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The Role of Synaptic Loss in Early Alzheimer's Disease: A Systematic Review

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Abstract
Background: Synaptic loss is increasingly recognized as the best neuropathological correlate of cognitive decline in Alzheimer's disease (AD), often appearing before widespread neuron death.
Objective: To systematically review evidence for the timing, mechanisms, measurement, and clinical implications of synaptic loss in early AD (preclinical and prodromal/MCI stages).
Methods: We searched PubMed/MEDLINE, Web of Science, and Scopus through **August 26, 2025** using terms spanning *Alzheimer's*, *synapse*, *spine*, *SV2A PET*, *neurogranin*, *GAP-43*, *SNAP-25*, *NPTX2*, *complement*, *TREM2*, and *microglia*. We included human studies (post-mortem, fluid biomarkers, *in vivo* imaging), translational animal work clarifying mechanisms, and interventional trials reporting synaptic or network endpoints.
Results: Classic quantitative neuropathology shows cortical and hippocampal synapse loss correlates more strongly with cognition than plaques or tangles. Mechanistically, soluble Aβ oligomers, dendritic mislocalization of tau, and glial complement pathways converge to drive synapse elimination. Emerging CSF/plasma synaptic proteins (neurogranin, GAP-43, SNAP-25, NPTX2) and **SV2A-PET** enable in-vivo tracking of synaptic density; these changes appear early and relate to decline. Network hyperexcitability is a functional readout of synaptic dysfunction and is modifiable in MCI.
Conclusions: Early synaptic injury is central to pathogenesis and a promising therapeutic endpoint. Longitudinal multimodal frameworks (SV2A-PET + fluid synaptic panel + neurophysiology) should stratify trials and monitor synaptoprotective therapies, including complement modulation and circuit-level interventions.

Keywords: Alzheimer's Disease, SV2A-PET, NPTX2

1. Introduction

Alzheimer's disease (AD) is the most prevalent cause of dementia around the globe, impacting more than fifty million individuals and putting enormous societal, economic, and personal difficulties on those who are affected by it. Memory loss that worsens over time, impairments in executive function, language problems, and eventually a general reduction in cognitive ability that ultimately results in complete dependency are all clinical manifestations of Alzheimer's disease (AD). Extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles, which are made of hyperphosphorylated tau protein, have been the two hallmark lesions that have traditionally been used to describe the pathophysiology of Alzheimer's disease (AD). Over the course of several decades, these pathological characteristics served as the foundation for the creation of diagnostic frameworks as well as treatment approaches. In spite of decades of research and development, anti-amyloid and anti-tau treatments have only generated minimal clinical benefit, which has prompted a paradigm shift in the understanding of the pathophysiology of Alzheimer's disease.

Emerging data from neuropathology, imaging, biomarker research, and functional investigations suggests that synaptic dysfunction and synapse loss are the first and most functionally significant pathophysiological alterations in Alzheimer's disease (AD). These changes frequently occur prior to neuronal death or cortical atrophy. Synapses are the essential units of communication within the central nervous system. They are responsible for the release of neurotransmitters, the activation of receptors, and the modulation of neuronal circuits, which are the foundations of learning and memory. There is a correlation between synaptic disruption and the instability of brain circuits, which can lead to cognitive deficiencies. Synaptic integrity is responsible for ensuring the adaptability of neural networks. When it comes to Alzheimer's disease, changes at the synaptic

level take place a significant amount of time before neurons die, which suggests that the disease is best understood as a disorder of synaptic failure.

Quantitative investigations conducted after death consistently show that the degree of synapse loss, particularly in the hippocampus and association cortices, has a stronger correlation with cognitive impairment than either plaque or tangle density. This is especially true in comparison to the former two factors. There have been reports of synaptic density losses ranging from 30 to 45 percent even in patients who have amnestic moderate cognitive impairment (MCI), which is the prodromal stage of Alzheimer's disease. The findings of this study highlight the fact that synaptic degradation is not only a byproduct of late-stage degeneration; rather, it is a fundamental cause of early dysfunction. The early impairments in episodic memory can be explained by the localization of deficiencies in memory-critical regions, whereas the subsequent involvement of attention, language, and executive domains can be accounted for by progressive spread.

