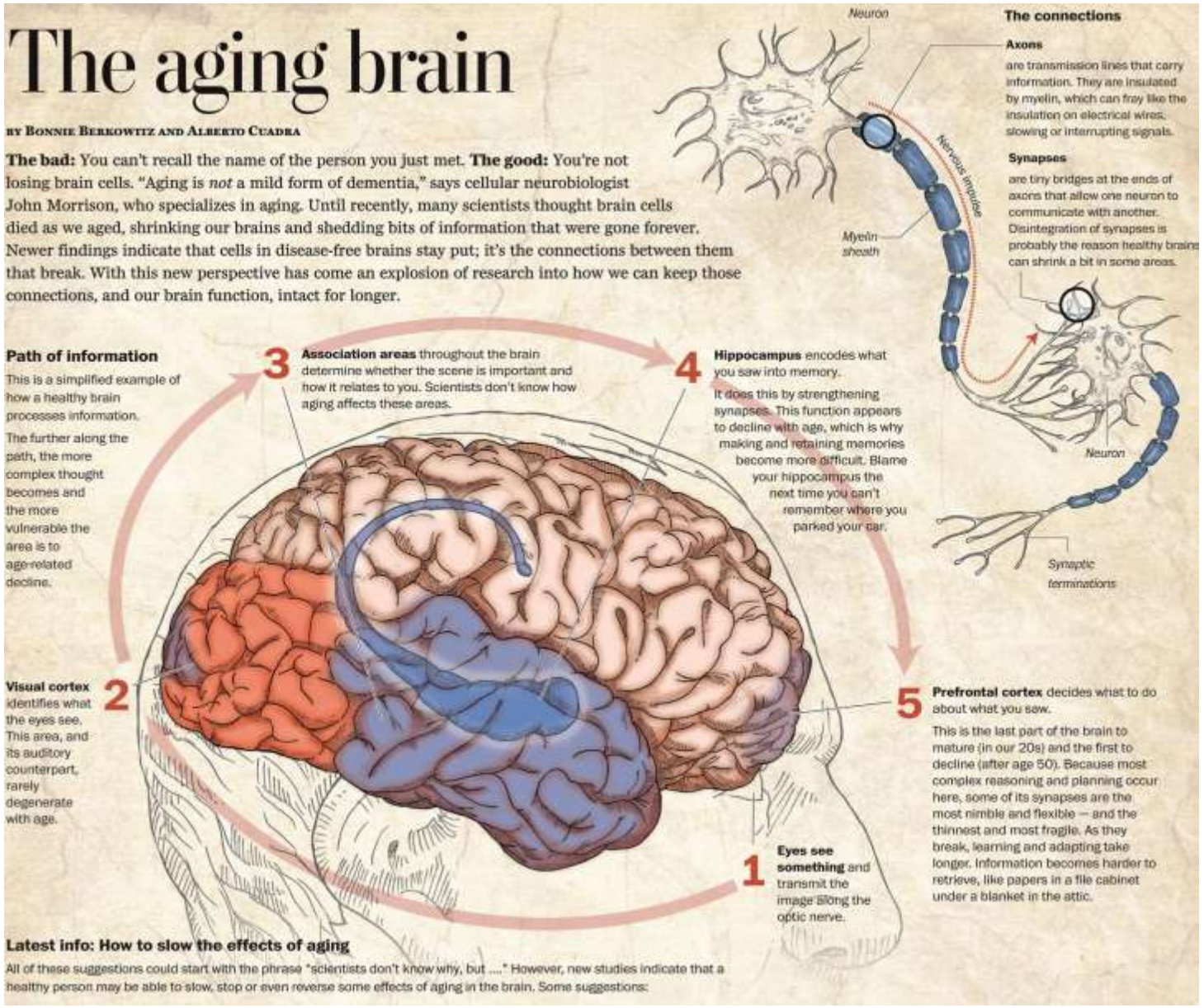
- There are about 100 *BILLION* neurons in the brain
- Each neuron has about 7000 SYNAPSES (chemical connections with other neurons)

FIXING FAULTY BRAIN WIRING: SYNAPSES AND NEUROTRANSMITTERS



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- Each neuron has about 7000 SYNAPSES (chemical connections with other neurons)
- NEUROTRANSMITTERS are the chemical messengers that allow neurons to communicate between synapses

FIXING FAULTY BRAIN WIRING: SYNAPSES AND NEUROTRANSMITTERS

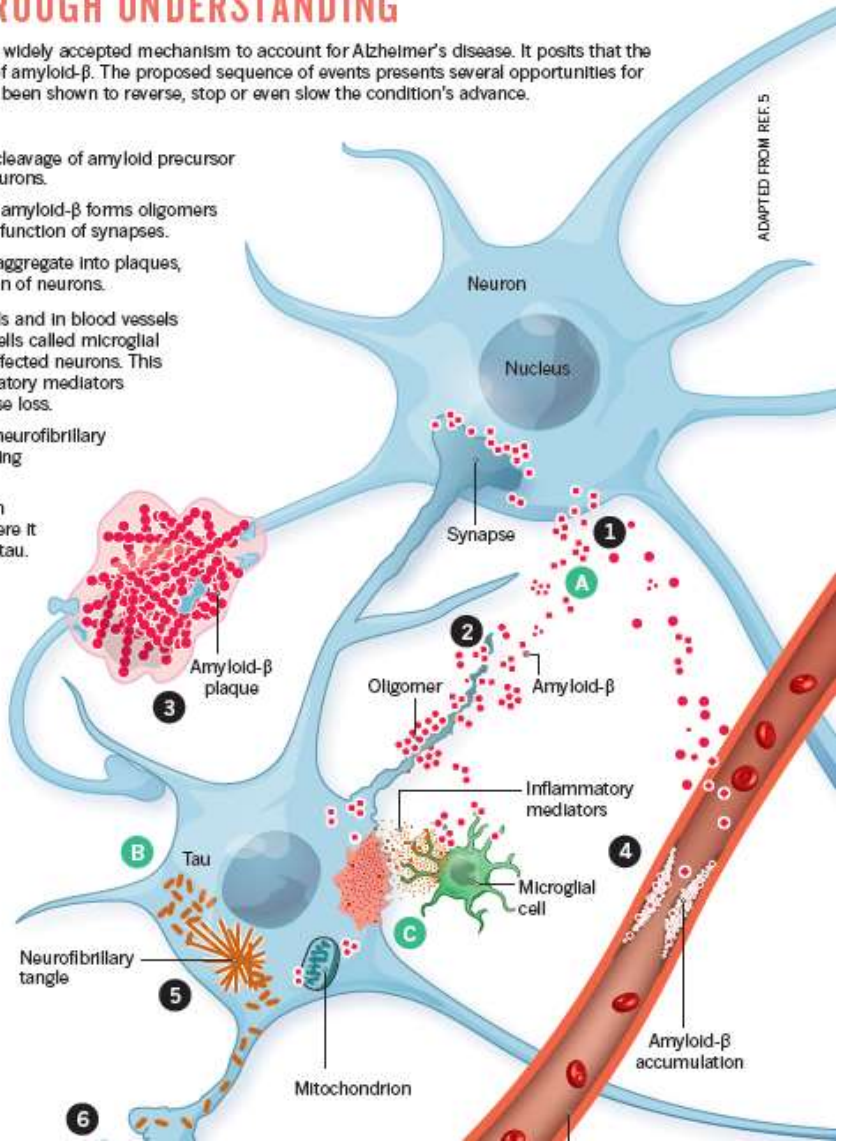
TREATMENTS THROUGH UNDERSTANDING

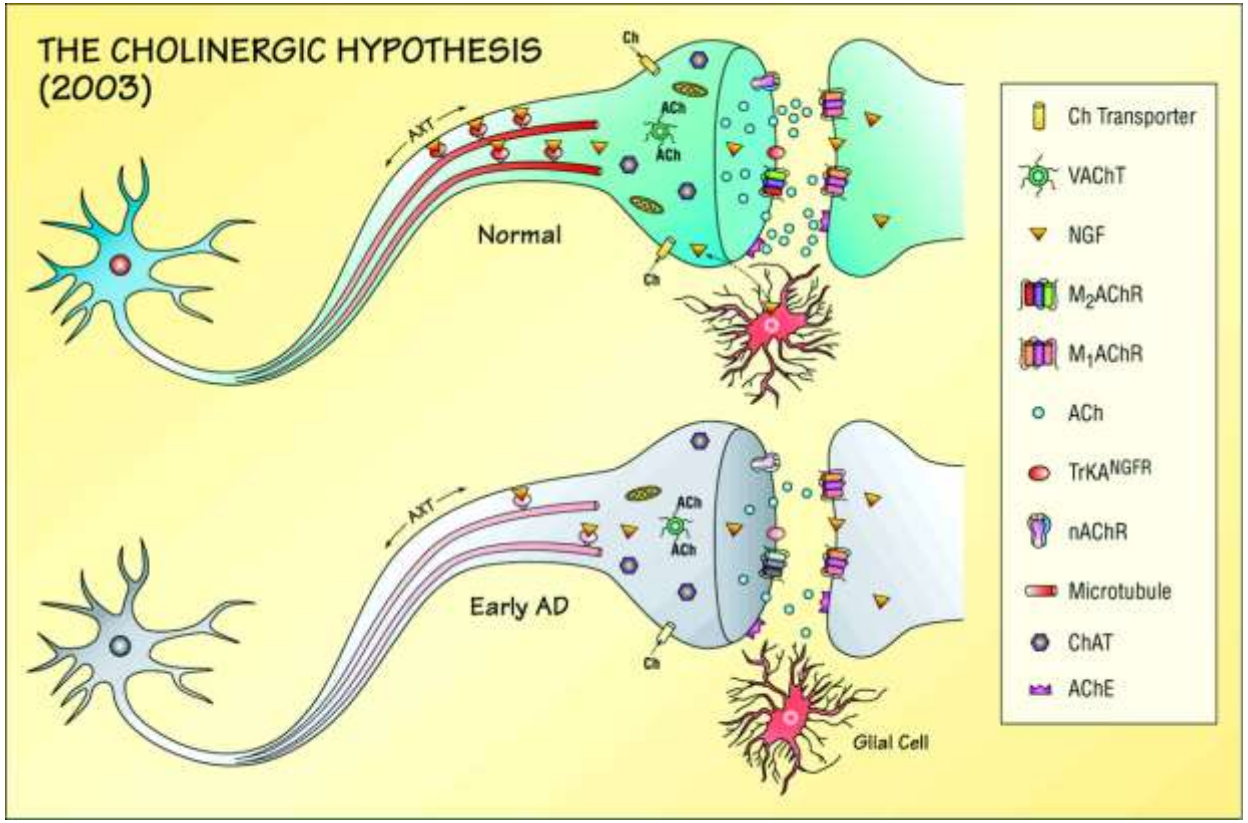
The amyloid hypothesis is the most widely accepted mechanism to account for Alzheimer's disease. It posits that the condition is driven by aggregation of amyloid-β. The proposed sequence of events presents several opportunities for intervention, but so far no drug has been shown to reverse, stop or even slow the condition's advance.

1. Amyloid-β is produced by the cleavage of amyloid precursor protein in the membrane of neurons.
2. In the space between neurons, amyloid-β forms oligomers that are thought to disrupt the function of synapses.
3. Fibrils of amyloid-β oligomers aggregate into plaques, which interfere with the function of neurons.
4. Amyloid-β deposits outside cells and in blood vessels of the brain activate immune cells called microglial cells that congregate around affected neurons. This triggers the release of inflammatory mediators and might contribute to synapse loss.
5. Misfolded tau aggregates into neurofibrillary tangles inside neurons, displacing intracellular organelles.
6. Misfolded tau can pass through synapses to other neurons, where it catalyses further misfolding of tau.

