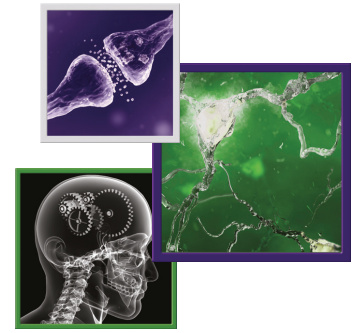
Plain Language Summary of Publication

Neurodegenerative Disease Management

Amyloid-β pathway in Alzheimer's disease: a plain language summary



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Summary

What is this summary about?

This plain language summary of an article published in *Molecular Psychiatry,* reviews the evidence supporting the role of the amyloid-β (Aβ) pathway and its dysregulation in Alzheimer's disease (AD), and highlights the rationale for drugs targeting the Aβ pathway in the early stages of the disease.

Why is this important?

Aβ is a protein fragment (or peptide) that exists in several forms distinguished by their size, shape/structure, degree of solubility and disease relevance. The accumulation of Aβ plaques is a hallmark of AD. However, smaller, soluble aggregates of Aβ – including Aβ protofibrils – also play a role in the disease. Because Aβ-related disease mechanisms are complex, the diagnosis, treatment and management of AD should be reflective of and guided by up-to-date scientific knowledge and research findings in this area.

This article describes the Aβ protein and its role in AD, summarizing the evidence showing that altered Aβ clearance from the brain may lead to the imbalance, toxic buildup and misfolding of the protein – triggering a cascade of cellular, molecular and systematic events that ultimately lead to AD.

What are the key takeaways?

The physiological balance of brain Aβ levels in the context of AD is complex. Despite many unanswered questions, mounting evidence indicates that Aβ has a central role in driving AD progression. A better understanding of the Aβ pathway biology will help identify the best therapeutic targets for AD and inform treatment approaches.

Where can I find the original article?

You can read the full article titled 'The Amyloid-β Pathway in Alzheimer's Disease' published in *Molecular Psychiatry* for free at:
https://www.nature.com/articles/s41380-021-01249-0

Who is this article for?

Physicians and practitioners who may encounter patients with or at risk of AD.

