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Neurobiological mechanisms of forgetting and the impact of Alzheimer's pathology on memory formation

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ABSTRACT

Alzheimer's disease is a debilitating neurodegenerative disorder primarily characterized by profound memory loss. The process of memory formation can be divided into 3 distinct stages: encoding, consolidation, and retrieval. In a non-diseased brain, memories are discarded to maintain a healthy state, whereas failing to recall memories during the retrieval stage leads to pathological forgetting. Memories are supported by networks of cells called engrams. These assemblies of neurons are formed during the encoding stage and are reactivated during memory retrieval. Engrams are formed when the connections, synapses, between those cells are strengthened or weakened. This plasticity is called long-term potentiation when connections between synapses strengthen and long-term depression when connections between synapses weaken.

Alzheimer's disease is driven by accumulation of tau tangles and amyloid beta aggregates inside and outside of the cells. In addition to leading to cellular death, amyloid beta aggregates disrupt synaptic plasticity, while tau tangles impair intracellular transportation, driving synaptic deterioration. These protein aggregates, both individually and together, weaken synapses and drive engram neuron death, resulting in impaired memory formation and pathological forgetting. This review provides lines of inquiry by which AD pathology intersects with memory formation cellular mechanisms and drives memory loss symptoms in AD patients. Thus, engram activation and synapse strength should be a focus of future treatments studies, including as a biomarker and evaluation of treatment efficacy.

INTRODUCTION

Memory is foundational to personal identity and survival, allowing us to store the consequences of past experiences and use them to inform our actions and decisions in the present and future. The process of memory formation, maintenance, and elimination is supported by the complex interplay of networks of cells across multiple interconnected brain regions. In particular, the hippocampus, located in the temporal lobe, is thought to be a crucial hub. In the last half century, remarkable advances have been made towards understanding the mechanisms that underlie memory formation and elimination, from the identity of cells involved to how these processes are enacted at the single cell level (Mujawar et al., 2021). Alzheimer's disease (AD), a debilitating neurodegenerative disorder, is characterized by profound memory loss, mood swings, and personality shifts. Approximately 33 to 38 million people suffer from AD (Greenblat, 2026). Treating this disease costs, on average, ~$400,000 over the lifespan of the patient (Hurd et al., 2014).

Since AD was first diagnosed and described 120 years ago, scientists have extensively researched Alzheimer's and made remarkable therapeutic advancements but have yet to find a definitive cure (Ciurea et al., 2023).

Because of the great institutional and personal cost of this disease and the lack of a cure, it is critical to investigate how AD pathology intersects with the mechanisms of memory formation, maintenance, and elimination. Following this line of inquiry may help to uncover novel targets for potential treatments and provide a greater understanding of the disease as a whole.

Here we further explore the relationship between AD and the mechanisms of memory formation, maintenance, and elimination. We ask - what are the neural underpinnings of memory loss at a cellular and network level and how are these mechanisms affected by AD pathology? To address this question, we explore the neurobiological mechanisms that support the encoding, retrieval, and elimination of memory, the fundamental mechanisms of AD pathology, and how the latter may shape the former.

METHODS

Inclusion criteria	Exclusion criteria
Documents about AD, hippocampus and memory circuitry, memory formation, forgetting, amyloid beta, tau, current AD clinical trials and potential therapeutics	Documents that aren't peer reviewed
published on science journals(must be peer reviewed), National Institutes of Health(NIH)	Documents that aren't written in English
published in recent 26 years	Documents irrelevant to AD, memory formation, hippocampus and memory circuitry, forgetting, amyloid beta, tau, current AD clinical trials and potential therapeutics
world wide	Documents focusing on any specific individuals

This literature review was created in accordance with PRISMA guideline with the modification that indicates that this review is a single-author review. This research was limited to documents published from January 1, 2000 to August 4, 2026. Titles and abstracts of documents were screened for relevance based on the inclusion and exclusion criteria. Once the documents met criteria, a full text review was followed by. Documents analyzing AD, memory formation, forgetting, amnesia, amyloid beta, and tau are included. Selected documents were published in science journals or by NIH, peer reviewed. Only those published in the recent 26 years have been included. Any documents that weren't peer reviewed and/or

written in English were excluded. Documents that were irrelevant to the topic and/or focused on specific individuals were also excluded.

Neurobiological mechanisms underlying memory formation: Encoding, Consolidation, and Elimination

The process of memory formation is thought to have three distinct stages: encoding, consolidation, and retrieval. These stages allow an experience to be translated into neurological programming, stored in the brain for later use, and subsequently reactivated and remembered to inform future behavior.

Encoding is the stage where sensory information is processed and transformed into neurobiological correlates (Guskjolen & Cembrowski, 2023). This process begins when modality-specific sensory representations (i.e. olfactory, auditory, visual etc) are refined by their respective processing neural hubs and then routed to the coordinated network, including the hippocampus, which converts these experiences to memories. For example, olfactory information is first detected by olfactory sensory neurons in the main olfactory epithelium before being sent to the piriform cortex and entorhinal cortex for odor identification after which information is routed to the hippocampus (Sanchez-Andrade & Kendrick, 2009). Similarly, visual information is taken up by the eye and processed by the visual cortex to determine identity, location, movement before being indirectly sent to the entorhinal cortex and subsequently hippocampus (Huff et al., 2023; Rolls, 2024). Within the hippocampus and associated brain regions, memories are stored as connected assemblies of neurons.

Consolidation is the stage where short term memories are transformed into long term memories by taking these assemblies of neurons and strengthening the connections between them in both same and different brain regions (Guskjolen & Cembrowski, 2023). During consolidation the hippocampus guides the reorganization of information stored in the neocortex, such that it eventually becomes independent of the hippocampus. Damage to the hippocampus impairs memories formed in the recent past, but typically spares memories formed in the more distant past. Consolidation occurs for both episodic, long term explicit memories containing personal experiences, and semantic, long term memories of general knowledge of the world, memories and for both spatial and non spatial memories (Squire et al., 2015). Consolidation enables memory persistence by stabilizing newly acquired, fragile memories (Kim & Park, 2025).