OPPORTUNITIES FOR INTERVENTION

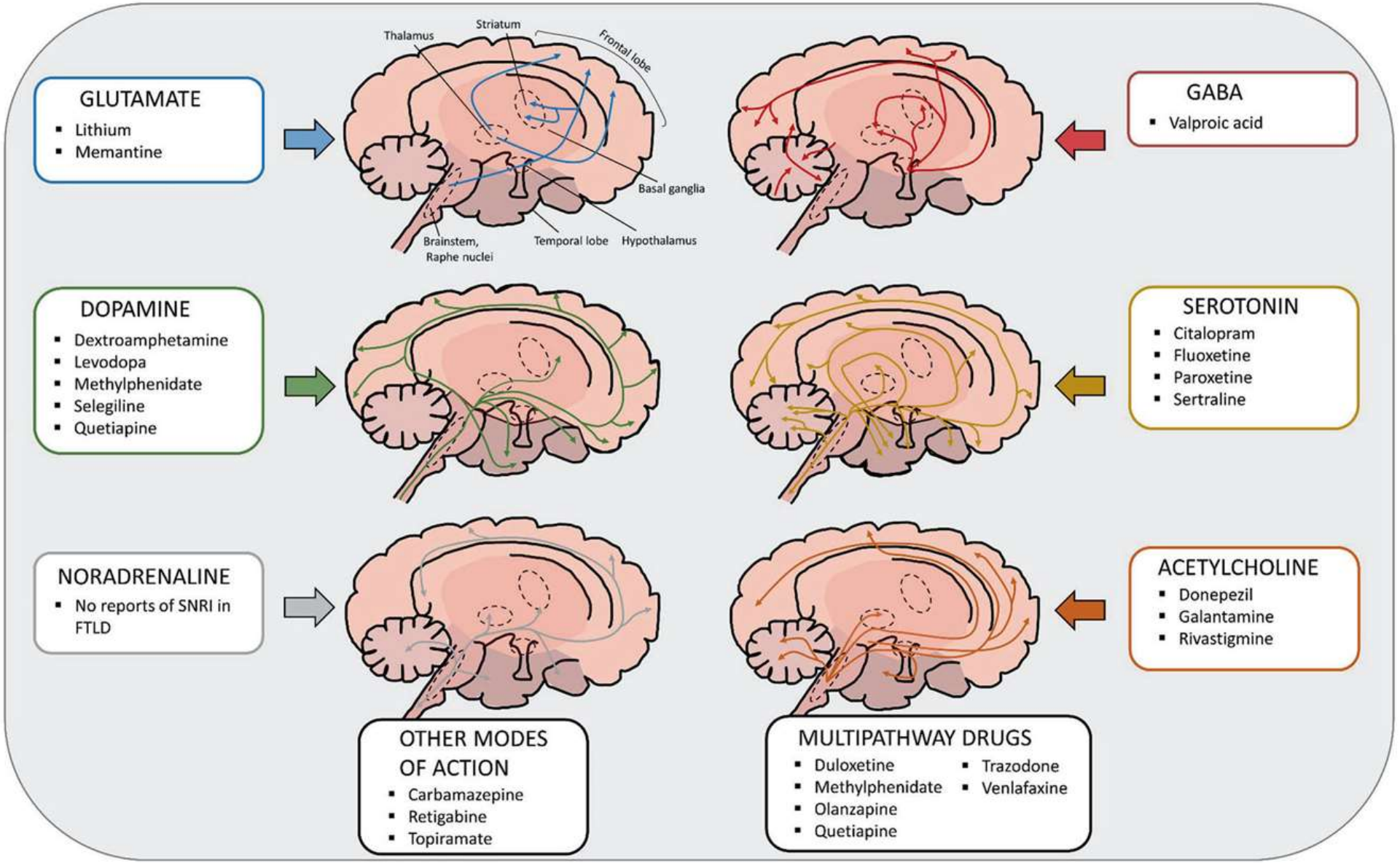
- **A** Inhibitors of the enzymes that cut amyloid precursor protein and antibodies that bind to various forms of amyloid-β have been tested without success (see page S4).
- **B** Immunotherapies and small molecules that inhibit the aggregation and spread of tau are also under development.
- **C** If inflammation is shown to contribute to Alzheimer's disease, anti-inflammatory drugs could provide benefits to those affected.





Source: Yanagisawa K, 2011

FIXING FAULTY BRAIN WIRING: SYNAPSES AND NEUROTRANSMITTERS



Source: Huber et all 2022

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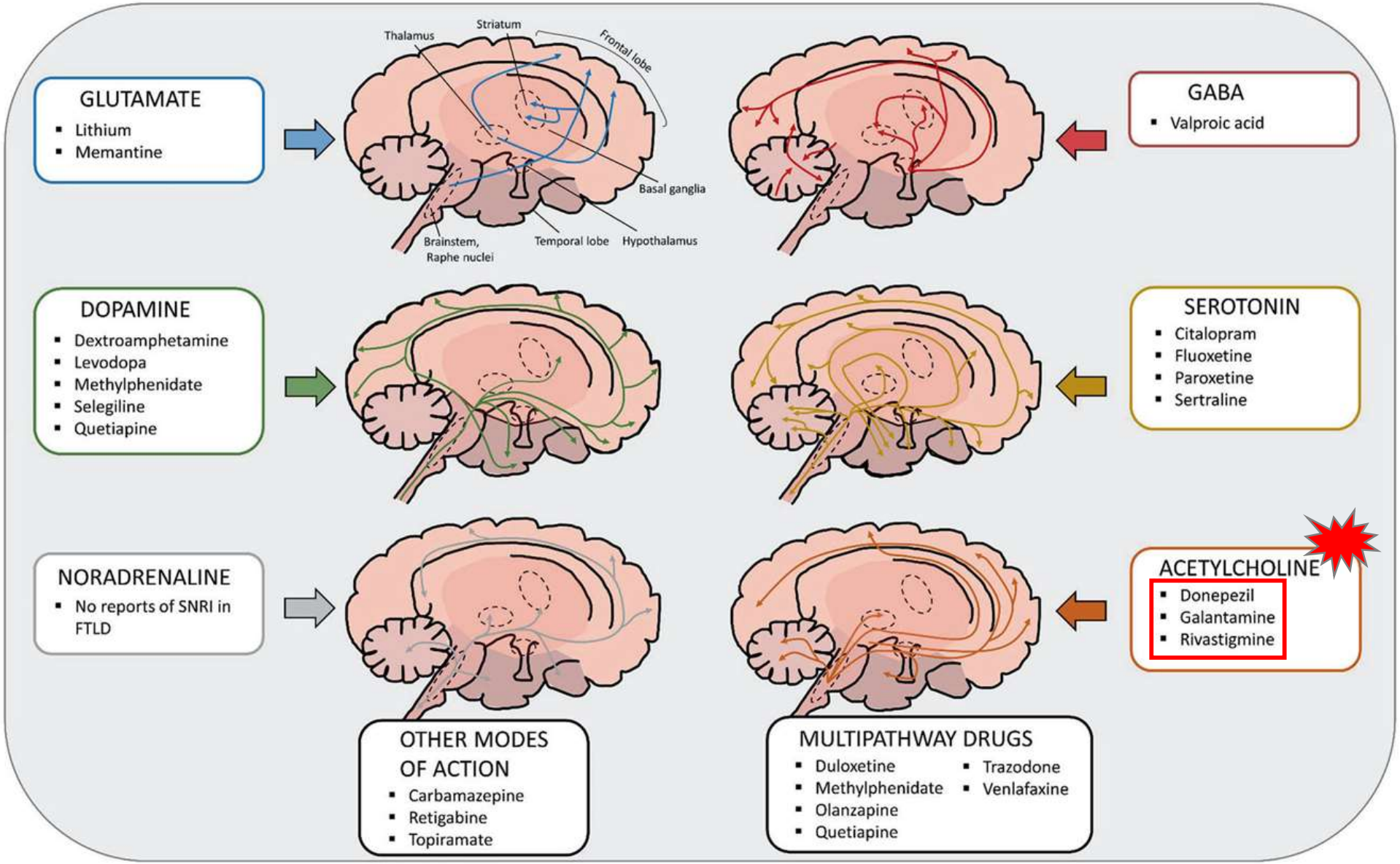
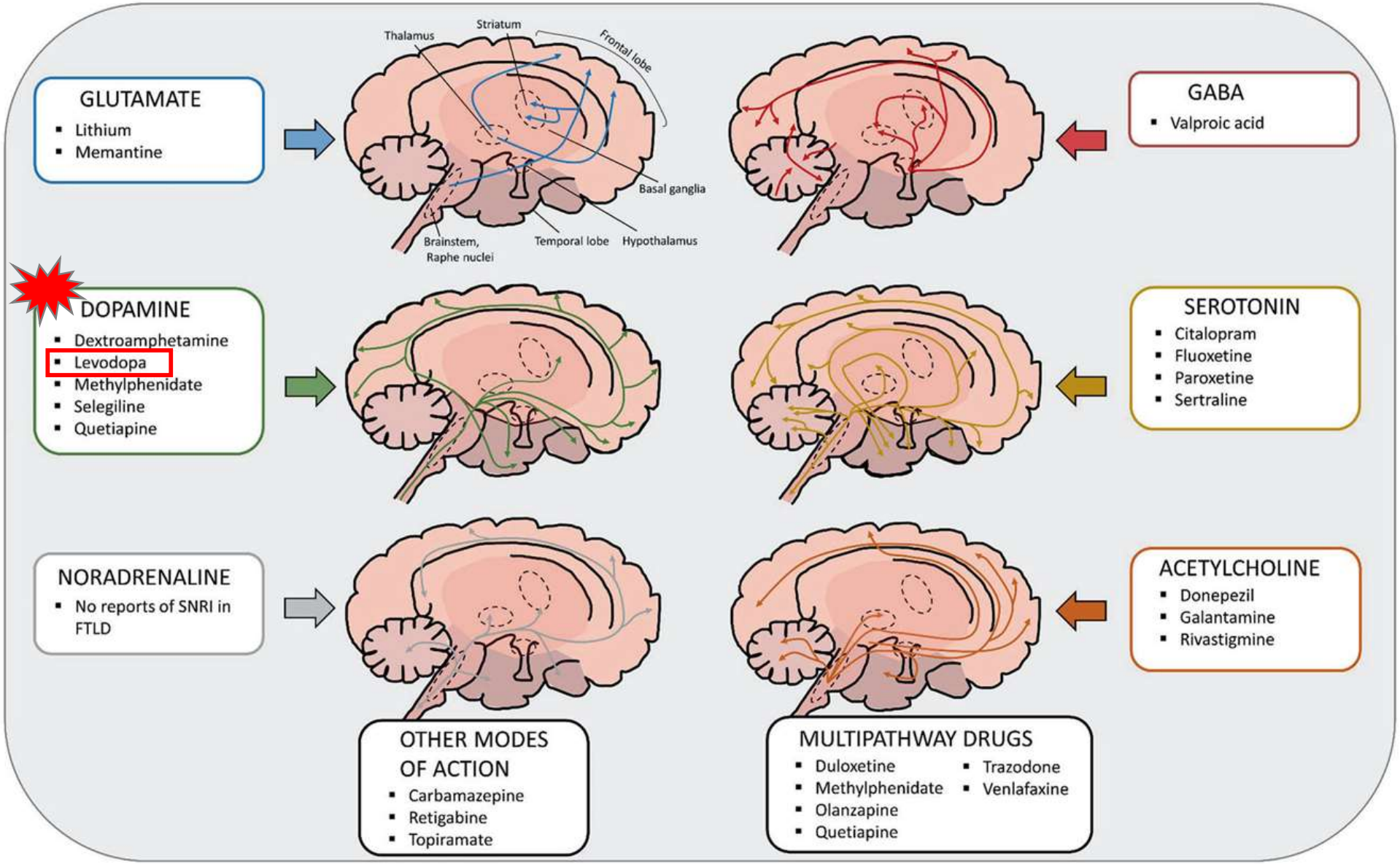
FIXING FAULTY BRAIN WIRING: TOO LITTLE ACETYLCHOLINE