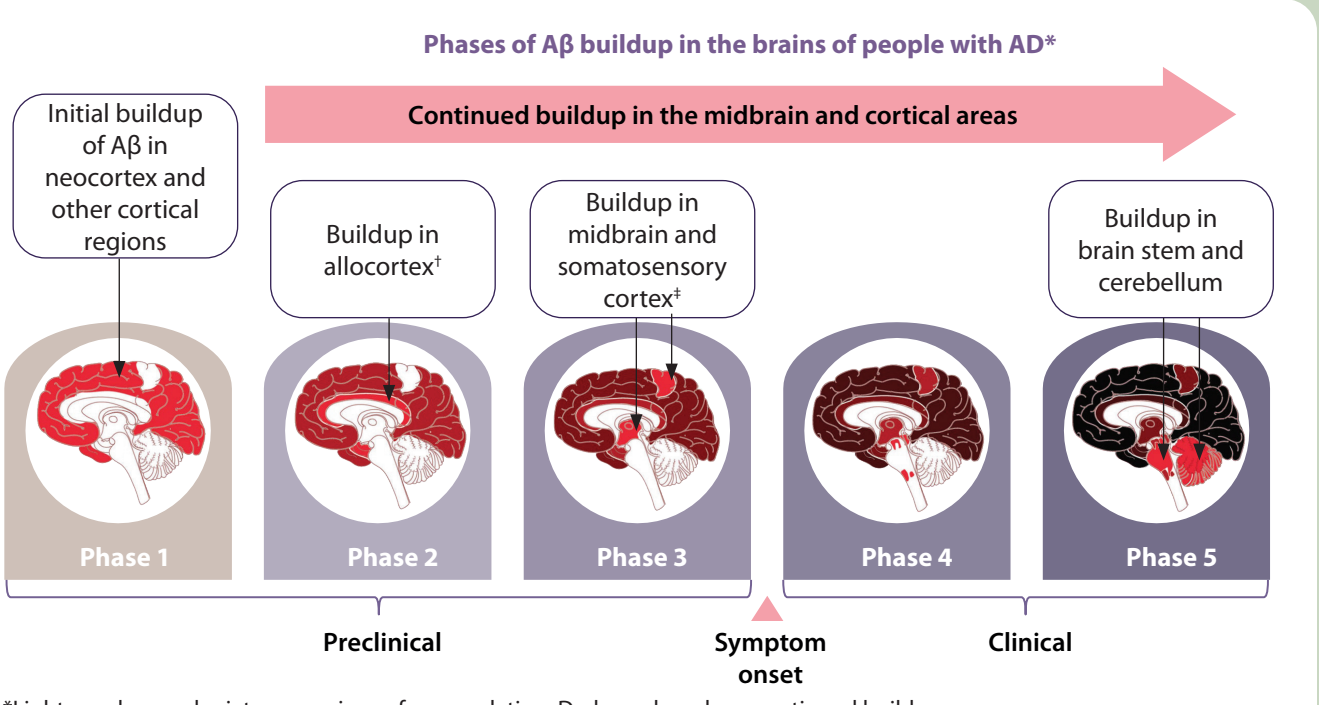
Future Medicine part of fsg

What is the purpose of this article?

- This article reviews the literature supporting the role of the Aβ pathway in AD and provides an overview of disease-related molecular and cellular changes caused by the interaction of Aβ with other important disease mechanisms, such as the protein tau.
- This review aims to help physicians and practitioners understand the different forms of Aβ and other AD mechanisms (e.g., tau protein, *APOE ε4*) that contribute to AD symptoms and progression.
- The evidence presented in this article highlights the rationale for using Aβ-targeting therapies to treat early AD and identifies knowledge gaps that remain with respect to the role of the Aβ pathway in AD.

AD is the leading cause of dementia

- AD affects nearly 45 million people worldwide and is the fifth leading cause of death.
- By the year 2050, the number of people living with AD dementia is expected to reach 13.8 million in the USA, 18.9 million in Western Europe and 36.5 million in East Asia.
- The brains of people with AD contain dense clumps of the proteins Aβ (plaques) and tau (tangles). Aβ plaques and tau tangles are both abnormal clumps of their respective proteins, but have different structures and effects on brain cells called neurons. While Aβ plaques form in the spaces between neurons, tau tangles gather inside them, forming knots of neurons. Brain imaging studies in people with AD have shown that Aβ first gathers in surface regions of the brain that have high metabolic activity, then spreads to other cortical areas, the brainstem and eventually to the cerebellum.