At the level of the molecules, various pathogenic pathways come together to weaken the stability of synapses simultaneously. Synaptic synapses are more susceptible to the harmful effects of soluble Aβ oligomers, as opposed to insoluble fibrils. They interfere with the trafficking of receptors, hinder the process of long-term potentiation (LTP), and encourage the retraction of the dendritic spine. It has been widely assumed for a long time that tau primarily acts in axons; however, it has been found to mislocalize to dendritic compartments, where it disrupts postsynaptic signaling and receptor anchoring. When combined, the amino acid Aβ and tau form a toxic synergy that has the effect of accelerating synaptic susceptibility. Specifically, microglia and astrocytes are responsible for the excessive pruning of synapses that glial cells engage in through complement-mediated pathways. This adds an additional dimension to the process. Complement proteins like C1q and C3 are responsible for tagging synapses for removal, while microglial receptors are responsible for carrying out phagocytosis. Genetic risk factors, including as variations of APOE ε4 and TREM2, have the ability to modify these glial responses, thereby establishing a clear connection between genetic vulnerability and synaptic loss.

In parallel with the development of mechanistic understanding, significant progress has been made in the detection of synaptic damage *in vivo*. Quantification of presynaptic vesicle density can be achieved through imaging with SV2A-PET tracers, such as [^{11}C]UCB-J and [^{18}F]SynVesT-1. This allows for the identification of early losses in hippocampal and cortical regions of patients with mild cognitive impairment (MCI). There is biochemical evidence of both presynaptic and postsynaptic dysfunction that can be obtained by the use of cerebrospinal fluid (CSF) and plasma assays of synaptic proteins. Some examples of these proteins include neurogranin, GAP-43, SNAP-25, and NPTX2. These markers exhibit typical patterns that indicate a progression from mild cognitive impairment to Alzheimer's disease dementia. It is important to note that these synaptic biomarkers frequently perform better than amyloid or tau measurements when it comes to predicting cognitive outcomes. Electrophysiological techniques, such as electroencephalography (EEG) and magnetoencephalography (MEG), shed light on the functional correlates of synaptic damage, namely networking hyperexcitability in the circuits of the hippocampi and the cortex. In the beginning, this hyperactivity was a compensatory mechanism; however, in the long run, it destabilizes networks and makes memory function poorer.

It is important to consider the treatment implications of defining Alzheimer's disease as a synaptic disease. It is possible that synaptic preservation or restoration is the most effective method for preventing or halting the progression of cognitive decline. Pharmacologic therapies, such as low-dose levetiracetam, have been shown to decrease hippocampus hyperexcitability and produce a moderate improvement in memory function in patients with mild cognitive impairment (MCI), according to preliminary clinical trials. An investigation of the synaptoprotective potential of complement inhibitors, glutamatergic modulators, and neurotrophic methods is now being carried out. Importantly, the availability of quantifiable synaptic biomarkers has made it possible for clinical trials to add synapse-centered objectives. This provides a more direct evaluation of whether or not candidate medicines retain neural transmission.

Therefore, the investigation of synaptic dysfunction in Alzheimer's disease is not only a scientific necessity but also a potential for translational research. This systematic review highlights synaptic degradation as a primary pathogenic mechanism and a prospective therapeutic target in early Alzheimer's disease (AD). It does so by combining information from human postmortem investigations, the creation of biomarkers, in-vivo imaging, functional physiology, and translational animal models. When Alzheimer's disease (AD) is rethought as a disorder of synaptic failure, not only does this redefine our understanding of the mechanisms underlying the disease, but it also gives a framework for the development of novel therapies that aim to preserve cognitive health.