Source: Huber et all 2022

FIXING FAULTY BRAIN WIRING: TOO LITTLE DOPAMINE IN PARKINSON'S DISEASE



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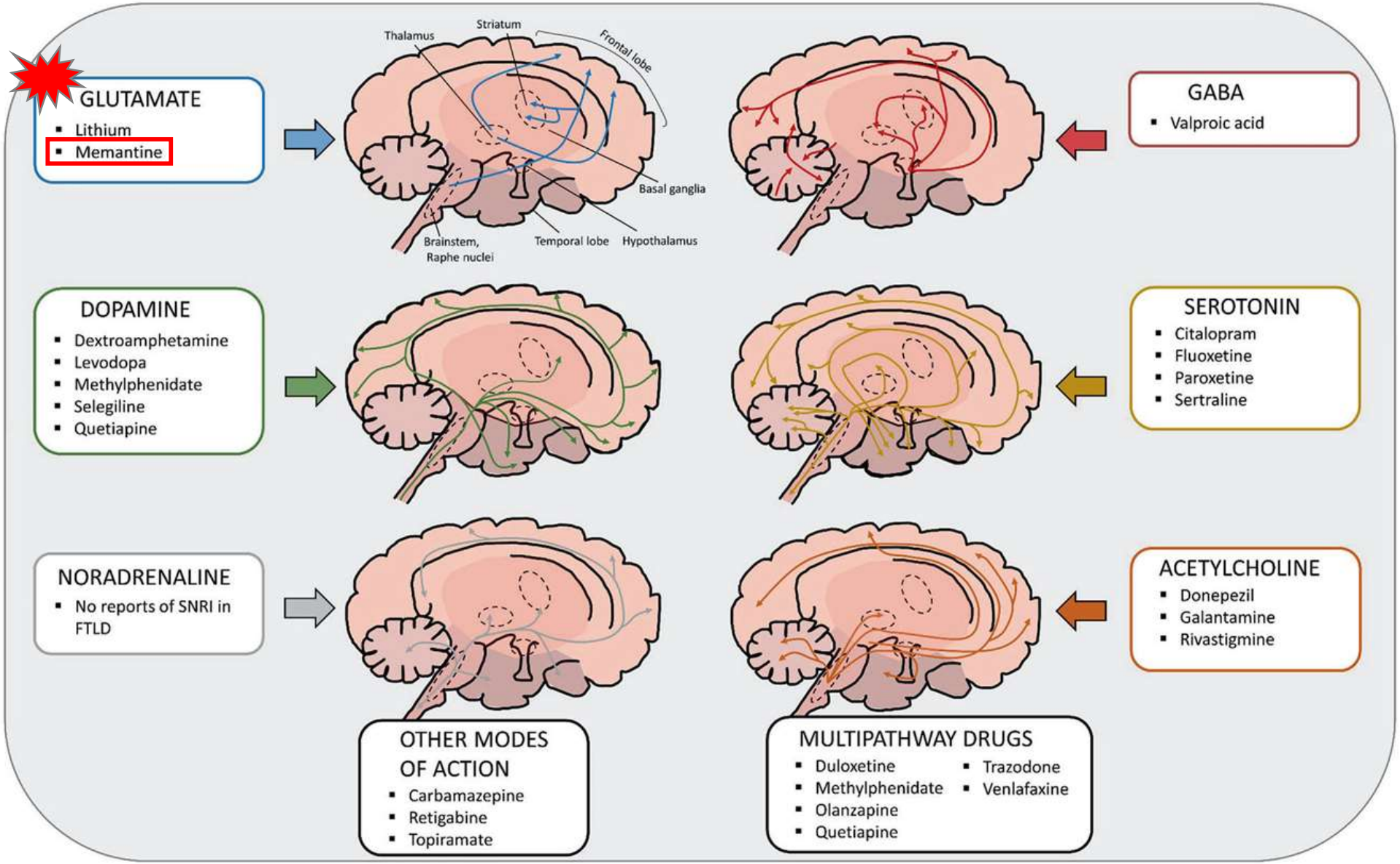
FIXING FAULTY BRAIN WIRING: TOO MUCH GLUTAMATE



Source: Huber et all 2022

RECOMMENDATIONS FOR BEST PRACTICES FOR TREATING DEMENTIA

Screen all elderly patients with a memory complaint*

- Evaluate cognition, function, and behavior
- Treat at time of diagnosis

Ongoing monitoring and evaluation

Reevaluate within 2 months and monitor every 6 months

Counsel patients and caregivers about realistic treatment expectations

Consider potentially reversible causes if patient currently on antidementia therapy is showing signs of rapid decline

Provide geriatric care management and counseling and refer patients and caregivers to AD support groups

Mild	Moderate	Severe
ChEI	Combination ChEI + memantine	Memantine + approved ChEI as needed
Add memantine to ChEI when patients progress to moderate AD		*Discontinue therapy* patient has lost all cognitive and functional abilities

***ChEI: Cholinesterase inhibitors** (Donepezil, Galantamine, Rivastigmine)

Adapted from: Fillit HM, et al. Am J Geriatr Pharmacother. 2006;4 (suppl A):S9-S24.

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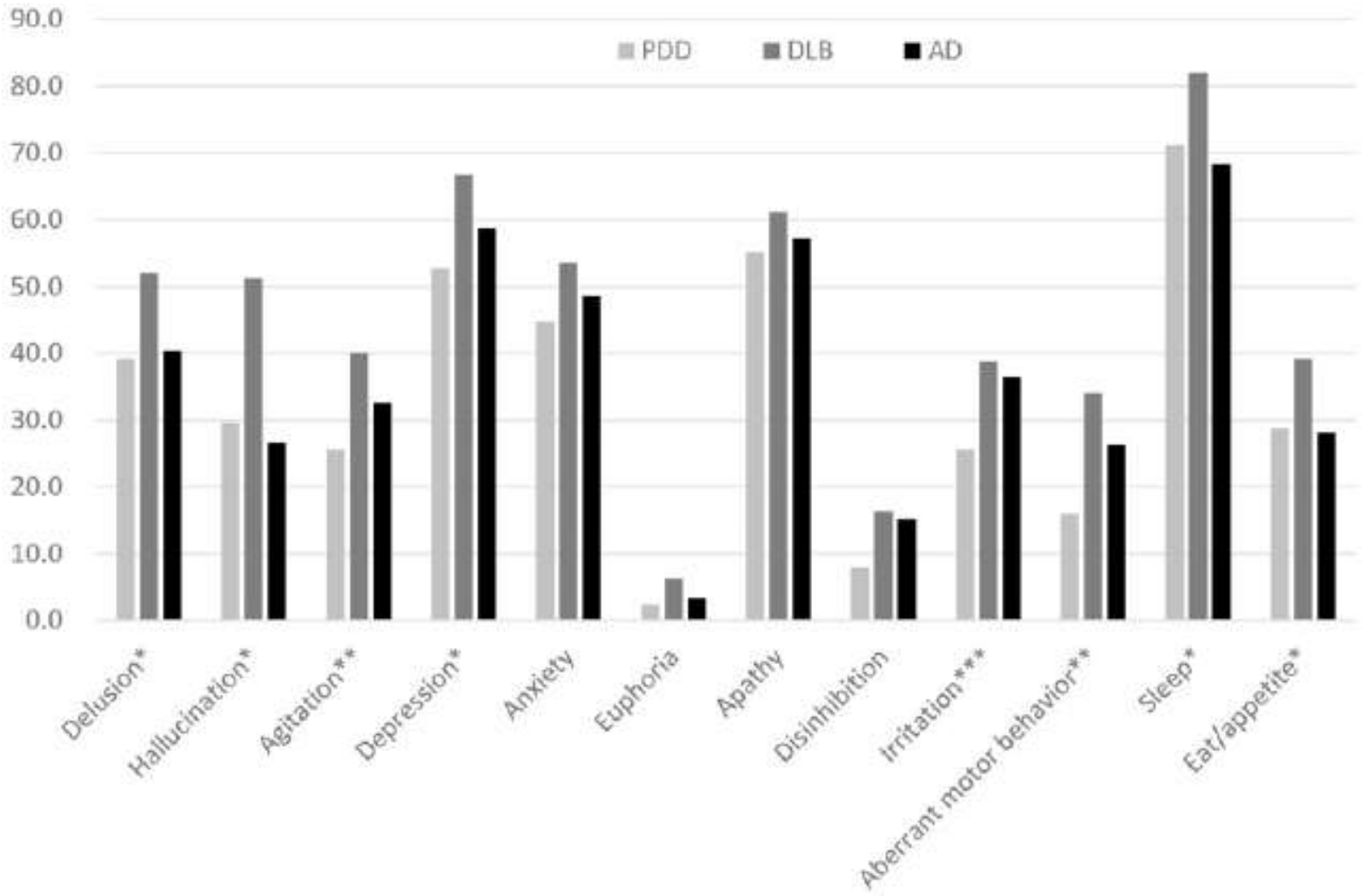
FIXING FAULTY BRAIN WIRING: MOOD AND BEHAVIOR



BOX 2-4 NEUROPSYCHIATRIC INVENTORY (NPI)

DESCRIPTION OF THE NPI

The NPI consists of 12 behavioral areas or domains:

1. Delusions
2. Hallucinations
3. Agitation
4. Depression
5. Anxiety
6. Euphoria
7. Apathy
8. Disinhibition
9. Irritability
10. Aberrant motor behavior
11. Night-time behaviors
12. Appetite and eating disorders

Frequency is rated as:

1. Occasionally—less than once a week
2. Often—about once per week
3. Frequently—several times a week but less than every day
4. Very frequently—daily or essentially continuously present

Severity is rated as:

1. Mild—produces little distress in the patient
2. Moderate—more disturbing to the patient but can be redirected by the caregiver
3. Severe—very disturbing to the patient and difficult to redirect

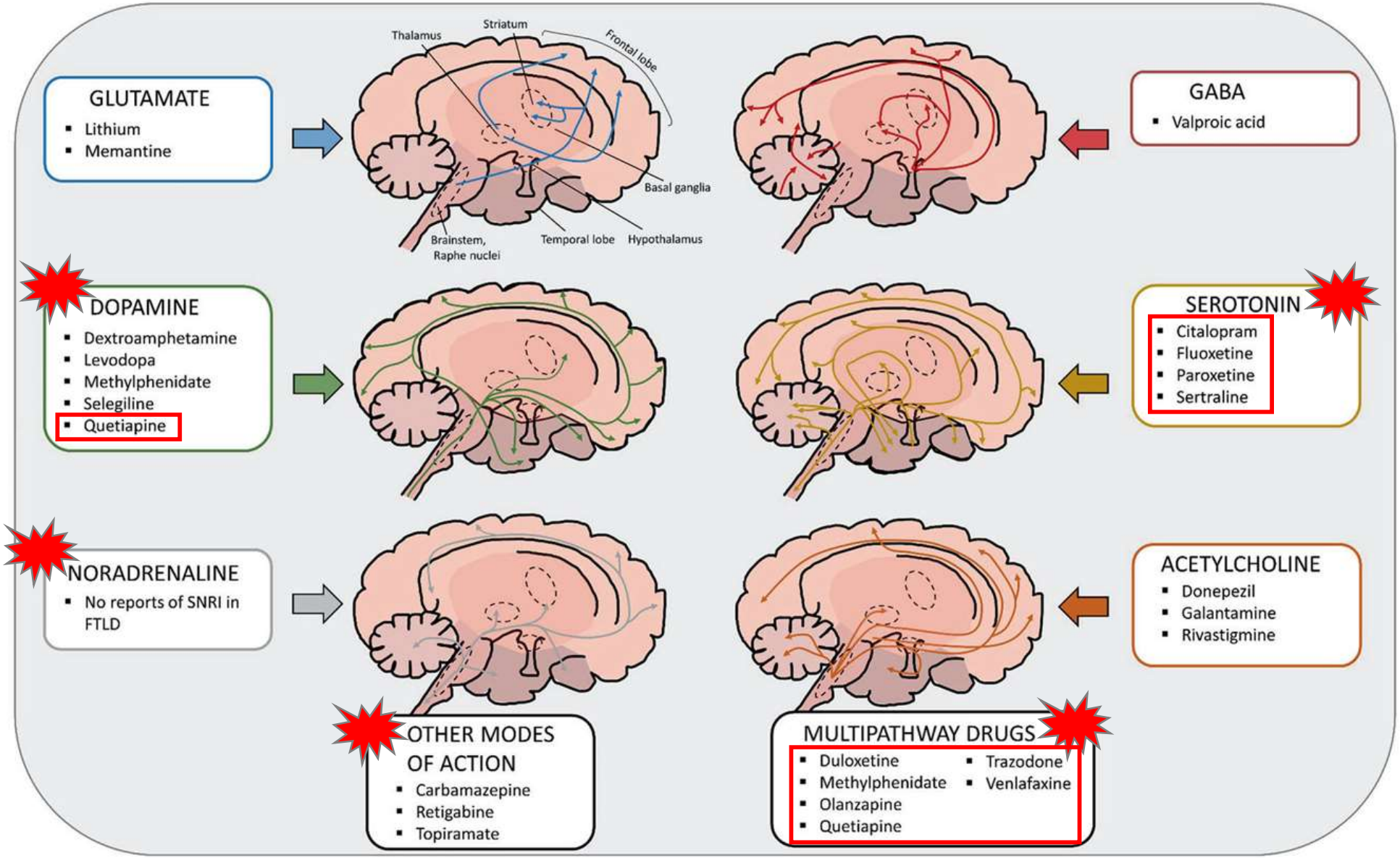
Distress is scored as:

0—no distress
1—minimal
2—mild
3—moderate
4—moderately severe
5—very severe or extreme

For each domain there are four scores: frequency, severity, total (frequency × severity), and caregiver distress. The total possible score is 144 (i.e., a maximum of 4 in the frequency rating ×3 in the severity rating ×12 domains).