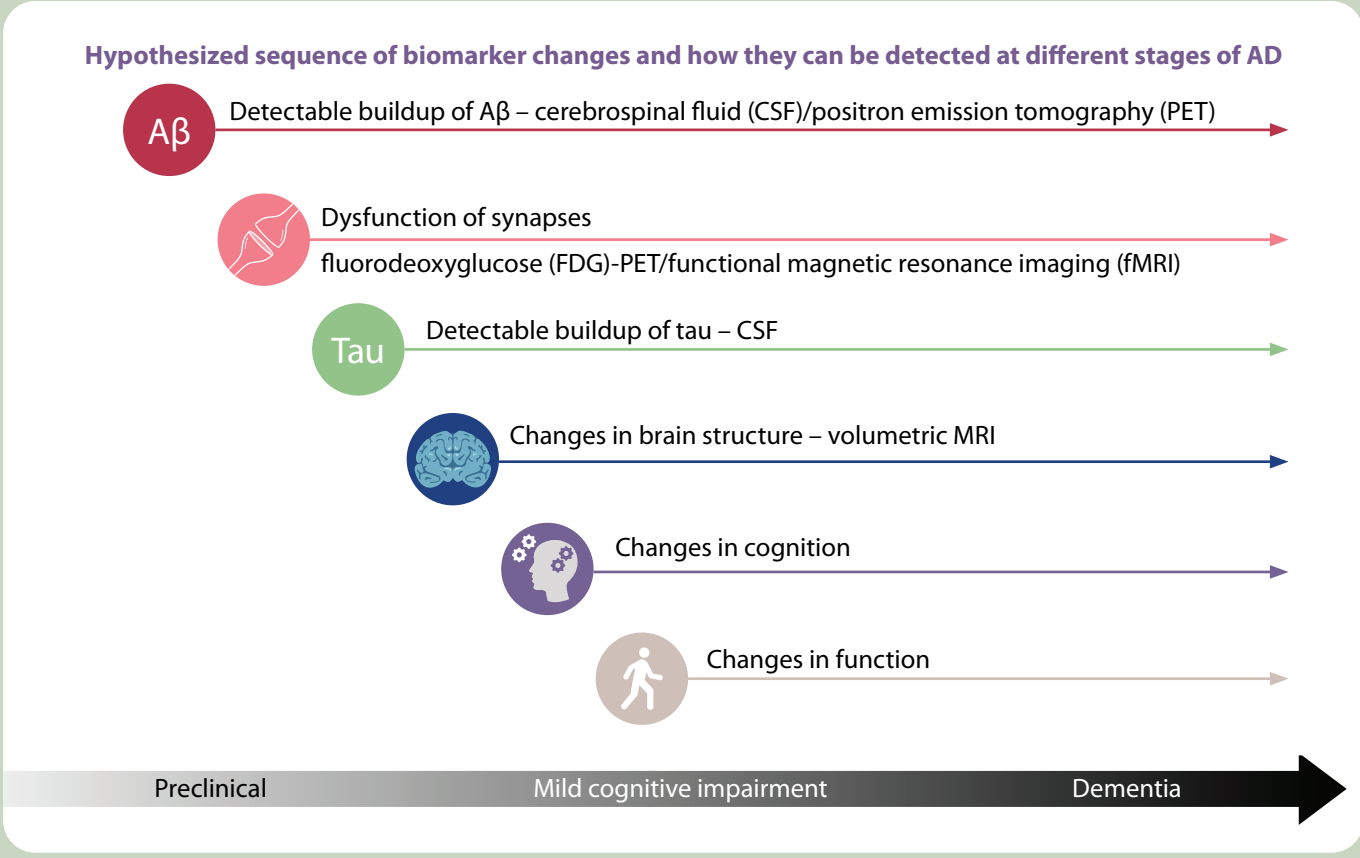


*Lighter red areas depict new regions of accumulation. Darker colors show continued buildup.
†Cerebral cortex that is not part of the neocortex.
‡The part of the neocortex that processes bodily sensation.

- When a protein misfolds, it fails to fold into its biologically functional, native form. The misfolding and buildup of Aβ protein is a distinctive feature of AD. Experiments suggest that an imbalance between the production of Aβ in the brain and its clearance from and breakdown within the brain occurs upstream of, and is associated with, Aβ misfolding in AD.

Several biological markers are affected as AD progresses

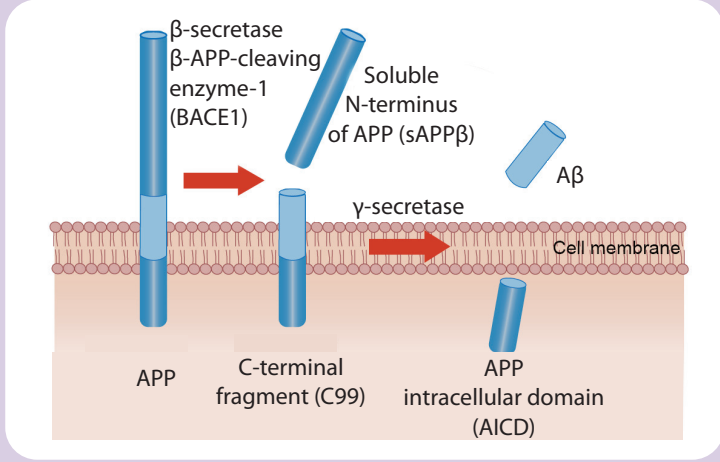
- Disease-associated processes involving Aβ occur decades before AD symptoms begin, during the preclinical stage of the disease.
- Evidence suggests that Aβ buildup in the brain is one of the earliest detectable biological markers that can indicate AD (i.e., biomarkers).



How is Aβ generated?

- Aβ is a fragment of a larger protein called APP – or amyloid precursor protein.
- APP is widely produced by brain neurons, vascular and blood cells (including platelets), and, to a lesser extent, astrocytes (star-shaped cells that hold nerve cells in place and help them develop and function).
- APP spans the cell membrane, which separates the inside and outside of the cell.
- Aβ is formed when APP is successively cleaved by 2 enzymes: β-secretase and γ-secretase. This process releases Aβ from the cell. The N-terminal APP fragment is also released, and the C-terminal fragment remains in the cell membrane.