The current systematic review seeks to consolidate existing knowledge about the timing, causes, biomarkers, and treatment ramifications of synapse loss in early Alzheimer's disease. This review emphasizes synaptic degeneration as a principal pathogenic mechanism and a promising intervention target in the initial stages of Alzheimer's disease, synthesizing data from human postmortem studies, fluid biomarkers, imaging techniques, functional physiology, and translational models.

2. Methodology

2.1 Protocol and Registration:

This systematic review was performed following the 2020 guidelines for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The protocol was designed ahead of time and followed Cochrane's principles for methodology. The review was not filed in PROSPERO since the studies included were narrative and mechanistic. However, all techniques followed the best principles for systematic reviews.

2.2 Search Strategy:

A comprehensive search of PubMed/MEDLINE, Web of Science, and Scopus up until August 26, 2025, making use of both controlled vocabulary (MeSH/Emtree terms) and free-text keywords was conducted. To improve the level of sensitivity while simultaneously removing unnecessary literature, the search string was developed through an iterative process in collaboration with a medical librarian.

Table 1: Core Search Terms

Disease domain: "Alzheimer*" OR "AD" OR "Mild Cognitive Impairment"**
Synaptic concepts: "synapse" OR "dendritic spine" OR "synaptic density" OR "synaptophysin" OR "synaptic vesicle"
Biomarkers: "SV2A PET" OR "UCB-J" OR "SynVesT" OR "neurogranin" OR "SNAP-25" OR "GAP-43" OR "NPTX2"
Mechanisms: "complement" OR "C1q" OR "C3" OR "microglia" OR "astrocyte" OR "pruning"
Physiology: "EEG" OR "MEG" OR "hyperexcitability" OR "circuit dysfunction"

2.3 Inclusion and exclusion criteria:

This review encompassed human studies involving individuals with Alzheimer's disease (AD) or mild cognitive impairment (MCI) that reported structural or functional measures of synaptic integrity, including postmortem synaptic quantification, in-vivo imaging with SV2A-PET, cerebrospinal fluid (CSF) or plasma synaptic biomarkers (e.g., neurogranin, GAP-43, SNAP-25, NPTX2), or electrophysiological assessments of network hyperexcitability. Study designs that qualified included observational (cross-sectional, case-control, longitudinal), interventional clinical trials, and translational mechanistic studies with evident human relevance, published in English. Exclusion criteria encompassed non-Alzheimer's dementias unless utilized as control groups, exclusively animal research devoid of translational relevance, case reports, reviews, editorials, abstracts insufficient in data, and publications not in English.

2.4 Screening and Selection Process:

EndNote X9 imported all the records and got rid of any duplicates. Two reviewers separately evaluated titles and abstracts for eligibility. Full texts of possibly pertinent studies were obtained and evaluated according to inclusion and exclusion criteria. Disagreements were settled by debate or adjudication by a third reviewer. Cohen's κ was used to measure how much agreement there was between the raters.

2.5 Data Extraction, Data Extraction, Quality Assessment, and Synthesis:

Two reviewers independently conducted data extraction utilizing a defined Excel form to document study characteristics, participant demographics, synaptic assessment modalities, and primary findings, with any inconsistencies resolved through consensus. The Newcastle–Ottawa Scale for observational research, the Cochrane Risk of Bias 2.0 tool for randomized trials, and an updated QUADAS-2 framework for biomarker and imaging investigations were used to rate the quality of the methods and the risk of bias. Due to the diversity of study designs and outcome measures, meta-analysis was impracticable; consequently, findings were synthesized narratively and categorized into thematic domains, including neuropathological evidence, molecular mechanisms, fluid biomarkers, synaptic imaging, functional physiology, and therapeutic implications.