Source: Budson A, 2015; Chiu P, 2016

FIXING FAULTY BRAIN WIRING: MOOD AND BEHAVIOR



Source: Huber et all 2022

OVERVIEW

- 1) Alzheimer's 101
  - Is it Alzheimer's or dementia?
  - Alzheimer's neurobiology basics
- 2) Symptomatic therapies Alzheimer's
  - Synapses and neurotransmitters
  - Not enough neurotransmitter: The case for Aricept
  - Too much neurotransmitter: The case for Namenda
  - Other neurotransmitters: Treating mood and thought disorders
- 3) The new era of disease modifying therapies

CHANGING THE COURSE OF DISEASE: LOWERING AMYLOID (AND TAU)

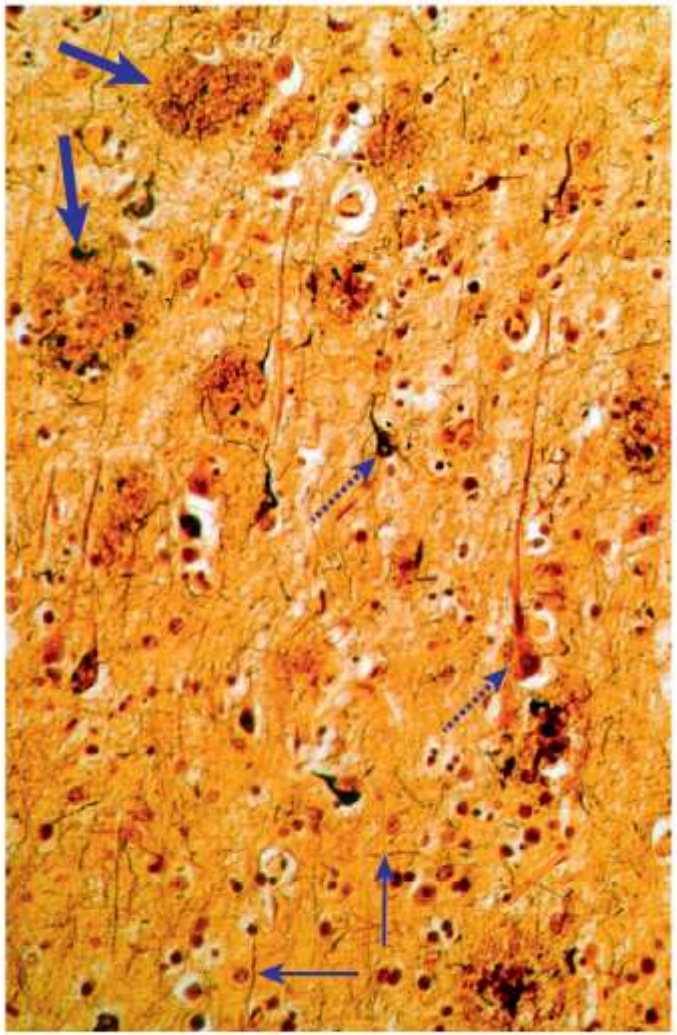
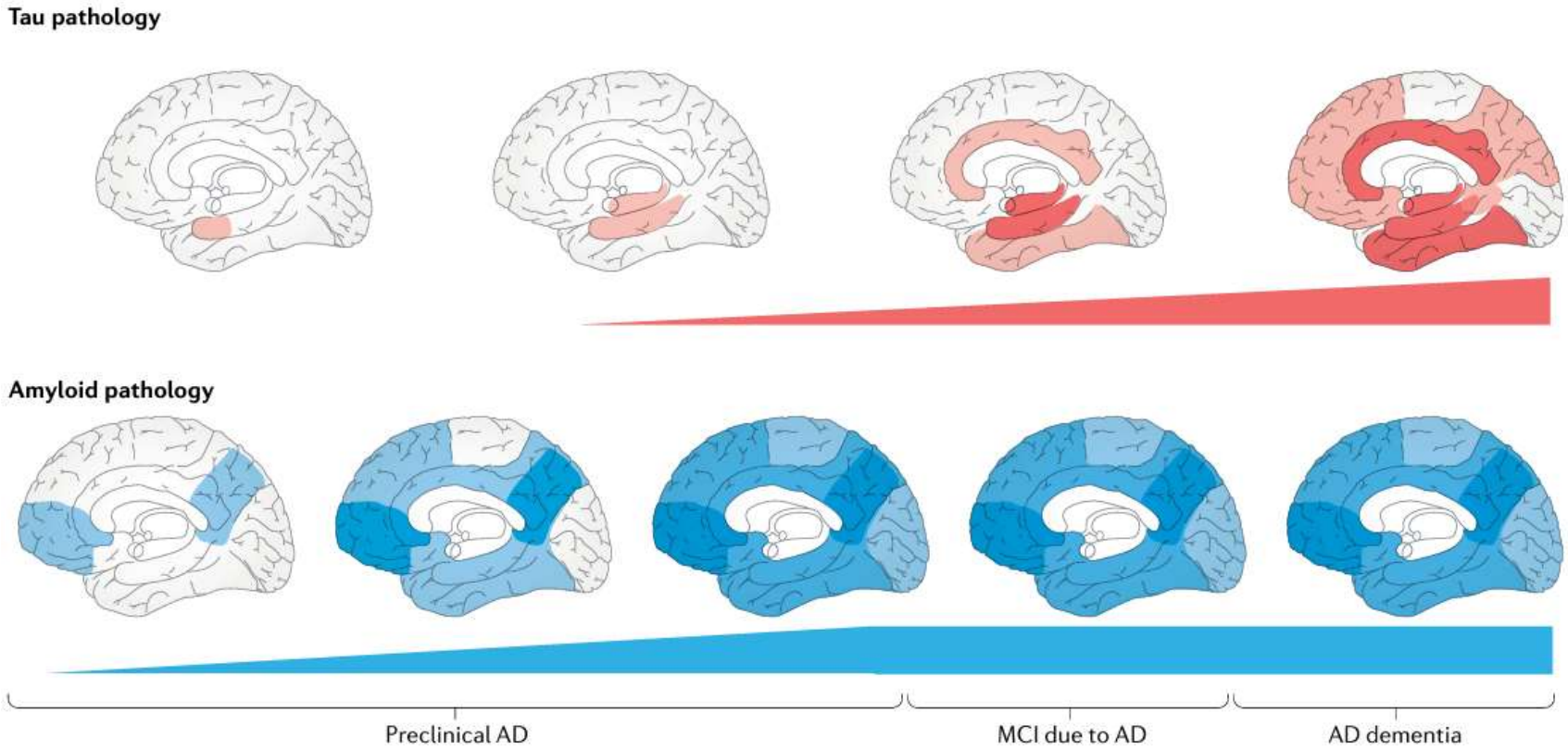


FIGURE 4-8 Light microscopic view of Alzheimer's pathology. Plaques (thick arrows), tangles (dotted arrows), and neuropil threads (thin arrows) in Alzheimer's disease.

Source: Memory Loss, Alzheimer's Disease, and Dementia A Practical Guide for Clinicians



Source: van der Kant et al 2019

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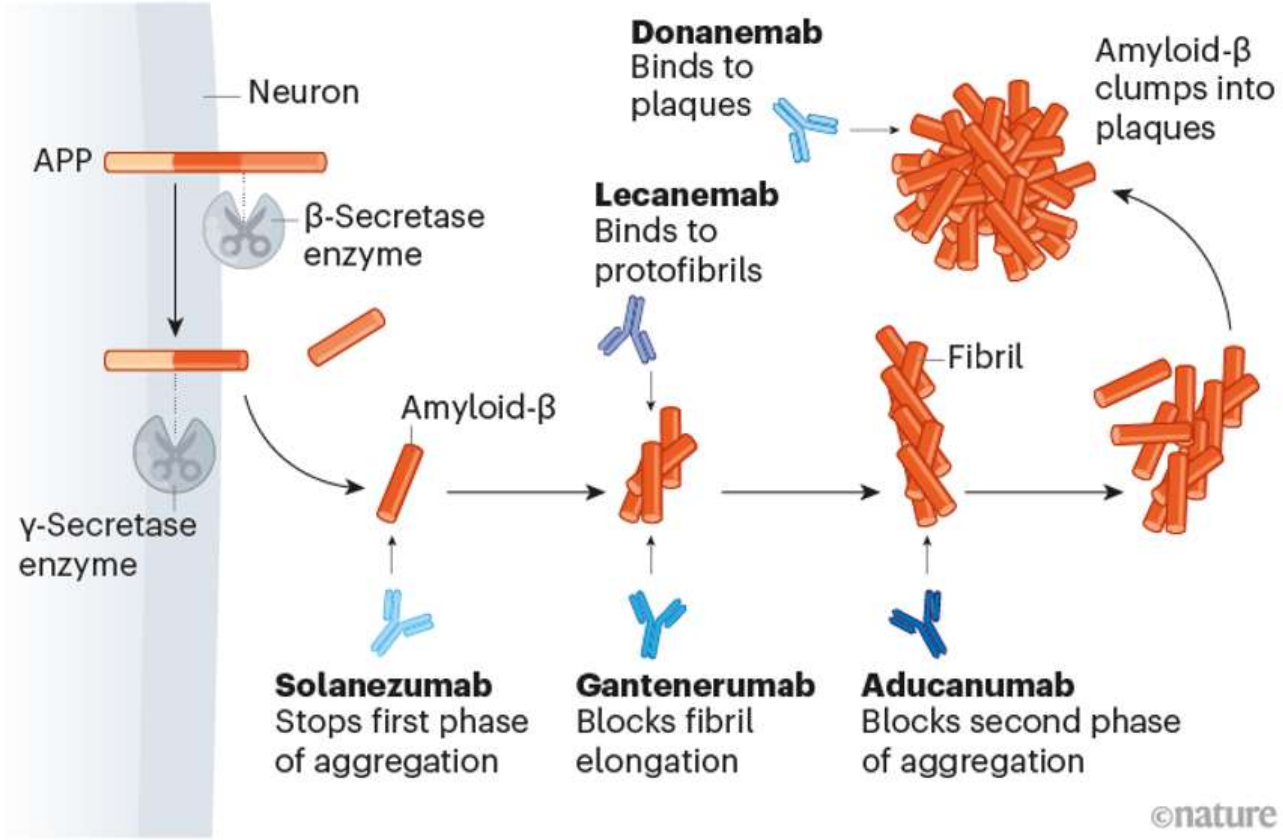
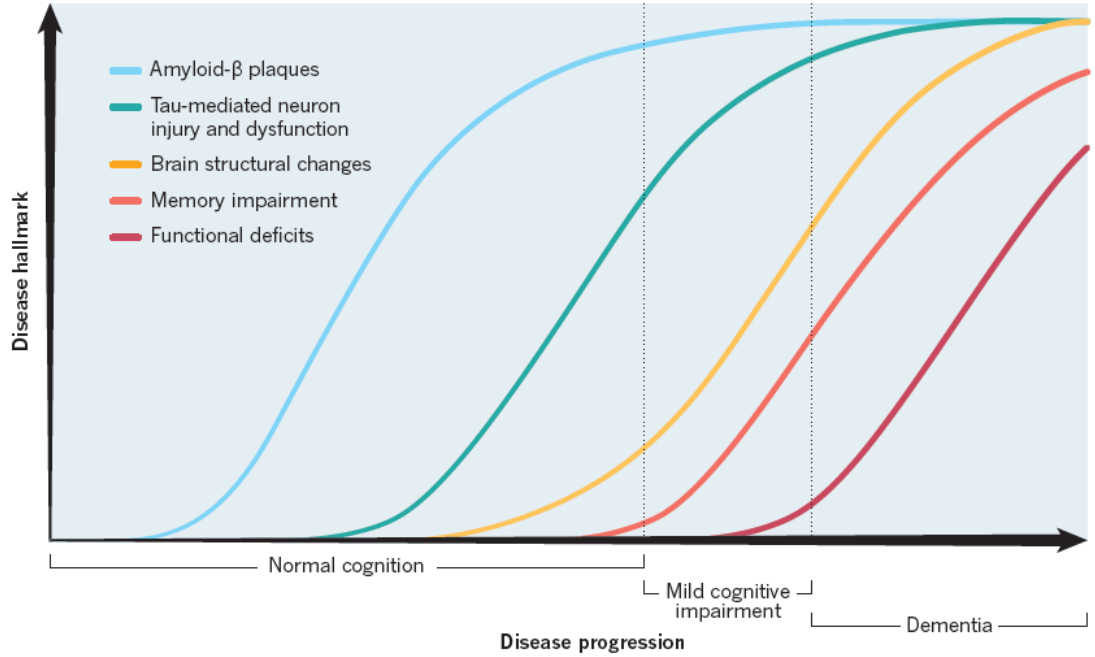


A SLOW MARCH

By the time that a person begins to experience the symptoms of Alzheimer's disease, the condition is already well-established in the brain. The accumulation of amyloid-β, generally thought to be the first step in disease progression, could precede symptoms by 10–15 years. Tau accumulation occurs later, much closer to the onset of neurodegeneration.