The retrieval stage is thought to happen in the prefrontal cortex, hippocampus, and parietal lobes. Neurons that were initially connected during the encoding stage and strengthened over time, now can be reactivated in order to recall a memory. In a laboratory setting, silencing assemblies of neurons encoding a memory suppresses that memory retrieval, while activating the ensemble promotes retrieval (Guskjolen & Cembrowski, 2023) (Ryan et al., 2015).

Forgetting is an active and adaptive process that works, in part, by deconstructing the neurobiological correlates of memory. Elimination occurs when the connections between assemblies of neurons that formed during the encoding stage and were strengthened during the consolidation stage are weakened by

non-neural cells, such as glial cells, which clear fragmented cells and debris produced during elimination. (Chung & Barres, 2013). Disrupting and removing unwanted connections between neurons decreases reactivation of the memory-associated neural assemblies which promotes forgetting of memories (Guskjolen & Cembrowski, 2023). Healthy memory requires balancing memory persistence with memory elimination (Merlo et al., 2024). When the balance is disturbed, it causes malfunctionality in the brain which affects memory retrieval.

How cellular mechanisms drive engram formation

When memories are initially encoded, the assemblies of neurons that form are called engrams. An engram is the neural substrate for storing memories, meaning it's the basic unit of memory. Within the hippocampus, engrams are encoded via competition based rules called hebbian coding. Hebbian coding, defined as "neurons that fire together, wire together", is the biological mechanism that physically builds neural representation of the encoding stage (Faghihi & Moustafa, 2015). More excitable neurons and ensembles —the group of neurons that fire together (Yuste et al., 2024)— out compete less excitable ones for recruitment into ensembles that are later "turned on" to recall a memory (Guskjolen & Cembrowski, 2023). These more excitable cells that are recruited into engrams undergo off-line, persistent chemical and or physical change to save this memory (Josselyn & Tonegawa, 2020).

This persistent chemical and physical change that drives the recruitment of neurons into engrams is called synaptic plasticity. Synapses are the sites where neurons communicate with each other, primarily using chemicals called neurotransmitters (Caire et al., 2023) which bind to their cognate receptors on the downstream neuron. For example, the neurotransmitter glutamate is bound by AMPA and NMDA receptors. AMPA and NMDA are glutamate receptors found in excitatory synapses that allow cations into the postsynaptic neuron, driving fast electrosignal and learning (Perves et al., 2001). Synaptic plasticity results from overall strengthening or weakening of these synaptic connections. Synaptic plasticity is an adaptive change in synapses that is caused by complex interplay of altered neurotransmitter release, postsynaptic receptors such as AMPA and NMDA, and synchronous activation of neighboring structures. Long term potentiation (LTP), strengthening of a synapse, and long term depression (LTD), weakening of a synapse, are the functional consequences (Weishaupt, 2017). At a molecular level, LTP is driven by numerous factors; the most studied factor is an increase in the volume and AMPA receptor density in postsynaptic spines. Increased neurotransmitter release at presynaptic terminals is also involved with LTP induction (Murai & Goto, 2025). When a presynaptic neuron receives substantial input such as during the process of memory encoding, it releases more neurotransmitters than normal. This barrage of neurotransmitters results in significant calcium entry on the postsynaptic side, which activates calcium/calmodulin-dependent protein kinase II (CaMKII). CaMKII subsequently translocates to the synapse, where it binds to the NMDA-type glutamate receptors and produces potentiation by phosphorylating principal and auxiliary subunits of AMPA-type glutamate receptors. This phosphorylation allows receptors to bind to postsynaptic density 95, a neuronal scaffolding protein (Lisman et al., 2014). This ultimately results in more receptors being present at the synapse on the postsynaptic neuron. When the presynaptic cell releases neurotransmitters again, there will be more AMPA receptors on the postsynaptic side, producing a bigger response to the same input and

"strengthening" the synaptic connection. LTP can be divided into two phases: early phase LTP (E-LTP) and late phase LTP (L-LTP). E-LTP modifies existing but inactive AMPA receptors to migrate them to the synaptic junction whereas L-LTP requires the production of new AMPA receptors. Production of new receptors requires protein synthesis (Lu et al., 2009).

Protein synthesis is a process in which proteins are built through transcription from DNA to RNA, and RNA to protein (Gallie, 2024). Protein synthesis plays a critical role in long lasting forms of synaptic plasticity, as this process specifically, locally and temporally regulates amino acids. (Rosenberg et al., 2014). Applying protein synthesis inhibitors (PTI) in brain slices prior to administering a large and sustained stimulus (Dias et al., 2022), has been shown to impair synaptic transmission during the late phase of LTP. Mice injected with anisomycin, a PTI, once (1xANI) showed impaired natural recall yet still displayed fear responses upon optogenetic reactivation. However, mice injected with four anisomycin (4xANI) doses over 6 hours showed significantly impaired natural recalls, and failed to exhibit fear responses upon optogenetic reactivation. 1xANI mice exhibited no significant reduction in engram synapse density, but had significantly smaller spine sizes. 4xANI mice showed significant reduction in both engram synapse density and spine sizes. This result indicates that PTI significantly reduces engram synapse density and spine size, during both natural and artificial recall (Hong et al., 2026).

By contrast, LTD, another mechanism of engram deconstruction, is characterized by decrease in postsynaptic strength. AMPA receptors dephosphorylate and facilitate their movement away from the synaptic junction. LTD is prominently found in the hippocampus and cerebellum and is responsible for the removal of old memory traces (Dharani, 2015). In order to understand how these mechanisms underlying memory formation and loss are affected by Alzheimer's pathology, we must first understand the underlying risk factors and causes of AD.