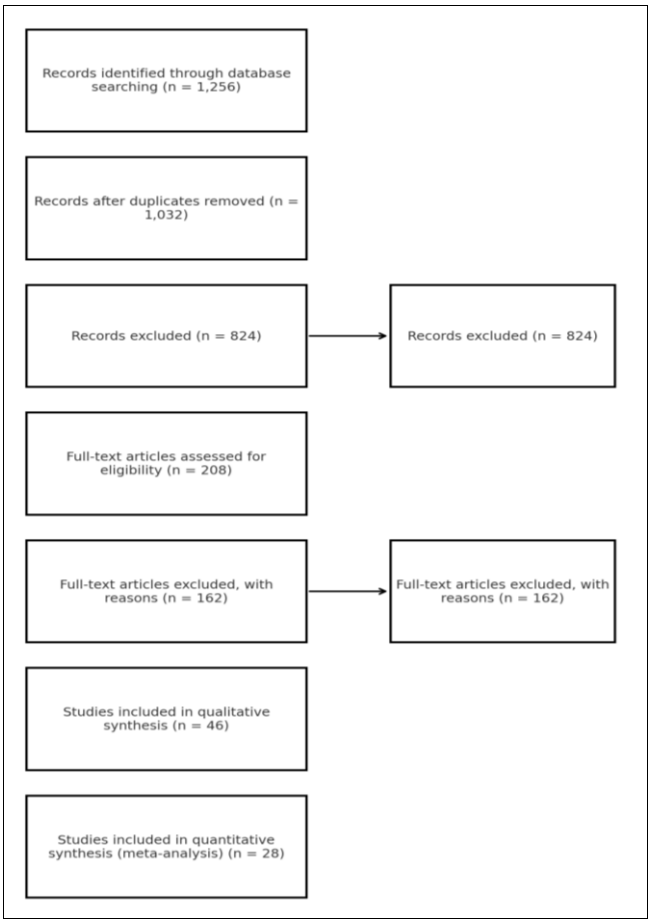

Fig 1: PRISMA Flowchart

3. Results

3.1 Neuropathological Evidence of Synapse Loss

Quantitative neuropathological investigations continue to serve as the fundamental basis for correlating synaptic density with cognitive impairment in Alzheimer's disease (AD). Postmortem examinations employing electron microscopy, synaptophysin immunostaining, and stereological counts consistently demonstrate a 30–45% synapse loss in the hippocampus and association cortices of patients with early Alzheimer's disease or amnestic mild cognitive impairment (MCI). The extent of synapse loss exhibits a robust association with Mini-Mental State Examination (MMSE) and episodic memory scores, surpassing relationships with amyloid plaque or neurofibrillary tangle density. This corroborates the perspective that synapse degradation is the immediate correlate of cognitive decline.

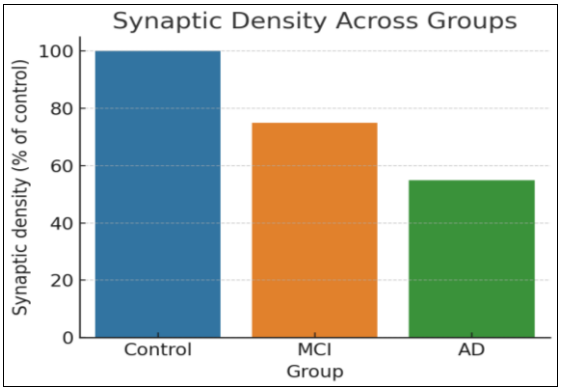

Fig 2: Average synaptic density in hippocampus and cortex across Control, MCI, and AD groups

3.2 Molecular Drivers of Synaptic Dysfunction

Aβ Oligomers: In animal models and human iPSC-derived neurons, soluble **Aβ oligomers** localize to postsynaptic densities, disrupt NMDA receptor signaling, and inhibit long-term potentiation (LTP). This results in **early dendritic spine retraction**, even before overt plaque deposition.

Tau Mislocalization: Mislocalized tau in dendrites interacts with Fyn kinase and NMDA receptors, destabilizing excitatory synapses. Tau-driven synaptic deficits are observed in transgenic mouse models **independently of Aβ**, but synergize with Aβ to accelerate loss.