Source: https://www.scientificamerican.com/article/treating-alzheimer-rsquo-s-before-it-takes-hold/

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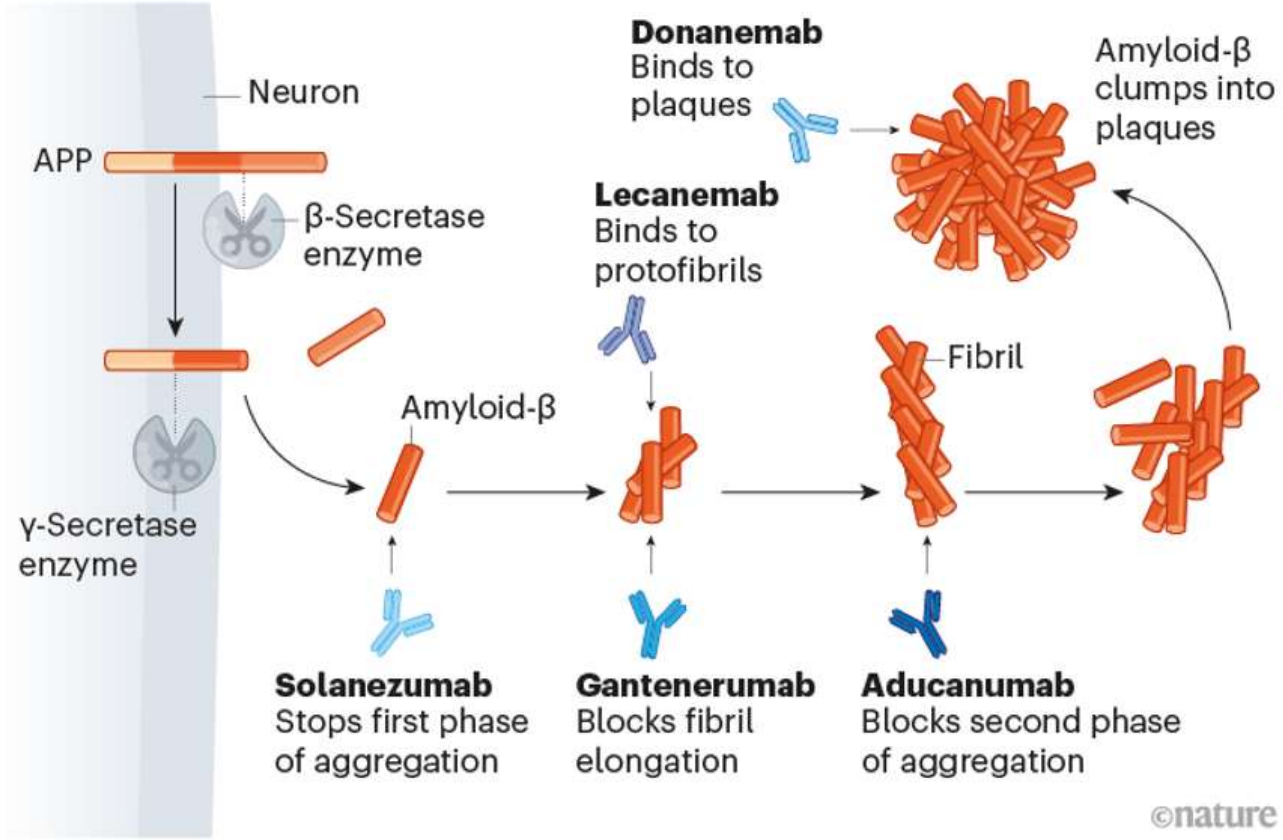

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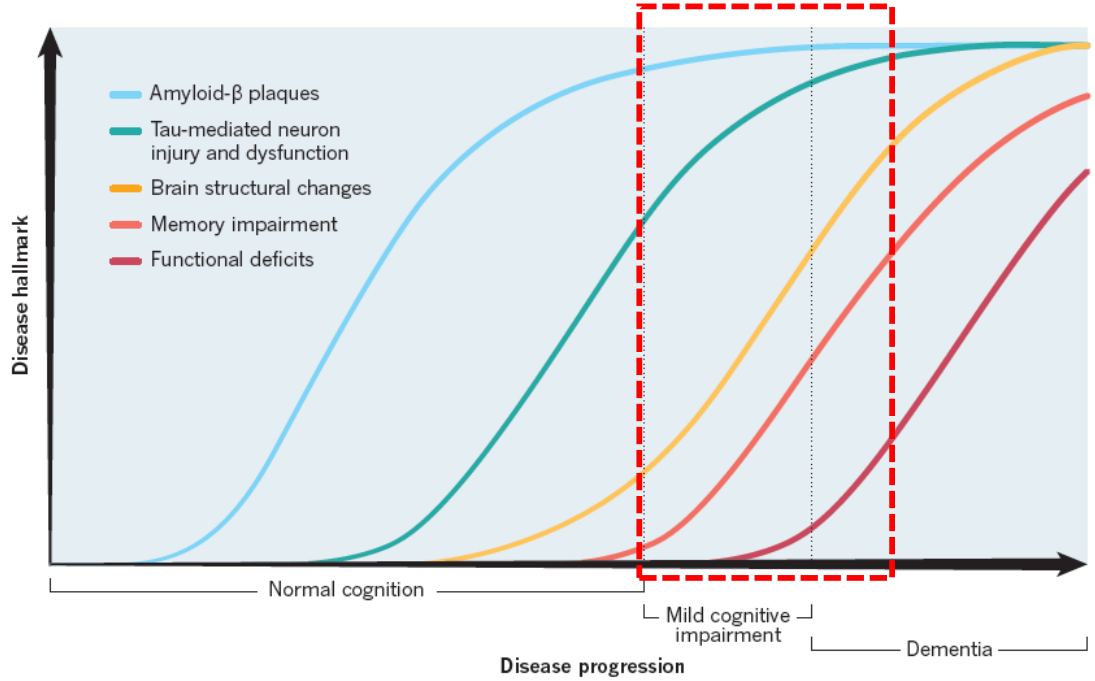

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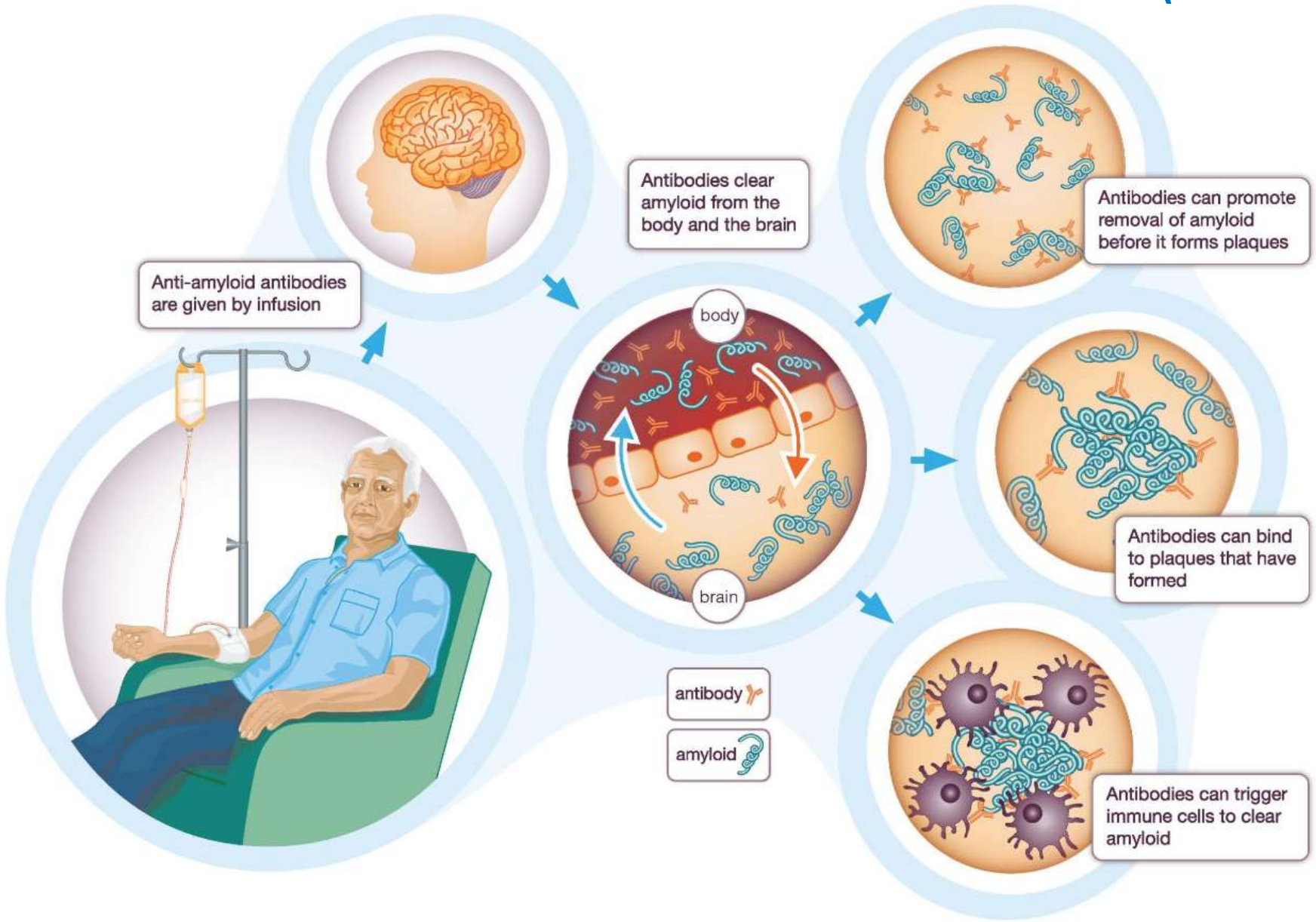
CHANGING THE COURSE OF DISEASE: LOWERING AMYLOID (AND TAU)



https://www.alzheimersresearchuk.org/news/answering-your-questions-about-aducanumab/

CHANGING THE COURSE OF DISEASE: LOWERING AMYLOID (AND TAU)

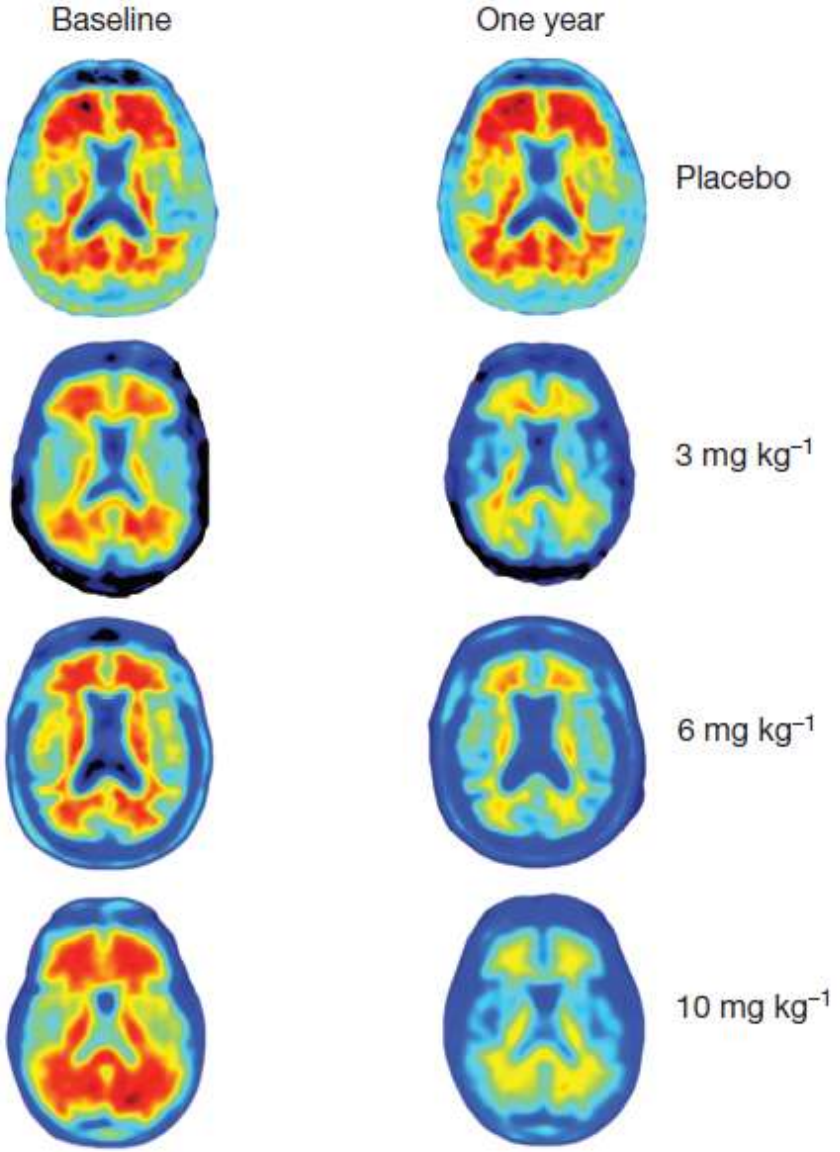
ARTICLE

doi:10.1038/nature19323

The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

Jeff Sevigny[1]*, Ping Chiao[1]*, Thierry Bussière[1]*, Paul H. Weinreb[1]*, Leslie Williams[1], Marcel Maier[2], Robert Dunstan[1], Stephen Salloway[3], Tianle Chen[1], Yan Ling[1], John O'Gorman[1], Fang Qian[1], Mahin Arastu[1], Mingwei Li[1], Sowmya Chollate[1], Melanie S. Brennan[1], Omar Quintero-Monzon[1], Robert H. Scannevin[1], H. Moore Arnold[1], Thomas Engber[1], Kenneth Rhodes[1], James Ferrero[1], Yaming Hang[1], Alvydas Mikulskis[1], Jan Grimm[2], Christoph Hock[2,4], Roger M. Nitsch[2,4]§ & Alfred Sandrock[1]§