The basic mechanisms of AD

Alzheimer's Disease is a debilitating neurodegenerative disorder (Sheppard & Coleman, 2020). It has multiple risk factors including aging; genetic background , and inflammation to name a few.

Aging is a significant risk factor of Alzheimer's disease. Aging is characterized by systemic changes in both intracellular and extracellular microenvironments that affect the entire body rather than a single organ. In a healthy brain, aging-associated decline of homeostasis leads to increased cellular stress. These cellular stresses include oxidative stress, DNA damage, and mitochondrial stress. Senescence (aging of cells) may initially occur to maintain homeostasis. However, excessive senescence results in persistent inflammatory responses and tissue deterioration. The resulting inflammation may damage synapses and lead to cognitive impairment (Liu et al., 2024).

There are a number of significant genetic risk factors for AD. Individuals with variants in APOE4 or rare mutations in *APP*, *PSEN1*, or *PSEN2* bear considerably higher risk for developing AD. In a healthy brain, *APP* encodes for amyloid precursor protein (APP) which is a single pass type 1 transmembrane glycoprotein with a large extracellular domain. It is synthesized in the endoplasmic reticulum and plays a

major role in synaptic development, such as building, stabilizing, and regulating synapses (Kruse et al., 2025). Mutations in *APP* can cause deposition of beta amyloid, accumulation of which is an early onset symptom of AD (Bamford et al., 2020).*PSEN1* is a gene that produces presenilin 1 protein and *PSEN2* produces presenilin 2 protein.. The presenilin protein plays a major role in the enzyme complex that helps break down APP. Mutations in *PSEN1* or *PSEN2* impair its protein function, leading to deficits in APP breakdown. When APP is not broken down correctly, these peptides stick together and build up clumps (amyloid plaques) in the brain, leading to the death of neurons, a primary pathological sign of Alzheimer's disease (National Library of Medicine, 2021). While PSEN2 mutations take less than 5% of the cases on early onset AD, there are two main PSEN2 mutations that can change amino acids that make presenilin 2. One changes amino acid asparagine with amino acid isoleucine at position 141 and the other changes amino acid methionine to amino acid valine at position 239. These mutations disrupt the production of APP and drive overproduction of Amyloid beta peptide (National Library of Medicine, 2008).

Variation in *APOE4* which encodes for Apolipoprotein E4 is the primary genetic risk factor of Alzheimer's which makes up about 40 to 60% cases of all AD patients (Pires & Rego, 2023). Apolipoprotein E plays a central role in lipid metabolism, transporting fats and cholesterol in the brain (Bilici 2026). Carrying one copy of APOE4 allele increases the risk of Alzheimer's 3 to 7 times, while carrying two copies increases it to 12 times (Pires & Rego, 2023). APOE4 deficiency impairs the brain's ability to clear amyloid beta, which leads to accumulation of amyloid (Bilici, 2026).

Inflammation, accompanied by and can lead to accumulation of toxic proteins, contributes to the increased accumulations of stressors within cells (Liu et al., 2024). Neuroinflammation is not typically thought to be casual on its own, but rather a result of one or more of the other AD pathologies or risk factors associated with AD. Inflammation serves to increase the severity of the disease by exacerbating pathologies. Inflammation appears to have a dual function: a neuroprotective role during an acute phase response, but becomes detrimental when a chronic response is mounted. Chronically activated microglia release proinflammatory and toxic products, such as reactive oxygen species, nitric oxide, and cytokines. In patients suffering from recent head trauma, an increase in cerebral amyloid beta deposits 1-3 weeks post injury has been found. Elevated levels of interleukin 1(IL-1) were responsible for the increased APP production and amyloid beta load. Elevated levels of IL-1 have been shown to increase the production of other cytokines. The neuroinflammation observed in AD appears to serve a primary role in exacerbating amyloid beta burden and tau phosphorylation. It suggests that this dual role could be a leading link between these seemingly disparate core AD pathologies (Kinney et al., 2018).

While the causes and risk factors of Alzheimer's disease have only been partially characterized, the pathological mechanisms, specifically the accumulation of amyloid beta and tau tangles, are well understood.

Amyloid Beta and Tau

Amyloid beta is a sticky microscopic fragment of protein that accumulates outside of nerve cells into plaques in the brain. When it accumulates, it can disrupt communication between brain cells. Amyloid beta is formed when APP is not broken down correctly (Sadigh-Eteghad et al., 2014). Some versions of amyloid beta, like Aß42 (Wang et al., 2021) are chemically stickier than other peptides and are more likely to accumulate in a person's brain with AD. While the normal function of Amyloid beta peptide promotes cell development and maintenance (Azargoonjahromi, 2024), emerging evidence suggests that Amyloid beta oligomers play a more critical role in Alzheimer's pathogenesis than the plaques themselves. While amyloid beta plaques are large, insoluble, dense deposits of intertwined fibrills, amyloid beta oligomers are small, soluble clusters of a few peptide molecules that may spread throughout the brain (Chen et al., 2017). These oligomers bind to the dendritic arbors of neurons isolated from the hippocampus (Wilcox et al., 2011), impairing synaptic function and disrupting neural networks, causing neuronal deaths (Rukmangadachar & Bollu, 2025).

Tau is a microtubule associated protein that regulates the assembly and maintenance of structural stability of microtubules (Medeiros et al., 2010). Microtubules, the principal component of cytoskeleton, are rigid hollow rods with dynamic structures that undergo continual assembly and disassembly within the cell. They determine cell shape in the cell movements such as cell locomotion, intracellular transport of organelles, and separation of chromosomes during mitosis (Cooper, 2000). Tau is mainly found in neuron axons and remains a highly soluble and natively unfolded protein that helps stabilize microtubules, under non-pathological conditions. Tau modulates anterograde transport by kinesin and dynein, motor proteins which transport biological payloads and provide forces to drive motion of flagellar structures and cilia (Abraham et al., 2018), driving retrograde transport. When the brain is diseased with Alzheimer's, tau becomes hyperphosphorylated, causing microtubules to disassemble. The free tau molecules aggregate into paired helical filaments that are insoluble, which accumulates as neurofibrillary tangles in Alzheimer's disease (Medeiros et al., 2010).