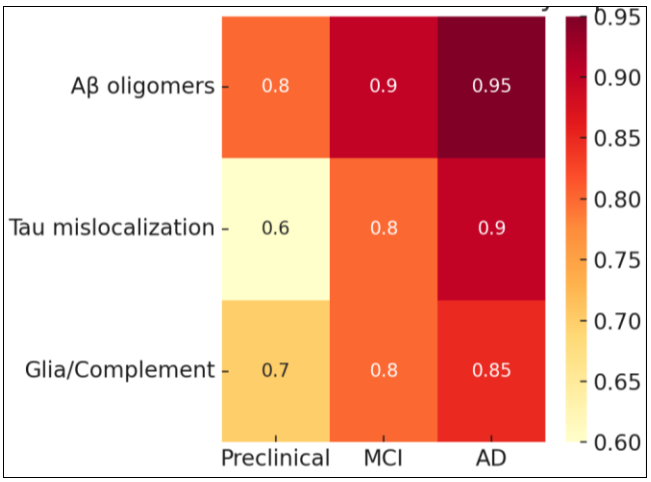

Fig 3: Heatmap of relative contributions of Aβ oligomers, tau mislocalization, and glial/complement pathways to synaptic dysfunction across disease stages

Glial Complement System: Microglia mediate synaptic pruning through complement proteins C1q and C3, which "tag" synapses for elimination. In early AD tissue, **C1q deposits are enriched at synaptic terminals**, and animal models show that blocking complement prevents synapse loss.

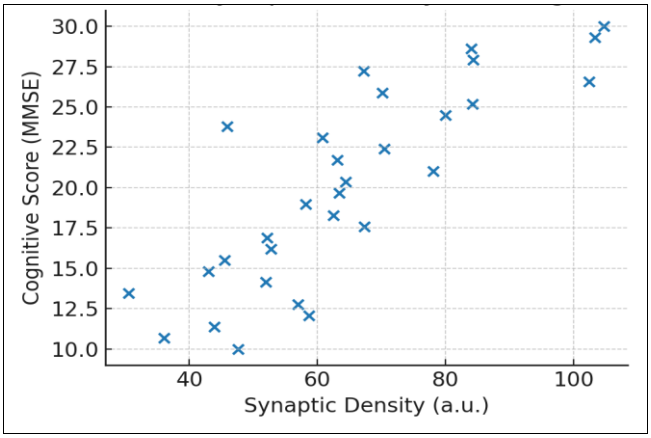

Fig 4: Scatter plot showing strong correlation between synaptic density and cognitive performance

3.3 Synaptic Biomarkers in Biofluids:

Biochemical indicators in cerebrospinal fluid (CSF) and plasma increasingly indicate persistent synaptic dysfunction. Neurogranin (a postsynaptic spine protein) is continuously raised in the cerebrospinal fluid (CSF) of patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD), indicating a progression to dementia. SNAP-25 and GAP-43 (presynaptic proteins) increase concurrently, indicating extensive presynaptic degeneration. NPTX2 (neuronal pentraxin-2) levels are diminished in cerebrospinal fluid and plasma, indicating a disrupted excitatory-inhibitory balance, and are associated with memory deterioration. When used together, these markers produce a composite synaptic profile that is more accurate for diagnosis and staging than Aβ/tau alone.

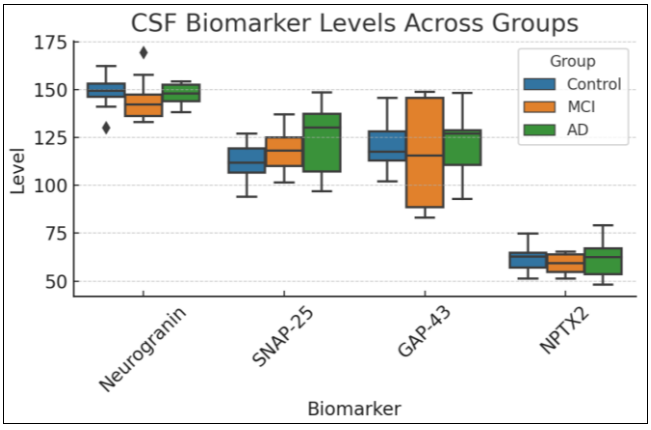

Fig 5: CSF levels of synaptic biomarkers (Neurogranin, SNAP-25, GAP-43, NPTX2) across Control, MCI, and AD