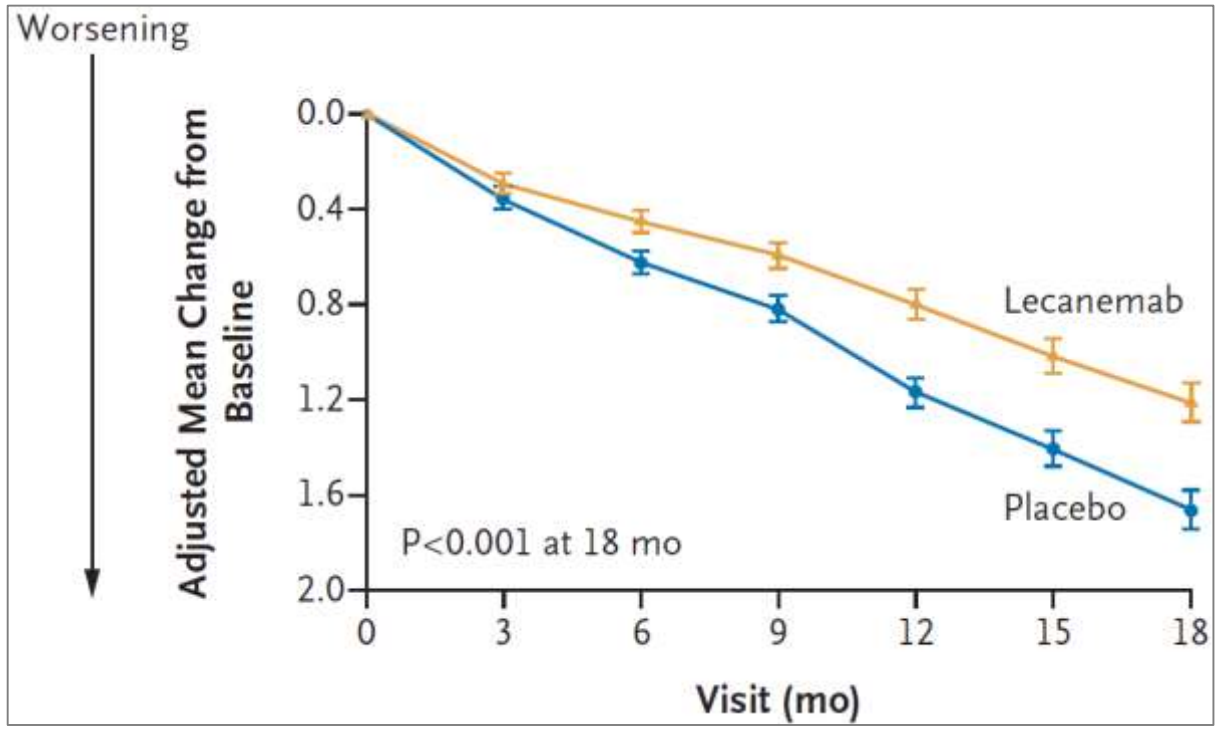
Alzheimer's disease (AD) is characterized by deposition of amyloid-β (Aβ) plaques and neurofibrillary tangles in the brain, accompanied by synaptic dysfunction and neurodegeneration. Antibody-based immunotherapy against Aβ to trigger its clearance or mitigate its neurotoxicity has so far been unsuccessful. Here we report the generation of aducanumab, a human monoclonal antibody that selectively targets aggregated Aβ. In a transgenic mouse model of AD, aducanumab is shown to enter the brain, bind parenchymal Aβ, and reduce soluble and insoluble Aβ in a dose-dependent manner. In patients with prodromal or mild AD, one year of monthly intravenous infusions of aducanumab reduces brain Aβ in a dose- and time-dependent manner. This is accompanied by a slowing of clinical decline measured by Clinical Dementia Rating—Sum of Boxes and Mini Mental State Examination scores. The main safety and tolerability findings are amyloid-related imaging abnormalities. These results justify further development of aducanumab for the treatment of AD. Should the slowing of clinical decline be confirmed in ongoing phase 3 clinical trials, it would provide compelling support for the amyloid hypothesis.



Source: Sevigny et al 2016

CHANGING THE COURSE OF DISEASE: LOWERING AMYLOID (AND TAU)

Preservation of cognition and functioning




The NEW ENGLAND JOURNAL of MEDICINE

JANUARY 5, 2023

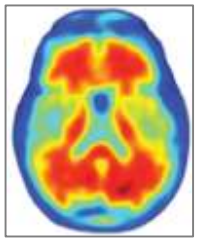
Lecanemab in Early Alzheimer's Disease

ABSTRACT

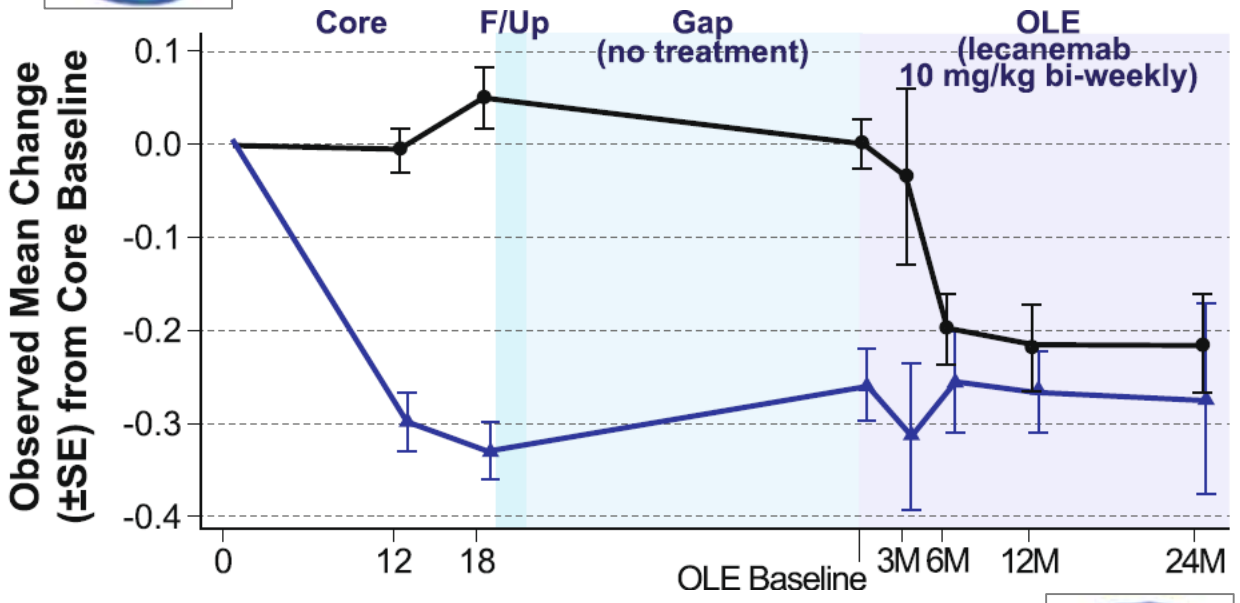
Lowering amyloid

Source: van Dyck, 2022

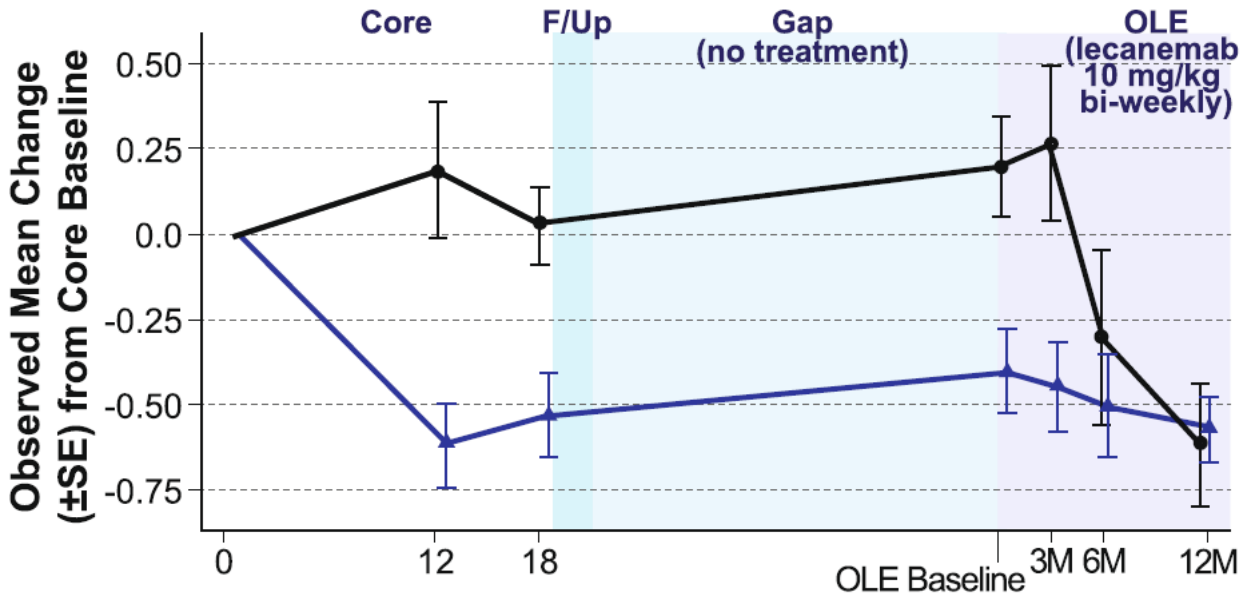
CHANGING THE COURSE OF DISEASE: LOWERING AMYLOID *AND TAU!*

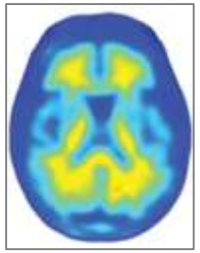


Lowering amyloid…



…leads to LOWERING OF TAU





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PREVENTING AD: LOWERING AMYLOID BEFORE MEMORY LOSS BEGINS

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Join a trial that aims to help prevent Alzheimer's disease, funded by the National Institutes of Health (NIH) and Eisai Inc., by testing an investigational treatment aimed at delaying memory loss before noticeable signs of Alzheimer's disease begin.