The amyloid pathway



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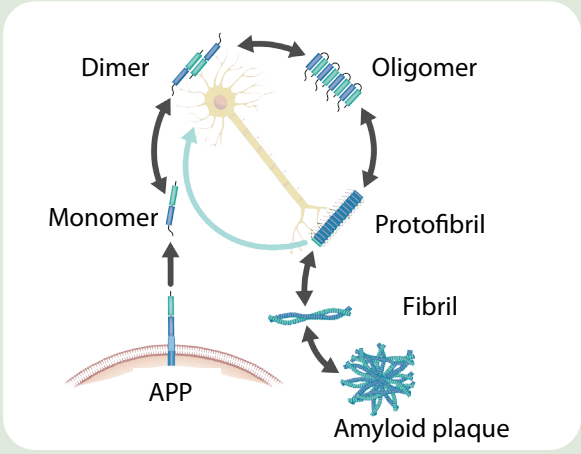
Aβ exists in several forms

Aβ aggregation species and reversible states: Aβ cycle

- After being produced as soluble monomers, Aβ is found in several different intermediate aggregation states – dimers and trimers, soluble oligomers and protofibrils – until it forms fibrils that build up into the plaques that characterize AD.
- The different Aβ species are distinguished by their aggregate size, shape and solubility.
- These Aβ species can transition from one state to another in both directions.



Soluble Aβ forms

Monomers

Single-protein, base forms of Aβ that undergo structural changes to form oligomers and fibrils

Dimers

Formed by 2 Aβ monomers

Oligomers

Large Aβ clumps that do not form pellets when separated in physiological fluids by a high-speed centrifuge

Protofibrils

Soluble, oligomeric species of Aβ that are precursors to insoluble fibrils and amyloid plaques

- Aβ monomers are involved in pathways that protect neurons, allow communication within cells and support functions at synapses.
- Soluble, low-number oligomers of human Aβ injected in rodent hippocampus can hinder important memory processes (e.g., synaptic plasticity).
- The 2 most relevant forms of Aβ peptide are Aβ40 (40 amino acid residues) and Aβ42 (42 amino acid residues).
- Aβ42 is less soluble than Aβ40 and is thus more likely to form aggregates.

Aβ protofibrils may be the most toxic Aβ species

- The Arctic APP mutation (E693G) causes early-onset AD and has been shown to specifically increase protofibril formation.
- Aβ protofibrils inhibit synaptic plasticity in mouse hippocampus, impairing memory and learning.
- In a transgenic mouse model with high protofibril levels, cognitive deficits occurred without plaques.
- Levels of Aβ protofibrils (but not total Aβ) in the brain correlate with spatial learning.