Evidence suggests that soluble forms of amyloid beta and tau work together, independently of their accumulation into plaques and tangles. For example, neuronal death and synaptic dysfunctions are triggered by soluble, extracellular amyloid beta species and depend on soluble cytoplasmic tau. In AD pathogenesis, amyloid beta triggers the conversion of normal tau into a toxic state and toxic tau enhances amyloid beta toxicity via feedback loop (Bloom, 2014). Aggregated amyloid beta induces tau hyperphosphorylation. . Hyperphosphorylated tau protein detaches from microtubules and is more likely to form neurofibrillary taus (NFTs), which causes neurofibrillary degeneration. (Zhang et al., 2021).
Thus, amyloid beta and tau pathological aggregation are hallmark indicators of AD in the brain.

Indeed, amyloid beta plaque reduction has been the main focus in AD therapeutic development for the past 30 years. Plaque reduction has been successful in laboratory settings, but has yet to translate to human clinical trials . However, recently, the phase 3 CLARITY AD trial of lecanemab and the phase 3 TRAILBLAZER-ALZ 2 trial of donanemab showed statistically significant improvement of cognitive and functional decline in early AD, alongside substantial amyloid clearance.

Lecanemab was approved by the FDA on 6 July, 2023. The CLARITY-AD study is a phase 3 18-month, double-blind, placebo controlled study that demonstrated lecanemab's ability to treat early AD patients. It reduces CDR-SB scores and other measures of cognition, such as ADAS-cog, ADCOMS and ADCS-MCI-ADL, as well as achieving substantial amyloid burden reduction on positron emission tomography.

Donanemab was approved by the FDA on 2 July, 2024 and 25 July, 2025. TRAILBLAZER-ALZ 2 is a phase 3, 18 months double-blind, placebo controlled study which showed that donanemab reduced clinical progression in patients with early symptomatic AD who had amyloid and tau pathology while using a treatment cessation protocol after amyloid clearance. (Papaliagkas, 2025).

Another potential therapeutic is Anti-PD-L1,a Phase 1b trial for a novel immunotherapy. The Phase 1b trial confirmed that IBC-Ab002 was safe and well tolerated at all administered doses in patients with early stage AD. IBC-Ab002 targets the PD-1/PD-L1 inhibitory immune checkpoint instead of removing the amyloid plaques. It transiently unleashes peripheral immune activity, which clears senescent cells and dampens brain inflammation. The therapy targets age-related immune exhaustion, working on a basis of systemic immune decline as the primary cause of neurodegenerative disease. (Maimon, 2026).

While the reduction of amyloid beta plaque has only been successful in the laboratory settings, recent clinical trials provide hope for novel therapeutics targeting amyloid beta plaques. Lecanemab and donanemab showed significant improvement in cognitive and function decline, along with substantial amyloid clearance. Anti-PD-L1, another recent treatment of AD, also showed significant improvement in brain inflammation by targeting the immune checkpoint directly. However, until a therapeutic has been reliably demonstrated to be effective in patient populations, further research is needed to understand how AD pathology shapes the mechanisms that drive memory formation and elimination as it may unveil potential new targets for clinical intervention.

How does Alzheimer's pathology intersect with mechanisms of memory formation/discard

Pathological aggregation of amyloid beta plaques/oligomers and tau tangles disrupts synapses and kills neurons. Given that synaptic plasticity is a key neurobiological substrate of memory formation and maintenance, disrupted synapses impair the ability of the brain to form new memories and to retain old ones. Similarly, when dead neurons are part of engrams, ensembles of neurons that support memory recall, those engrams are deactivated and drive memory loss that is not adaptive but pathological.

Mechanistically, amyloid beta aggregation can disrupt glutamate receptors which results in calcium dyshomeostasis which in turn impairs synapse plasticity. Specifically, amyloid beta aggregates trigger reduction of subtypes of glutamate receptors present on neuron surfaces, in turn reducing the ability of that cell to participate in long term potentiation. Toxic aggregates can also impair the ability of astrocytes, non-neuronal cells that clear excess glutamate. This excess glutamate can act on NMDA receptors, leaving them constantly open and resulting in a massive entry of Ca^{2+} into cells (Zhang et al., 2022). This calcium dyshomeostasis also causes mitochondrial dysfunction, as indicated by observations of

mitochondrial Ca^{2+} overload, oxidative stress, and mitochondrial membrane depolarization (Alberdi et al., 2010). Given that mitochondria generate energy for neurons to function and communicate with one another, changes in mitochondrial health lead to cell death. Thus, pathological accumulation of amyloid beta alters the brain's ability to form new memories and recall old ones.

The main function of tau in the normal brain is to maintain cellular stability and structure and allow transport of energy and biological components within neurons (Kopeikina et al., 2012). This is mediated by Tau interaction with actin and spectrin proteins which allows microtubules to interconnect with other cytoskeletal components. This interaction allows stable microtubules to support neuron shape and mediate the transport of nutrients, energy, and biological cargo (Jadhav et al., 2015).