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PREVENTING AD: LOWERING AMYLOID BEFORE MEMORY LOSS BEGINS

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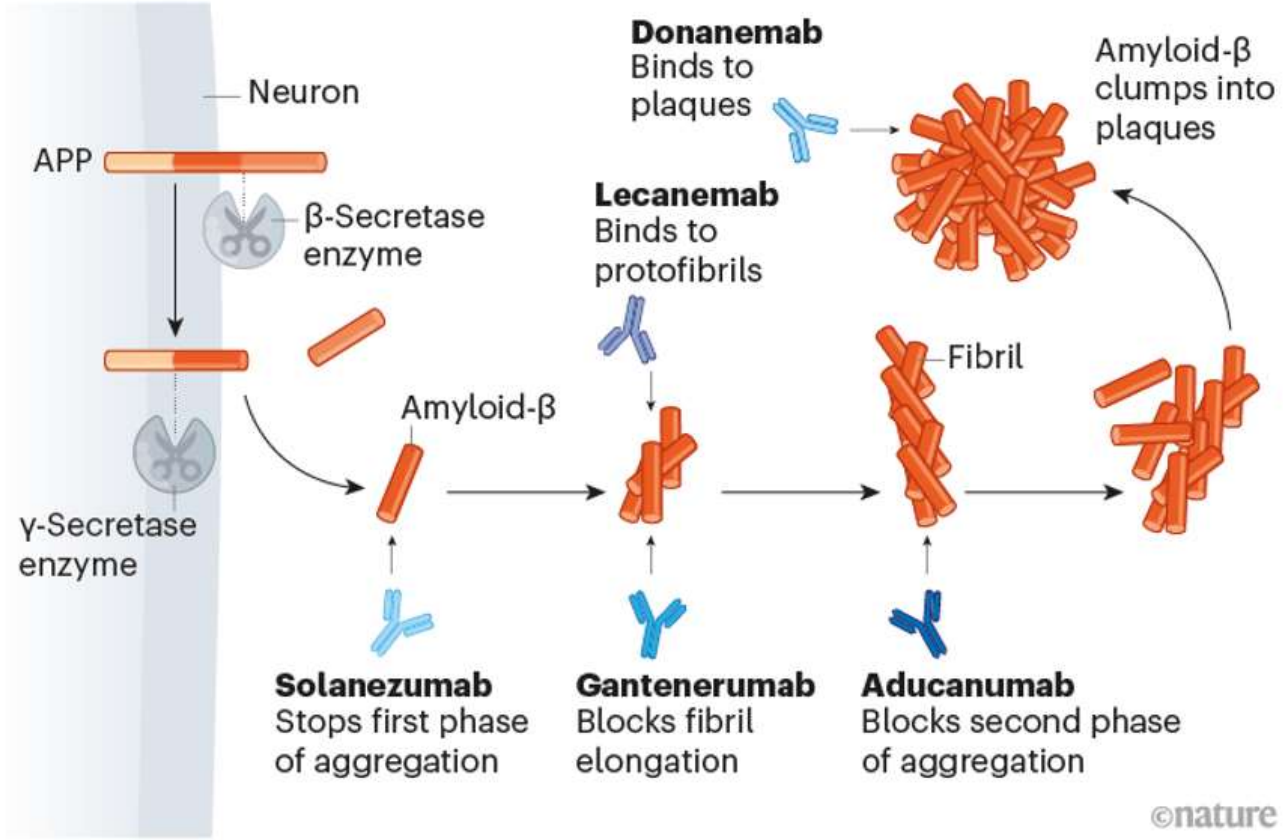

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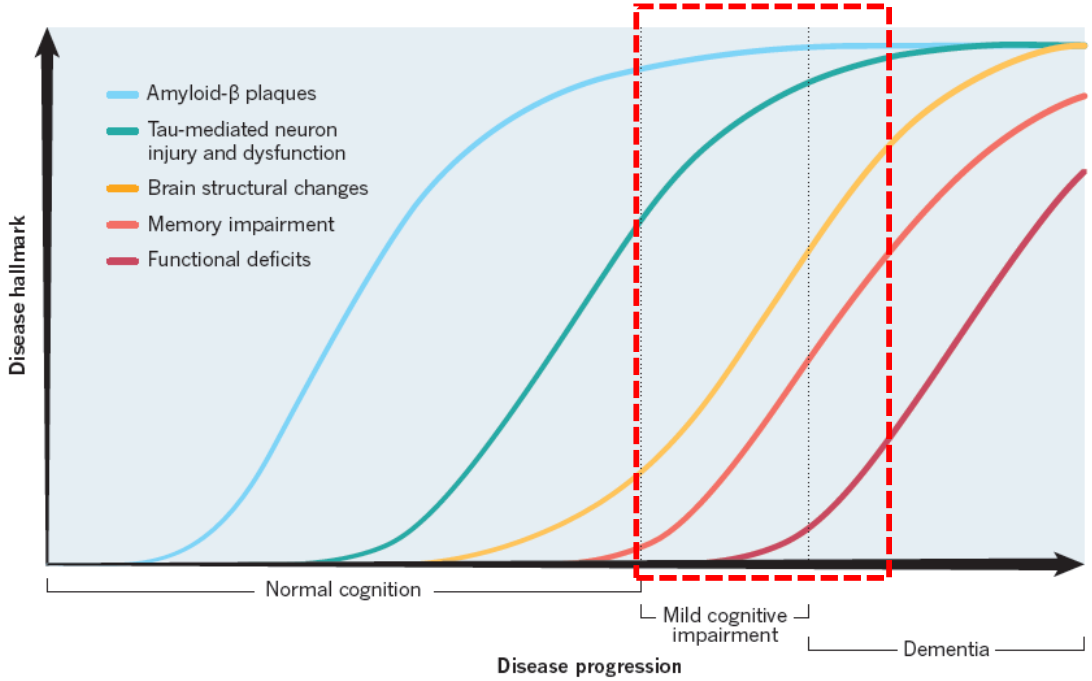

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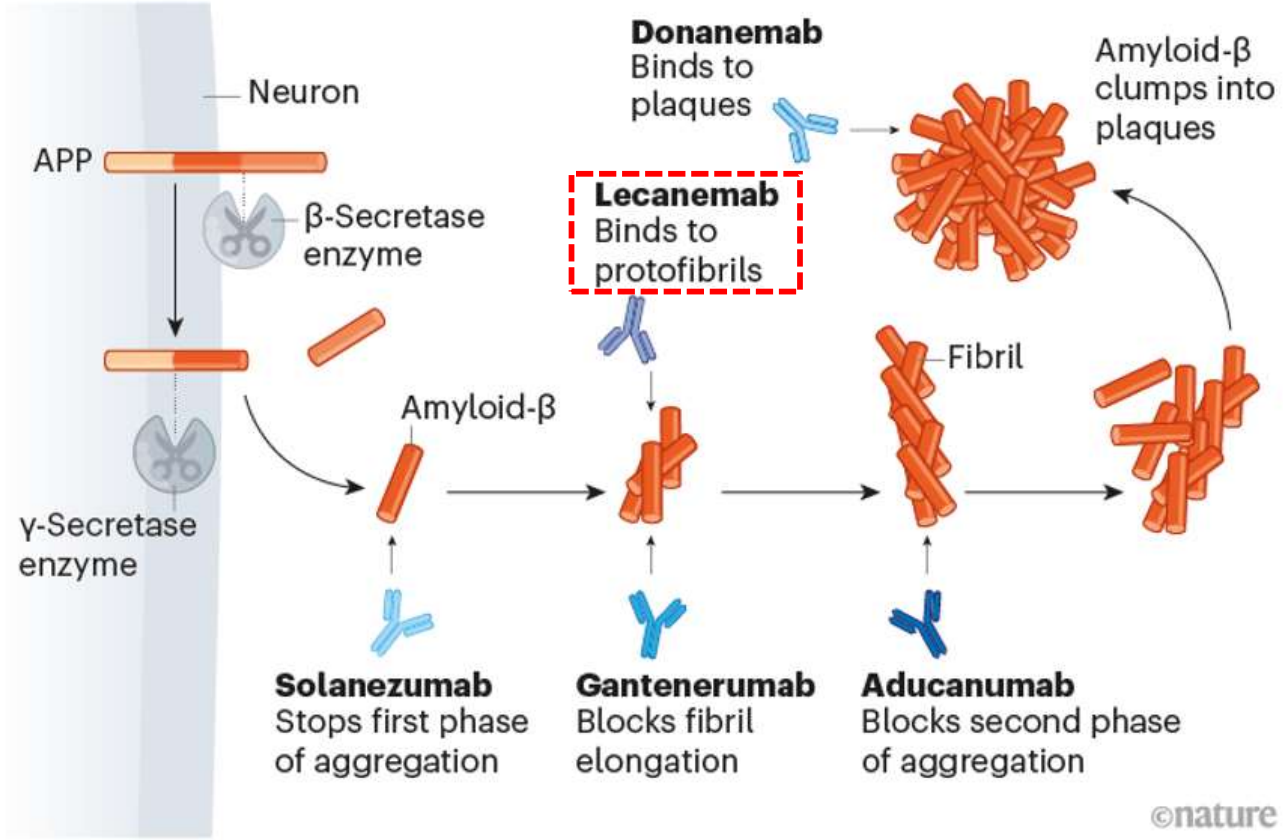

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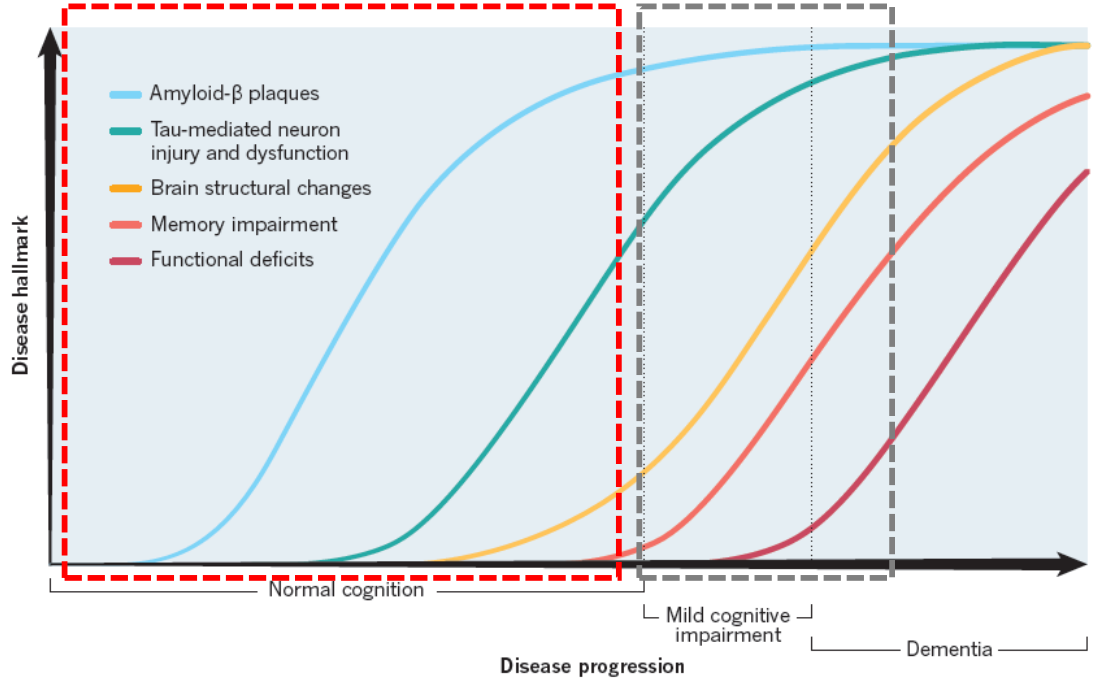

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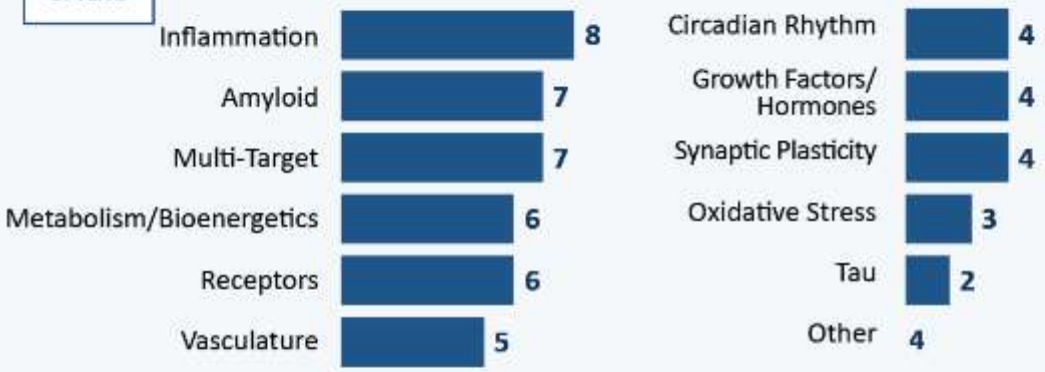
CHANGING THE COURSE OF DISEASE: THE RESEARCH PIPELINE