Fibrils

Insoluble Aβ forms

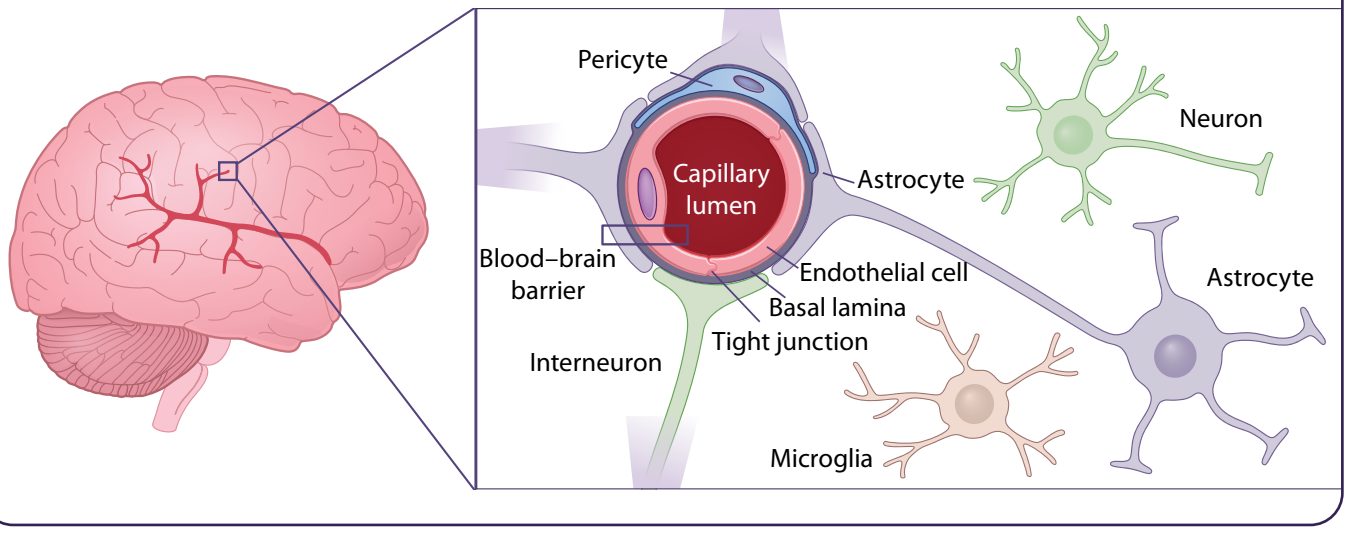
Amyloid plaques

- Aβ plaques are made up of Aβ fibrils, insoluble fibers that do not easily break down.
- Aβ fibrils occur in many forms with different solubility levels, accumulation rates and toxicity levels in neurons.
- Aβ fibrils and (to a lesser extent) plaques are associated with synaptic dysfunction in animal models of AD and in people with AD.

Aβ clearance from the brain

- Under normal conditions, the blood–brain barrier protects the brain from toxic metabolites and maintains a highly regulated internal environment in the brain.
- Aβ clearance depends partly on bulk flow through cerebrospinal fluid across the blood–brain barrier, the perivascular circulation and the glial–lymphatic (glymphatic) system in the brain. Processes outside the central nervous system also contribute to clearance.
- In healthy adults, the average rate of Aβ production as well as clearance is about 8% per hour.
- Small reductions in Aβ clearance from the brain are thought to be enough to cause Aβ to build up.

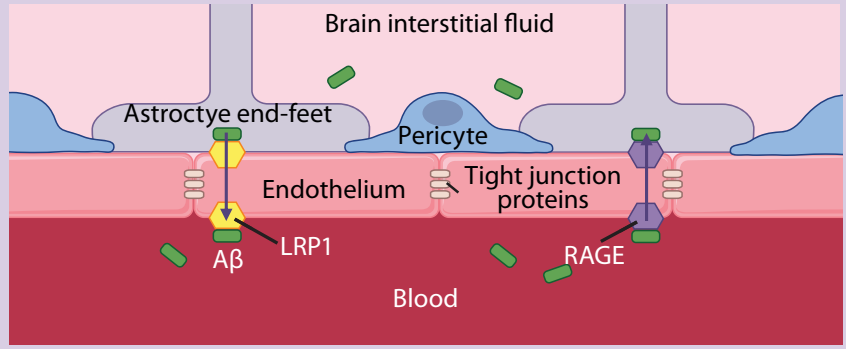
The core structure of the blood–brain barrier consists of endothelial cells connected by tight junctions, astrocytic end-feet, pericytes and smooth muscle cells that ensure a selectively penetrable system



Aβ clearance occurs through…

- Preliminary research associated AD with reduced expression of receptors that move soluble Aβ from the brain to the blood and increased expression of receptors that move free Aβ from the blood to the brain.

Endothelial cells and pericytes



LRP1: Lipoprotein receptor-related protein-1; RAGE: Receptor for advanced glycation endproducts.

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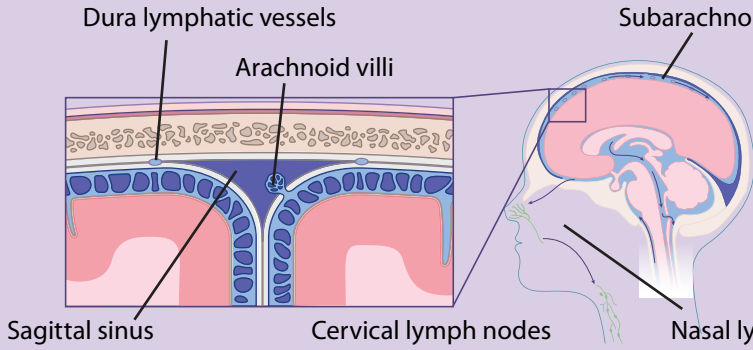
Brain interstitial fluid bulk-flow and CSF absorption



- The structure of the blood–CSF barrier is affected in aging and AD, leading to abnormal Aβ clearance.
- Flow and absorption of CSF to other biofluid systems are also altered during brain aging and are risk factors for AD.