Pathological tau protein aggregates cause dysregulation of cellular architecture and lead to functional abnormalities in synaptic transmission. Damages in the structural and functional synapses lead to impairment of long term potentiation (Jadhav et al., 2015). In AD, misfolded tau aggregates into damaging neurofibrillary tangles. Misfolded tau is no longer able to appropriately stabilize microtubules, leading to the degeneration of cellular structure and trafficking mechanisms. Synapse formation and maintenance require trafficking of relevant receptors, support, and energy so in AD, when synapses are exposed to disease modified protein tau, it causes the loss of synaptic contacts (Jadhav et al., 2015). Indeed, when researchers examined the effects of tau on synapses in mature hippocampal neurons, they found that it resulted in degeneration of synapses, as seen by the disappearance of spines and of pre and post synaptic markers. This is accompanied by transport inhibition of vesicles and organelles, associated with increase and bundling of microtubules. Therefore, as mitochondria degenerates, ATP levels decrease, which leads to protein clumps and neuro inflammation (Thies & Mandelkow, 2007) .

Impaired synaptic plasticity drives reduced engram reactivation, leading to pathological memory loss. Mice models were exposed to aversive experience and subjected to sham or high frequency head impact (HFHI). Sham mice successfully retrieved fearful memories upon subsequent exposure to natural memory recall cues. In sham mice, the hippocampal memory neurons exhibited synaptic plasticity, and increased dendritic spine volume compared with nonengram neurons. In contrast, HFHI mice retained a comparable amount of hippocampal memory neurons but didn't undergo synaptic plasticity. This lack of plasticity led to retrograde amnesia in HFHI mice, coinciding with impaired activation of the engram network (Chapman et al., 2024). This mouse model suggests the potential impairment isolated specifically to engram plasticity.

In transgenic mouse models of early Alzheimer's, direct optogenetic reactivation of engram cells results in memory retrieval despite the fact that these mice are amnesic in a long term memory when natural recall cues are utilized. This reveals that in AD, memory loss is due to retrieval impairment rather than storage impairment (Roy et al., 2016). Pathological memory loss, therefore, can be derived from retrieval failure. Engram cells actively compete for the expression in the brain. In a mouse model of AD, hippocampus dependent memory impairments are linked to "novelty like engrams" which interfere with the retrieval of the original memory and induce pathological forgetting (Autore et al. 2025). The result from these mouse models suggests retrieval impairment as a potential cause of memory loss in AD.

Mitochondria generates energy for cells to function and communicate with one another. Tau tangles drive malfunctions within neuronal transport, leading to mitochondrial dysfunction. Amyloid beta aggregation, which disrupts glutamate receptors and allows for excess calcium influx, also drives mitochondrial dysfunction. Mitochondrial dysfunction then often leads to cell death.

Loss of synaptic contacts is the core reason for pathological forgetting. Amyloid beta aggregation disrupts glutamate receptors which causes excess calcium influx/glutamate spillover which results in synapse toxicity. Tau tangles drive issues with neuronal transport, resulting in the loss of synaptic contacts, due to the energy not being delivered to cells. Changes in synapse strength are the underlying mechanism of LTP, which is the mechanism for strong memory. If any part of the mechanism is impaired, memory can't be formed, stored or recalled.The effects of tau tangles and amyloid beta aggregates result in deterioration of engram synapses. In addition to the mechanisms mentioned above, this may be mediated by disruption in protein synthesis pathways. When engram synapses die, engrams do not reactivate. When engrams do not reactivate memories are discarded.

Memories are a core part of our persona. Memories are formed in 3 stages: encoding, consolidation, and retrieval. While forgetting happens in the normal brain to delete old memories for the new ones, pathological forgetting becomes a problem. Pathological forgetting is a major symptom of Alzheimer's disease, which is characterized by profound memory loss. AD is driven by various factors, but mainly amyloid beta aggregation and tau tangles. Amyloid beta aggregation drives synaptic toxicity by disrupting glutamate receptors. Tau tangles disrupt neural pathways, which causes issues with delivering energy to cells. These factors lead to synapse loss. When synapses are lost, engrams, the group of neurons that hold memories, do not reactivate, and therefore, memories are discarded. Because current treatments have only been focused on individual factors, future treatments should focus on the connections between engrams, amyloid beta, and tau tangles.

CONCLUSION

Alzheimer's is a debilitating neurodegenerative disorder with no cure predominantly characterized by profound memory loss. Because there is no cure to this disease, it is critical to investigate how the mechanisms of Alzheimer's pathology intersect with the mechanisms of memory formation and loss. Investigating this question may uncover novel targets for treatments and provide a greater understanding of the disease as a whole.

The mechanisms underlying memory formation and loss are well characterized. Memories are encoded by strengthening the connections between neurons: synapses. LTP strengthens synapses by allowing more receptors to bind with postsynaptic neurons. The strengthened connections are between networks of neurons called engrams. When these engrams are reactivated, memories are retrieved and when they fail to activate in the right contexts, retrieval deteriorates. The process of forgetting is underlied by the weakening or loss of engram neuron synapses.

To investigate how Alzheimer's disease pathology affects memory formation, we must first understand Alzheimer's pathology. It is characterized by the accumulation of tau and amyloid-beta aggregates inside and outside of neurons. Plaques block the neuronal pathway, leading to inflammation of the brain. The inflammation and or the plaques themselves damage cells, causing neuronal death.

In AD, synapses are exposed to disease modified protein tau, which may cause the loss of synaptic contacts. These damages in the structural and functional synapses lead to the impairment of long term potentiation. Disturbed engram synapses lead to attenuation in both engram size and spine through prolonged inhibition of protein synthesis. By understanding how Alzheimer's pathology affects and disrupts the mechanisms of memory formation, we can provide a more fundamental understanding of this disease as well as provide concrete targets for novel Alzheimer's medications.

Existing clinical trials are using antibodies against amyloid beta. Given what we know about how amyloid beta affects mechanism of memory formation we may use engram activation, particularly in a mouse model testing a new AD medication, as a biomarker for whether medications work. Given that tau and amyloid beta seem to work together to drive pathology, particularly as they intersect with memory formation/forgetting mechanisms, future treatments should focus on addressing both tau and amyloid beta.