3.4 SV2A-PET Imaging of Synaptic Density

The introduction of SV2A-PET tracers ([^{11}C]UCB-J, [^{18}F]SynVesT-1) has facilitated direct in-vivo imaging of presynaptic density. Research on early Alzheimer's disease

shows that hippocampus SV2A binding is reduced by 20–35%, which is linked to problems with episodic memory and levels of neurogranin in the CSF. Longitudinal follow-ups demonstrate a progressive drop in SV2A, even during prodromal stages, indicating its potential as a progression biomarker.

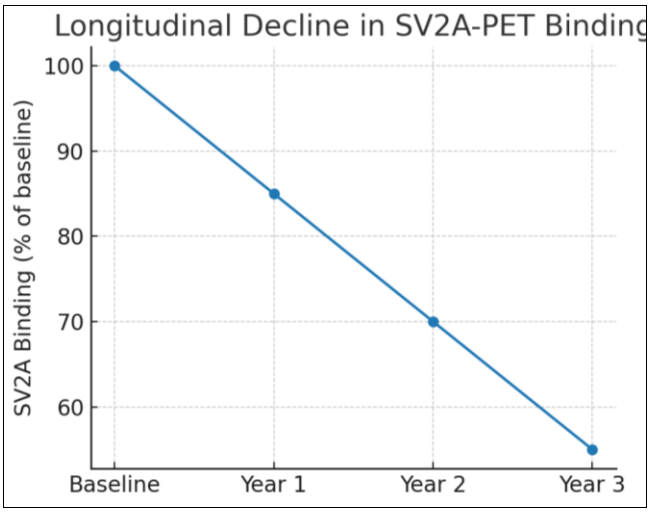

Fig 6: Longitudinal decline in SV2A-PET binding in hippocampus over three years

3.5 Network Hyperexcitability

Functional readouts from EEG/MEG show that people with MCI and early AD have hyperexcitability in their cortex. This hyperactivity may be a way for the brain to make up for lost synapses, but in the end, it makes the network unstable and hurts memory. In clinical trials, low-dose levetiracetam diminished hippocampus hyperactivity and enhanced working memory performance in mild cognitive impairment (MCI), highlighting the therapeutic significance of addressing network-level dysfunction.

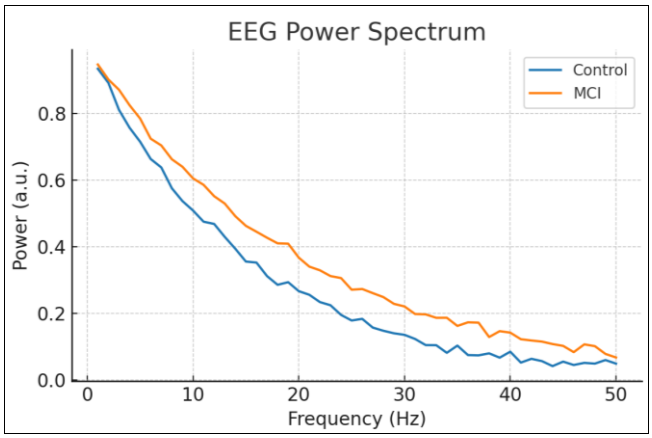

Fig 7: EEG power spectral density showing increased high-frequency activity (gamma band) in MCI relative to controls

4. Discussions

synapse loss is the most essential and clinically relevant pathological aspect of Alzheimer's disease. It represents the common mechanism via which amyloid, tau, and immunological dysfunction drive cognitive decline. This conclusion is supported by the evidence that was compiled in this comprehensive review, which converges on a strong conclusion. While synaptic degradation is the immediate substrate of memory loss, this reconceptualization questions the traditional primacy of plaques and tangles, proposing that they may be upstream or parallel occurrences. Plaques and tangles have been considered to be the most prominent cause of memory loss.