Breakdown by enzymes inside and outside of cells

- Many genes identified in genome-wide studies and established as risk factors for AD are linked to Aβ degradation through the endosomal–lysosomal system or ubiquitin–proteasome pathway.
- The endosomal–lysosomal system allows for correct absorption, trafficking, recycling and degradation of molecules within the cell. The ubiquitin–proteosome pathway maintains protein quality by destroying misshapen and dysfunctional proteins.

Genetic evidence supporting the role of Aβ in AD

Early-onset AD

APP*, *PSEN1* and *PSEN2

Mutations in these genes have been linked to AD.

In mouse models, each of these mutations causes Aβ imbalance, with protein misfolding, aggregation and buildup into brain Aβ plaques.

In humans, a child who has one parent with one of these mutations has a 1 in 2 chance of inheriting it.

- These mutations result in genetic early-onset AD, which accounts for ~1% of cases.

Late-onset AD

More than 50 other genes, many of which are linked to Aβ homeostasis (balance), are associated with risk of late-onset AD; the most prominent among these is *APOE*.

The role of the APP gene in AD is also supported by a rare, protective Icelandic mutation:

APP A673T (or A2T)

Aβ and *APOE*:

There are 3 major versions (or alleles) of the apolipoprotein E (*APOE*) gene:
- Every person has some combination of 2 copies of the *APOE* gene (e.g., *APOE ε3*/*APOE ε3*, *APOE ε3*/*APOE ε4*, *APOE ε3*/*APOE ε2*).

APOE ε2	***APOE ε3***	***APOE ε4***
Least common (8%)	Most common (77%)	• Most significant risk gene identified for late-onset AD (1 copy increases risk by ~3-fold; 2 copies increase risk by up to 15-fold). • Also linked to early-onset AD.

- In brain tissue from people with AD, ***APOE ε4*** is related to the buildup of misfolded Aβ in neurons, the formation of toxic Aβ and the buildup of plaques.
- Brain imaging and CSF studies consistently associate *APOE ε4* with higher cerebral Aβ buildup in cognitively healthy elderly individuals and across the full clinical continuum of AD.
- Age worsens the effects of *APOE ε4* on Aβ metabolism, suggesting a possible interaction between *APOE* and aging-related metabolic changes.

Aβ and tau

There is extensive experimental evidence that altering Aβ homeostasis could affect tau pathology

Aβ as an upstream event in AD

- Experimental data indicate that Aβ may be an upstream event in AD, triggering downstream changes involving the tau pathway, neuroinflammation, synaptic dysfunction and neuronal damage and loss (neurodegeneration).

Aβ as a trigger or driver of AD

- Most studies report that tau markers, more than Aβ markers, change with other markers of neurodegeneration and long-term measures of cognitive functioning.
- According to brain imaging studies of both early- and late-onset AD, disease-associated changes in Aβ likely foster the development of tau pathology.

Aβ and tau have independent effects

- Experimental models indicate that soluble forms of Aβ and tau synergize to exert synaptic toxicity independently of their assembly into plaques and tangles.

An upstream role of Aβ on tau imbalance

- Several findings from mouse models support an upstream role of Aβ in tau imbalance (dyshomeostasis), in which Aβ facilitates the conversion of tau from a normal to a toxic state, creating a feedback loop that enhances Aβ toxicity.
- Similar studies suggest that Aβ, particularly soluble oligomers of Aβ42, could trigger changes in tau that are associated with AD.