Pharmacological — 73 TRIALS

Phase I & Phase II

60 trials

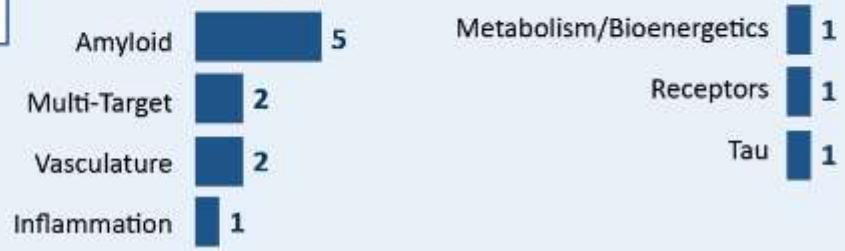
Targeted Disease Process



Phase II/III & Phase III

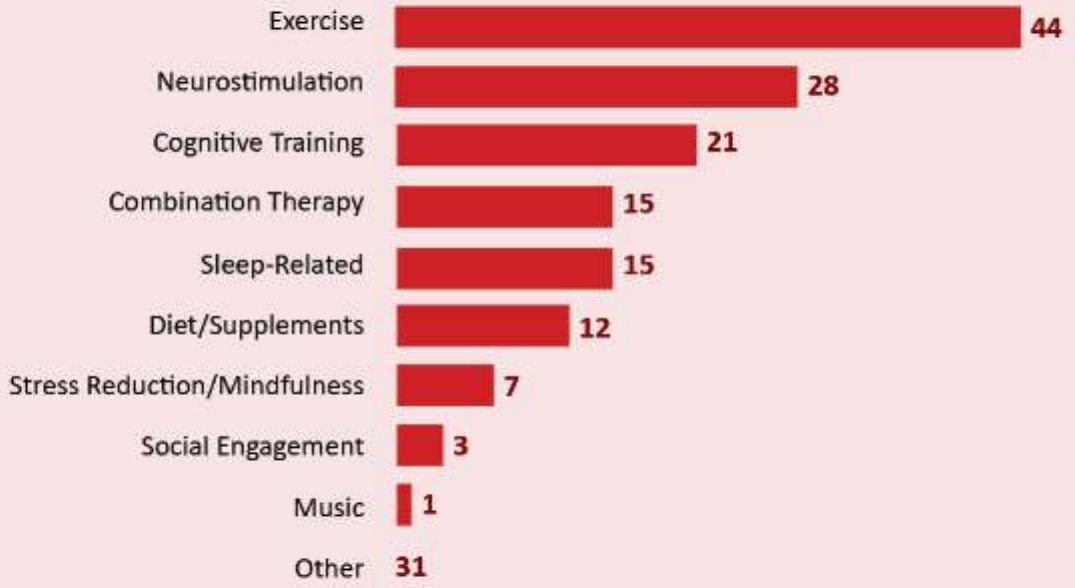
13 trials

Targeted Disease Process



Non-Pharmacological — 177 TRIALS

Modality



For more information please visit
www.nia.nih.gov/research/ongoing-AD-trials

NIH National Institute on Aging

Data last updated: December 2023.

Source: www.nia.nih.gov/research/ongoing-AD-trials

CHANGING THE COURSE OF DISEASE: BENDING THE CURVE OF LIFELONG RISK

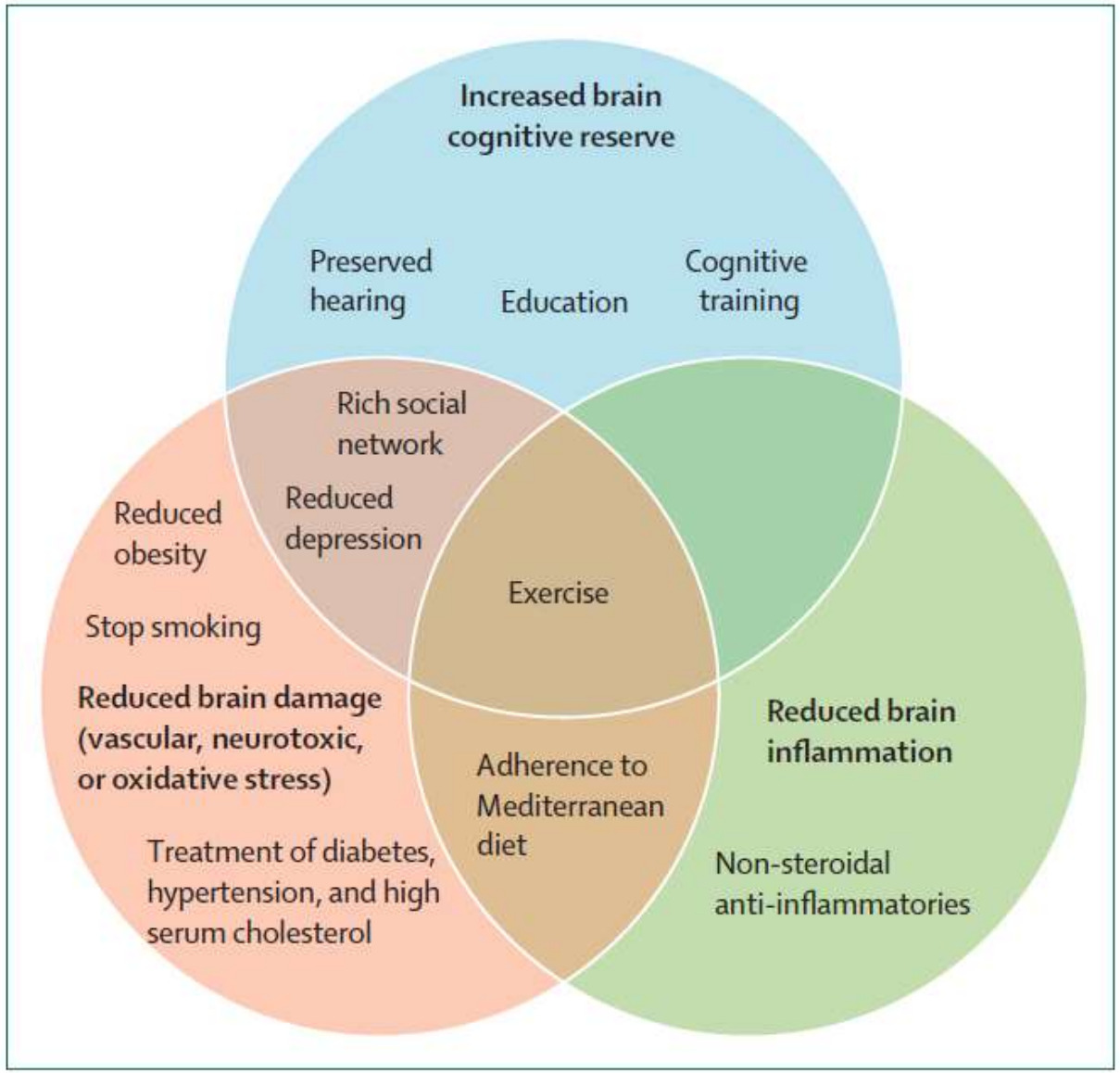


Figure 5: Potential brain mechanisms for preventive strategies in dementia

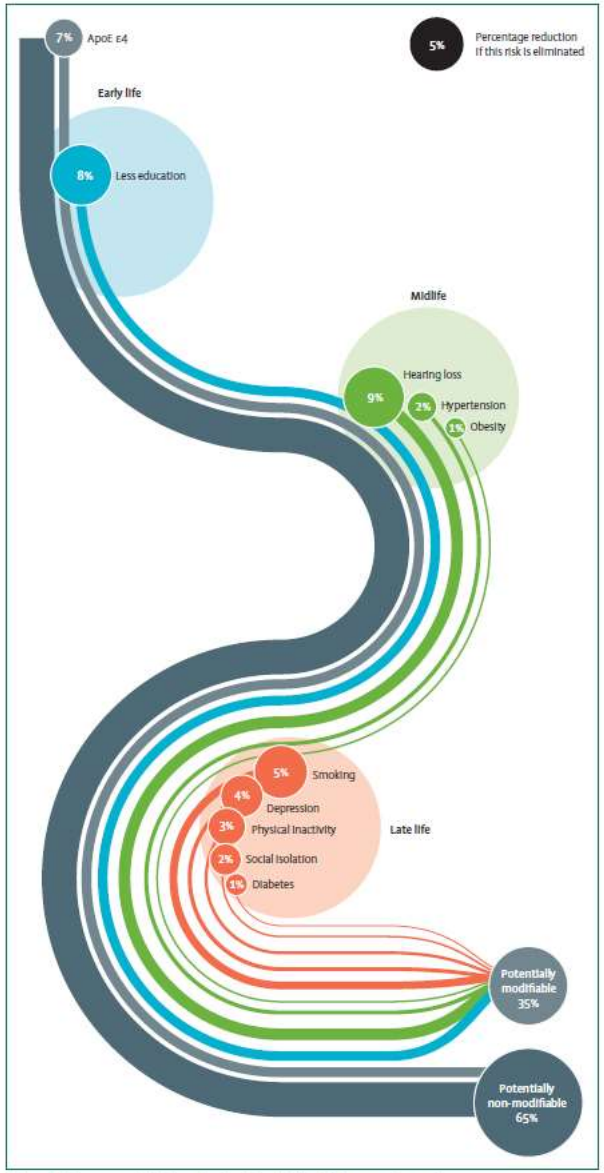


Figure 4: Life-course model of contribution of modifiable risk factors to dementia
Numbers are rounded to nearest integer. Figure shows potentially modifiable or non-modifiable risk factors.

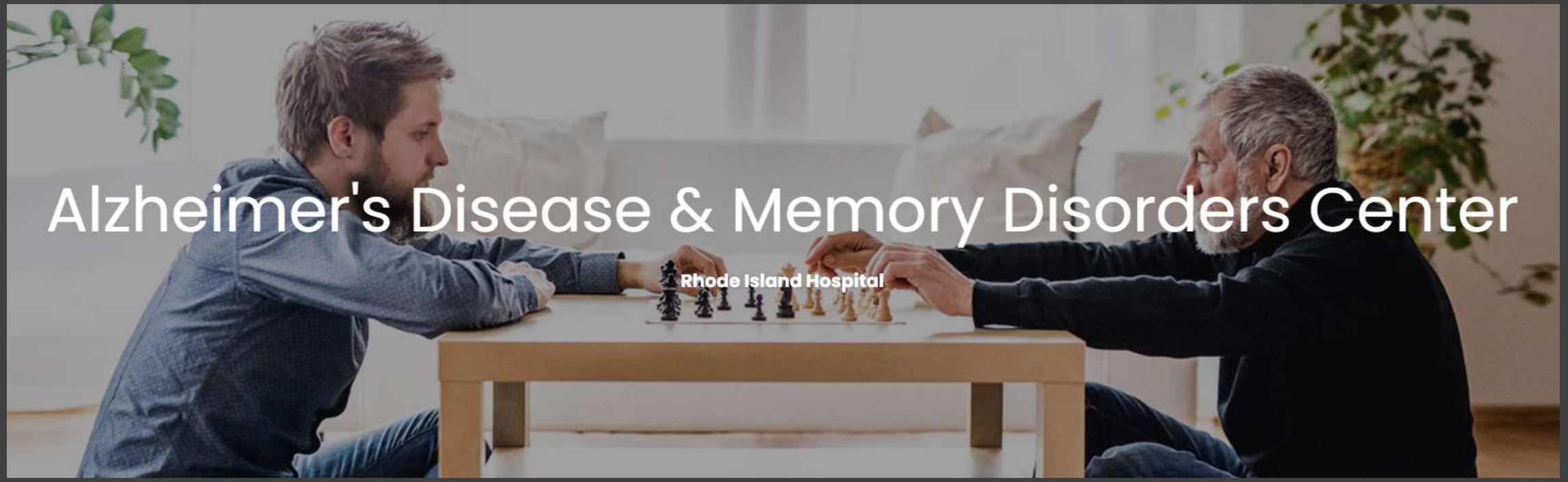
Source: Livingston G, 2017

LEARNING OBJECTIVES

- ATTAIN A BASIC FOUNDATION OF PATHOLOGIC BRAIN CHANGES IN ALZHEIMER'S DISEASE

- UNDERSTAND HOW SYMPTOMATIC THERAPIES TARGET CERTAIN ASPECTS OF ALZHEIMER'S DISEASE RELATED BRAIN CHANGES

- FROM THIS PERSPECTIVE, FURTHER UNDERSTAND OF THE RATIONALE BEHIND NEWLY FDA APPROVED DISEASE MODIFYING THERAPIES FOR ALZHEIMER'S DISEASE



THANK YOU!

Contact:
1-844-563-6679 (1-844-5-MEMORY)
memory@lifespan.org

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