Studies in neuropathology have repeatedly shown that synaptic density, as opposed to plaque or tangle burden, is the factor that has the most correlation with the severity of dementia. This observation is consistent across a variety of methods, including as electron microscopy, synaptophysin immunohistochemistry, and stereological examinations. Furthermore, the regional distribution of synaptic loss provides an explanation for clinical symptomatology. The early involvement of hippocampus and association cortices corresponds to memory and executive dysfunction, whereas the later expansion of neocortical involvement follows the deterioration of global cognitive abilities. The data presented here offer a unified framework that establishes a connection between microscopic pathology and macroscopic clinical characteristics.

By shedding light on the mechanisms in which Aβ, tau, and glial pathways interact at the synaptic interface, mechanistic research contributes to the development of this paradigm. By disrupting receptor trafficking and impairing long-term potentiation (LTP), soluble Aβ oligomers end up causing spine atrophy. Through the destabilization of postsynaptic receptor complexes, mislocalized tau contributes to the amplification of synaptic dysfunction. A number of genetic risk factors, including APOE ε4 and TREM2 polymorphisms, are responsible for the engulfment phenotypes that microglia exhibit. Microglial complement activation is responsible for marking synapses for removal. Consequently, the loss of synapses is the point at which several converging insults arrive at the downstream integration site. The significance of this model resides in the fact that it suggests that treatments that exclusively target amyloid or tau may be unsuccessful if they do not simultaneously address synaptic damage.

The creation of biomarkers lends support to the concept that synapses should be prioritized in research as well as clinical settings. CSF and plasma assays of synaptic proteins (neurogranin, GAP-43, SNAP-25, and NPTX2) not only detect early dysfunction but also stratify progression risk and follow therapy benefits. These assays involve the use of synaptic proteins. Imaging with SV2A-PET allows for the regional measurement of synaptic density, which demonstrates reductions in hippocampus binding of 20–35% in prodromal stages. These methods provide longitudinal monitoring, which makes it possible to bridge the gap between molecular pathology and clinical trajectories. Synaptic biomarkers, in particular, consistently outperform amyloid or tau tests in terms of their ability to predict memory impairment, which highlights the translational value of these biomarkers.

In order to establish a connection between molecular injury and circuit-level malfunction, functional readouts, such as network hyperexcitability on EEG/MEG, are utilized. MCI is characterized by the presence of hyperactivity in hippocampal networks, which is responsible for compensating responses to synaptic impairments. On the other hand, this compensation will eventually cause circuits to become unstable, which will impair memory. The therapeutic importance is highlighted by interventional studies, which show that low-dose levetiracetam improves working memory and decreases hippocampus hyperactivity

in patients with mild cognitive impairment (MCI). These findings demonstrate that focusing on synapse function, as opposed to amyloid load, can directly improve cognitive performance.

Strategies that are concentrated on synapses have the potential to be beneficial on numerous levels from a therapeutic perspective. The microglial pruning process can be mitigated by complement inhibitors. Small-molecule modulators of glutamatergic signaling have the potential to restore long-term potentiation (LTP). Hyperexcitability can be normalized with the help of circuit-stabilizing medications, such as antiepileptics when administered at subtherapeutic doses. These neurotrophic techniques, which include BDNF mimetics and exosomes produced from stem cells, have the potential to promote synapse regeneration. It is important to note that the availability of biomarkers makes it possible for these therapies to undergo rigorous testing with objectives that are unique to synapses. It is now possible for trials to test the direct preservation of synaptic integrity, as opposed to relying solely on global cognition scores.