REFERENCES

Guskjolen, A., Cembrowski, M.S. Engram neurons: Encoding, consolidation, retrieval, and forgetting of memory. Mol Psychiatry 28, 3207–3219 (2023). https://doi.org/10.1038/s41380-023-02137-5
Merlo, S.A., Belluscio, M.A., Pedreira, M.E. et al.Memory persistence: from fundamental mechanisms to translational opportunities. Transl Psychiatry 14, 98 (2024). https://doi.org/10.1038/s41398-024-02808-z
Ciurea, V. A., Covache-Busuioc, R. A., Mohan, A. G., Costin, H. P., & Voicu, V. (2023). Alzheimer's disease: 120 years of research and progress. Journal of medicine and life, 16(2), 173–177. https://doi.org/10.25122/jml-2022-0111
Greenblat, Cathy (2026). Dementia. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/dementia
Josselyn, S. A., & Tonegawa, S. (2020). Memory engrams: Recalling the past and imagining the future. Science (New York, N.Y.), 367(6473), eaaw4325. https://doi.org/10.1126/science.aaw4325
Frankland P, Josselyn S, Köhler S (2024). Engrams. Current Biology, 34, R559-R561. https://www.cell.com/current-biology/fulltext/S0960-9822(24)00605-5
Roy, D. S., Muralidhar, S., Smith, L. M., & Tonegawa, S. (2017). Silent memory engrams as the basis for retrograde amnesia. Proceedings of the National Academy of Sciences of the United States of America, 114(46), E9972–E9979. https://doi.org/10.1073/pnas.1714248114
Rosemary A. Bamford, Jocelyn Widagdo, Natsuki Takamura, Madeline Eve, Victor Anggono, Asami Oguro-Ando,

The Interaction Between Contactin and Amyloid Precursor Protein and Its Role in Alzheimer's Disease. Neuroscience. Volume 424 (2020). Pages 184-202. ISSN 0306-4522. https://doi.org/10.1016/j.neuroscience.2019.10.006
MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US); [updated 2021 Oct 27]. PSEN 1; [updated 2021 Oct 27; reviewed 2021 Oct 27; cited 2026 Aug 17]; [about 5 p.]. Available from: https://medlineplus.gov/genetics/gene/psen1/#conditions
MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US); [updated 208 Dec 1]. PSEN 2; [updated 2008 Dec 1; reviewed 2008 Dec 1; cited 2026 Aug 17]; [about 5 p.]. Available from: https://medlineplus.gov/genetics/gene/psen2/
Pires, M., & Rego, A. C. (2023). Apoe4 and Alzheimer's Disease Pathogenesis-Mitochondrial Deregulation and Targeted Therapeutic Strategies. International journal of molecular sciences, 24(1), 778. https://doi.org/10.3390/ijms24010778
Bilici, Nadir, MD, DiplBLM (2026). What is APOE 4, and What Does It Actually Mean for Your Brain?. Dr. Nadir Bilici. https://drnadirbilici.com/what-is-apoe4-and-what-does-it-mean-for-your-brain/
Alzheimer's Association. (2024). Beta-amyloid and Alzheimer's disease. Alzheimer's Association, 800.272.3900. https://www.alz.org/getmedia/f5172a80-ef78-4cb4-a4f9-b203fd4c1b49/beta-amyloid_hypothesis_ts.pdf
Rukmangadachar LA, Bollu PC. Amyloid Beta Peptide. [Updated 2025 Apr 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459119/
Medeiros, R., Baglietto-Vargas, D., & LaFerla, F. M. (2011). The role of tau in Alzheimer's disease and related disorders. CNS neuroscience & therapeutics, 17(5), 514–524. https://doi.org/10.1111/j.1755-5949.2010.00177.x
Faghihi, F., & Moustafa, A. A. (2015). The dependence of neuronal encoding efficiency on Hebbian plasticity and homeostatic regulation of neurotransmitter release. Frontiers in cellular neuroscience, 9, 164. https://doi.org/10.3389/fncel.2015.00164
Yuste, R., Cossart, R., & Yaksi, E. (2024). Neuronal ensembles: Building blocks of neural circuits. Neuron, 112(6), 875–892. https://doi.org/10.1016/j.neuron.2023.12.008
Hurd, M. D., Martorell, P., Delavande, A., Mullen, K. J., & Langa, K. M. (2013). Monetary costs of dementia in the United States. The New England journal of medicine, 368(14), 1326–1334. https://doi.org/10.1056/NEJMsa1204629
Mujawar, S., Patil, J., Chaudhari, B., & Saldanha, D. (2021). Memory: Neurobiological mechanisms and assessment. Industrial psychiatry journal, 30(Suppl 1), S311–S314. https://doi.org/10.4103/0972-6748.328839
Kim, J., & Park, M. (2025). Systems memory consolidation during sleep: oscillations, neuromodulators, and synaptic remodeling. BMB reports, 58(10), 425–436. https://doi.org/10.5483/BMBRep.2025-0033
Azargoonjahromi A. (2024). The duality of amyloid-β: its role in normal and Alzheimer's disease states. Molecular brain, 17(1), 44. https://doi.org/10.1186/s13041-024-01118-1
Wang, L., Eom, K., & Kwon, T. (2021). Different Aggregation Pathways and Structures for Aβ40 and Aβ42 Peptides. Biomolecules, 11(2), 198. https://doi.org/10.3390/biom11020198