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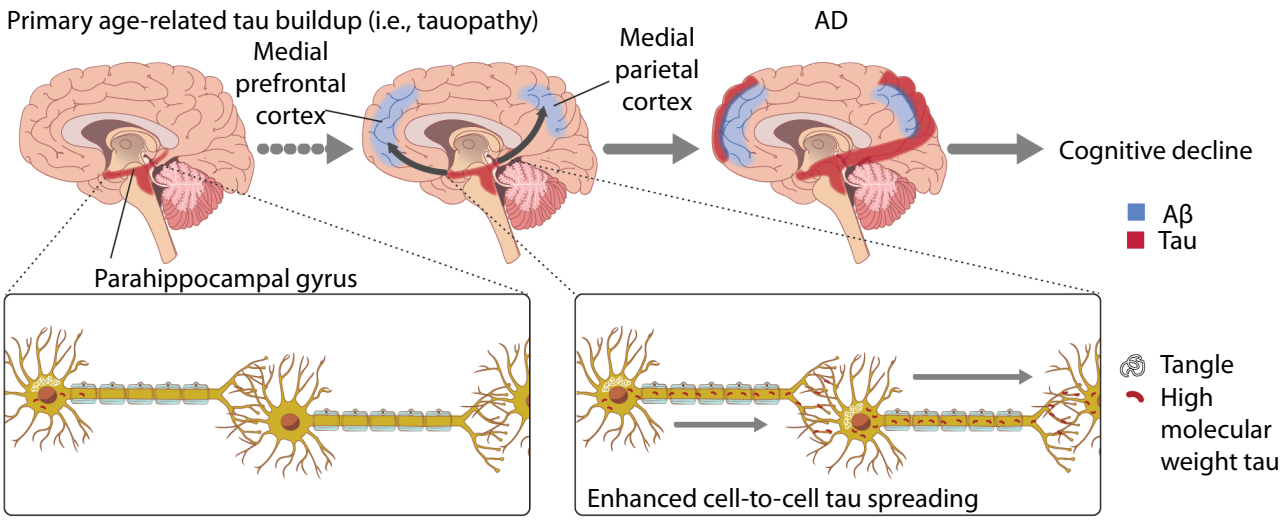

Aβ–tau synergy: Aβ pathology may be an early event in AD that triggers tau spreading, leading to cortical neurodegeneration. Buildup of tau neurofibrillary tangles and Aβ plaques coincides in cortical brain regions of people with AD, supporting Aβ-dependent tau generation. Rare species of tau (high molecular weight tau) that are heavily phosphorylated and soluble can spread from one neuron to another. The spreading is enhanced in the brains of patients with both plaques and tangles.

3 core CSF biomarkers of AD

Aβ42	Phosphorylated tau (p-tau)	Total tau (t-tau)

- Simultaneous low Aβ42 and high t-tau and p-tau concentrations strongly suggest an AD diagnosis. **~90% specificity, 90–95% sensitivity.**
- Tau/Aβ42 can predict cognitive decline in nondemented older adults and people with subjective cognitive decline, an AD risk factor.
- **>90%** average sensitivity of low CSF Aβ42 for detecting cortical Aβ deposition.

Blood-based biomarkers of AD

- Evidence suggests that Aβ changes in blood/plasma mirror those in CSF.
- Plasma Aβ42/Aβ40 performs well at predicting brain amyloid (based on amyloid PET).
- Reduced plasma Aβ42/Aβ40 is associated with increased AD risk.
- As blood-based biomarkers are less expensive and time-consuming to measure, their availability will help accelerate diagnoses and drug development pipelines.

What are the take-home messages?

- The balance (homeostasis) of Aβ and its physiology in the brain in the context of disease are complex.
- Despite unanswered questions, the majority of evidence indicates that Aβ has a central role in driving AD progression.
- A comprehensive understanding of the Aβ pathway can guide the selection of the best therapeutic targets and approaches for treating AD.

Where can readers find more information?

The review article discussed in this summary, 'The Amyloid-β Pathway in Alzheimer's Disease', was published in *Molecular Psychiatry* in August 2021, and is free to read at: https://www.nature.com/articles/s41380-021-01249-0
Several figures used in this article have been adapted from figures used in the original publication.

Educational resources
Further reading on select topics in this article:
- Amyloid beta: structure, biology and structure-based therapeutic development: https://www.nature.com/articles/aps201728
- APOE and Alzheimer's disease: advances in genetics, pathophysiology, and therapeutic approaches: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8096522/
- Biomarkers: our path towards a cure for Alzheimer disease: https://journals.sagepub.com/doi/full/10.1177/1177271920976367
- The complexity of tau in Alzheimer's disease: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7060758/

Resources for non-healthcare professionals:
- Alzheimer's disease genetics fact sheet: https://www.nia.nih.gov/health/alzheimers-disease-genetics-fact-sheet
- How biomarkers help diagnose dementia: https://www.nia.nih.gov/health/how-biomarkers-help-diagnose-dementia
- Tau protein and Alzheimer's disease: what's the connection? https://www.brightfocus.org/alzheimers/article/tau-protein-and-alzheimers-disease-whats-connection
- Alzheimer's: is it in your genes? https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/in-depth/alzheimers-genes/art-20046552
- Early-onset Alzheimer's disease: https://www.brightfocus.org/alzheimers/news/early-onset-alzheimers-disease

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