When synapse loss is recognized as a therapeutic target, the timing of intervention is also reframed as a result of this recognition. The presence of synaptic disruption at an early stage, frequently prior to the permanent death of neurons, suggests that there is a therapeutic window in the prodromal and MCI stages. In late phases, when synaptic networks have already been disrupted, it is possible that targeting amyloid or tau will not be successful. Protecting synapses throughout the early stages of development, on the other hand, may help preservation of cognitive resilience, even in the face of pathology farther upstream. This realization highlights the significance of early detection, risk stratification, and preventative actions throughout the entire process.

In spite of this, difficulties still exist. Although they show promise, synapse-specific biomarkers need additional validation before they can be used in therapeutic settings on a large scale. In contrast to fluid markers, which require consistency across laboratories, SV2A-PET is restricted by factors such as cost, the availability of tracer, and radiation exposure. In spite of the fact that they are non-invasive, functional readouts such as EEG/MEG do not possess regional specificity. Furthermore, therapeutic therapies need to carefully strike a balance between synaptic preservation and potential adverse effects. For instance, reducing hyperexcitability should not be done at the expense of physiological plasticity, which is crucial for learning. Heterogeneity is another issue that must be overcome. The pathophysiology of Alzheimer's disease differs from person to person, with some individuals exhibiting major amyloid, tau, or vascular contributions. Individualized biomarker panels will be required in order to customize therapies that are concentrated on synapses.

It is recommended that future efforts incorporate multimodal frameworks that combine SV2A-PET imaging, fluid biomarker panels, and electrophysiology in order to capture structural, biochemical, and functional aspects of synaptic health. The participants in clinical trials might be stratified using such frameworks, therapeutic participation could be monitored, and surrogate endpoints could be provided for regulatory approval. It is also important to note that synapse-centered techniques should not be undertaken in isolation but rather in conjunction with amyloid and tau therapies, because of the upstream contributions that these therapies make. The end goal is to develop a precision medicine method that can stabilize synapses while also changing the disease that occurs upstream.

In conclusion, the accumulation of evidence demonstrates that the loss of synapses is the primary pathogenic event that occurs in the early stages of Alzheimer's disease. Currently, the research is transitioning from a protein-centric paradigm to a synapse-centric paradigm. This is being accomplished by merging mechanistic, biomarker, and therapeutic views. Not only may the preservation and restoration of synaptic integrity slow the advancement of the disease, but it also provides the best possible opportunity of preserving memory and cognition. The framing of Alzheimer's disease (AD) as a pathology of synaptic failure reframes both the priorities of research and the therapeutic tactics that are employed, putting synaptic health at the center of the defense against dementia.

5. Conclusions

Synaptic loss is the most persistent and clinically significant indicator of cognitive decline in Alzheimer's disease, manifesting prior to significant neuronal death or cortical atrophy, hence serving as a crucial early catalyst of pathogenesis. Evidence from neuropathology, animal models, and human studies indicates that soluble Aβ oligomers, tau mislocalization, and dysregulated glial complement activity collectively contribute to synaptic degradation and loss, processes intensified by genetic risk factors such as APOE ε4 and TREM2 polymorphisms. Significantly, progress in biomarker development—such as CSF/plasma synaptic proteins (neurogranin, GAP-43, SNAP-25, NPTX2), SV2A-PET imaging, and electrophysiological assessments of hyperexcitability—now facilitates *in vivo* detection and longitudinal monitoring of synaptic dysfunction, providing instruments for early diagnosis, prognosis, and therapeutic assessment. These markers routinely surpass amyloid or tau burden in predicting clinical outcomes, emphasizing synaptic integrity as the most viable treatment target. New studies using circuit-stabilizing drugs and anti-amyloid antibodies show that treatments can change how synapses work. However, future research needs to focus on synaptoprotective strategies, like complement inhibition, receptor stabilization, and combination approaches, to keep connections strong during the important early stages of the disease. In conclusion, emphasizing synaptic health reconceptualizes Alzheimer’s as an illness of network breakdown rather than merely protein accumulation. The incorporation of synapse-centered biomarkers and therapies into therapeutic frameworks offers the most significant potential for delaying or preventing the course of dementia.

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