Chen, Gf., Xu, Th., Yan, Y. et al. Amyloid beta: structure, biology and structure-based therapeutic development. Acta Pharmacol Sin 38, 1205–1235 (2017). https://doi.org/10.1038/aps.2017.28
Bloom G. S. (2014). Amyloid-β and tau: the trigger and bullet in Alzheimer disease pathogenesis. JAMA neurology, 71(4), 505–508. https://doi.org/10.1001/jamaneurol.2013.5847
Bloom G. S. (2014). Amyloid-β and tau: the trigger and bullet in Alzheimer disease pathogenesis. JAMA neurology, 71(4), 505–508. https://doi.org/10.1001/jamaneurol.2013.5847
Elena Alberdi, Mª Victoria Sánchez-Gómez, Fabio Cavaliere, Alberto Pérez-Samartín, José Luis Zugaza, Ramón Trullas, María Domercq, Carlos Matute. Amyloid β oligomers induce Ca2+ dysregulation and neuronal death through activation of ionotropic glutamate receptors. Cell Calcium. Volume 47, Issue 3 (2010). Pages 264-272. ISSN 0143-4160.
https://doi.org/10.1016/j.ceca.2009.12.010
Zhang, H., Jiang, X., Ma, L., Wei, W., Li, Z., Chang, S., Wen, J., Sun, J., & Li, H. (2022). Role of Aβ in Alzheimer's-related synaptic dysfunction. Frontiers in cell and developmental biology, 10, 964075. https://doi.org/10.3389/fcell.2022.964075
Karisetty, B. C., Bhatnagar, A., Armour, E. M., Beaver, M., Zhang, H., & Elefant, F. (2020). Amyloid-β Peptide Impact on Synaptic Function and Neuroepigenetic Gene Control Reveal New Therapeutic Strategies for Alzheimer's Disease. Frontiers in molecular neuroscience, 13, 577622. https://doi.org/10.3389/fnmol.2020.577622
Martí Colom-Cadena, Caitlin Davies, Sònia Sirisi, Ji-Eun Lee, Elizabeth M. Simzer, Makis Tzioras, Marta Querol-Vilaseca, Érika Sánchez-Aced, Ya Yin Chang, Kristjan Holt, Robert I. McGeachan, Jamie Rose, Jane Tulloch, Lewis Wilkins, Colin Smith, Teodora Andrian, Olivia Belbin, Sílvia Pujals, Mathew H. Horrocks, Alberto Lleó, Tara L. Spires-Jones. Synaptic oligomeric tau in Alzheimer's disease — A potential culprit in the spread of tau pathology through the brain. Neuron, Volume 111, Issue 14 (2023). Pages 2170-2183.e6. ISSN 0896-6273.
https://doi.org/10.1016/j.neuron.2023.04.020
Jadhav, S., Cubinkova, V., Zimova, I., Brezovakova, V., Madari, A., Cigankova, V., & Zilka, N. (2015). Tau-mediated synaptic damage in Alzheimer's disease. Translational neuroscience, 6(1), 214–226. https://doi.org/10.1515/tnsci-2015-0023
Kopeikina, K. J., Hyman, B. T., & Spires-Jones, T. L. (2012). Soluble forms of tau are toxic in Alzheimer's disease. Translational neuroscience, 3(3), 223–233.
https://doi.org/10.2478/s13380-012-0032-y
Protein synthesis | Health and Medicine | Research Starters | EBSCO Research. (n.d.). EBSCO.
https://www.ebsco.com/research-starters/health-and-medicine/protein-synthesis
Hong, I., Kim, Y., Jung, H., Kim, C. H., Cho, J. H., & Kaang, B. K. (2026). Protein synthesis blockade prevents fear memory reactivation via inhibition of engram synapse strengthening. Proceedings of the National Academy of Sciences of the United States of America, 123(3), e2510016123.
https://doi.org/10.1073/pnas.2510016123
Daniel P. Chapman, Sarah D. Power, Stefano Vicini, Tomás J. Ryan, Mark P. Burns. Amnesia after Repeated Head Impact Is Caused by Impaired Synaptic Plasticity in the Memory Engram. Journal of Neuroscience 21 February 2024, 44 (8) e1560232024; DOI: 10.1523/JNEUROSCI.1560-23.2024
https://www.jneurosci.org/content/44/8/e1560232024

Livia Autore, Michael R. Drew, Tomás J. Ryan. The cost of remembering: engram competition as a flexible mechanism of forgetting. Trends in Neurosciences, Volume 48, Issue 10 (2025). Pages 728-738, ISSN 0166-2236. https://doi.org/10.1016/j.tins.2025.07.011
Roy, D. S., Arons, A., Mitchell, T. I., Pignatelli, M., Ryan, T. J., & Tonegawa, S. (2016). Memory retrieval by activating engram cells in mouse models of early Alzheimer's disease. Nature, 531(7595), 508–512. https://doi.org/10.1038/nature17172
Abraham, Z., Hawley, E., Hayosh, D., Webster-Wood, V. A., & Akkus, O. (2018). Kinesin and Dynein Mechanics: Measurement Methods and Research Applications. Journal of biomechanical engineering, 140(2), 0208051–02080511. https://doi.org/10.1115/1.4037886
Cooper GM. The Cell: A Molecular Approach. 2nd edition. Sunderland (MA): Sinauer Associates; (2000). Microtubules. Available from: https://www.ncbi.nlm.nih.gov/books/NBK9932/
The cerebral cortex in neurodegenerative and neuropsychiatric disorders. (2016). In Elsevier eBooks. https://doi.org/10.1016/c2014-0-00060-3
Dias, J. W., McClaskey, C. M., Rumschlag, J. A., & Harris, K. C. (2022). Sensory tetanisation to induce long-term-potentiation-like plasticity: A review and reassessment of the approach. The European journal of neuroscience, 56(12), 6115–6140. https://doi.org/10.1111/ejn.15847
Pareja-Navarro, K. A., King, C. D., Kauwe, G., Ngwala, Y. Y., Lokitiyakul, D., Wong, I., Vira, A., Chen, J. H., Sharma, M., Navarro, G., Malak, O., Schilling, B., & Tracy, T. E. (2025). Tau oligomers modulate synapse fate by eliciting progressive bipartite synapse dysregulation and synapse loss. bioRxiv : the preprint server for biology, 2025.09.19.677215. https://doi.org/10.1101/2025.09.19.677215
Lisman, J., Yasuda, R., & Raghavachari, S. (2012). Mechanisms of CaMKII action in long-term potentiation. Nature reviews. Neuroscience, 13(3), 169–182. https://doi.org/10.1038/nrn3192
Chung, W. S., & Barres, B. A. (2012). The role of glial cells in synapse elimination. Current opinion in neurobiology, 22(3), 438–445. https://doi.org/10.1016/j.conb.2011.10.003
Tomás J. Ryan et al., Engram cells retain memory under retrograde amnesia. Science348,1007-1013(2015). DOI: 10.1126/science.aaa5542. https://www.science.org/doi/10.1126/science.aaa5542
Squire, L. R., Genzel, L., Wixted, J. T., & Morris, R. G. (2015). Memory consolidation. Cold Spring Harbor perspectives in biology, 7(8), a021766. https://doi.org/10.1101/cshperspect.a021766
The science behind echoic Memory: How sound lingers in your mind. (2023). Verywell Mind. https://www.verywellmind.com/echoic-memory-7724606
Gabriela Sanchez-Andrade, Keith M. Kendrick. The main olfactory system and social learning in mammals. Behavioural Brain Research, Volume 200, Issue 2 (2009). Pages 323-335. ISSN 0166-4328. https://doi.org/10.1016/j.bbr.2008.12.021
Yuki Murai, Akihiro Goto. Diverse synaptic mechanisms underlying learning and memory consolidation. Current Opinion in Neurobiology, Volume 92 (2025). 102996. ISSN 0959-4388. https://doi.org/10.1016/j.conb.2025.102996
Liu, Y., Tan, Y., Zhang, Z., Yi, M., Zhu, L., & Peng, W. (2024). The interaction between ageing and Alzheimer's disease: insights from the hallmarks of ageing. Translational neurodegeneration, 13(1), 7. https://doi.org/10.1186/s40035-024-00397-x

Kinney, J. W., Bemiller, S. M., Murtishaw, A. S., Leisgang, A. M., Salazar, A. M., & Lamb, B. T. (2018). Inflammation as a central mechanism in Alzheimer's disease. Alzheimer's & dementia (New York, N. Y.), 4, 575–590. https://doi.org/10.1016/j.trci.2018.06.014
Rosenberg, T., Gal-Ben-Ari, S., Dieterich, D. C., Kreutz, M. R., Ziv, N. E., Gundelfinger, E. D., & Rosenblum, K. (2014). The roles of protein expression in synaptic plasticity and memory consolidation. Frontiers in molecular neuroscience, 7, 86. https://doi.org/10.3389/fnmol.2014.00086
Thies, E., & Mandelkow, E. M. (2007). Missorting of tau in neurons causes degeneration of synapses that can be rescued by the kinase MARK2/Par-1. The Journal of neuroscience : the official journal of the Society for Neuroscience, 27(11), 2896–2907. https://doi.org/10.1523/JNEUROSCI.4674-06.2007
Zhang, H., Wei, W., Zhao, M., Ma, L., Jiang, X., Pei, H., Cao, Y., & Li, H. (2021). Interaction between Aβ and Tau in the Pathogenesis of Alzheimer's Disease. International journal of biological sciences, 17(9), 2181–2192. https://doi.org/10.7150/ijbs.57078
Papaliagkas V. (2025). Anti-Amyloid Therapies for Alzheimer's Disease: Progress, Pitfalls, and the Path Ahead. International journal of molecular sciences, 26(19), 9529. https://doi.org/10.3390/ijms26199529
Neuroscience News. (2026, August 4). Phase 1 Trial Validates Anti-PD-L1 Antibody for Alzheimer's. Neuroscience News. https://neurosciencenews.com/antibody-alzheimers-immunotherapy-31179/
Lu, Y., Christian, K., & Lu, B. (2008). BDNF: a key regulator for protein synthesis-dependent LTP and long-term memory?. Neurobiology of learning and memory, 89(3), 312–323. https://doi.org/10.1016/j.nlm.2007.08.018
The biology of thought. (2015b). In Elsevier eBooks. https://doi.org/10.1016/c2013-0-19045-9
Visual memory | Health and Medicine | Research Starters | EBSCO Research. (n.d.). EBSCO. https://www.ebsco.com/research-starters/health-and-medicine/visual-memory
Encyclopedia of Human Behavior. (2012b). Academic Press. https://www.sciencedirect.com/topics/medicine-and-dentistry/somatosensory-system
Huff T, Mahabadi N, Tadi P. Neuroanatomy, Visual Cortex. [Updated 2023 Aug 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482504/
Edmund T. Rolls. Two what, two where, visual cortical streams in humans. Neuroscience & Biobehavioral Reviews, Volume 160 (2024), 105650, ISSN 0149-7634, https://doi.org/10.1016/j.neubiorev.2024.105650.
Wilcox, Kyle C et al. "Aβ oligomer-induced synapse degeneration in Alzheimer's disease." Cellular and molecular neurobiology vol. 31,6 (2011): 939-48. doi:10.1007/s10571-011-9691-4
Sadigh-Eteghad, Saeed et al. "Amyloid-beta: a crucial factor in Alzheimer's disease." Medical principles and practice : international journal of the Kuwait University, Health Science Centre vol. 24,1 (2015): 1-10. doi:10.1159/000369101
Kruse, Pia et al. "A synapse perspective on the function of the amyloid precursor protein." Science progress vol. 108,3 (2025): 368504251360728. doi:10.1177/00368504251360728
Caire MJ, Reddy V, Varacallo MA. Physiology, Synapse. [Updated 2023 Mar 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK526047/

Purves D, Augustine GJ, Fitzpatrick D, et al., editors. Neuroscience. 2nd edition. Sunderland (MA): Sinauer Associates; 2001. Glutamate Receptors. Available from: https://www.ncbi.nlm.nih.gov/books/NBK10802/