OXFORD JOURNAL
OF STUDENT
SCHOLARSHIP

Microglia and Network Redundancy Loss in Early Alzheimer's Disease

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ABSTRACT

Although amyloid-beta plaques and tau tangles are typically used to characterize AD, synapse loss is commonly regarded as the final common pathway leading to cognitive decline. Cognitive symptoms can emerge as synapses and circuits deteriorate, even before significant neuronal loss occurs.

Peer-reviewed studies on synapse loss, microglial phagocytosis, complement signaling, APOE ε4, TREM2, astrocyte-microglia interactions, spatial transcriptomics, and network vulnerability in AD were synthesized through a literature review. Evidence from experimental models, human tissue, cell studies, biomarkers, imaging, and spatial methods was evaluated.

The evidence supports a context-dependent view of glial activity, in which microglia and astrocytes normally protect neural tissue by clearing debris and regulating inflammation, but these same functions can contribute to synaptic vulnerability under AD conditions. Several other mechanisms such as complement signaling, APOE ε4, and TREM2 also contribute to this shift.

Together, these findings suggest that synapse loss contributes to circuit impairment by reducing network redundancy. Synapse loss becomes clinically important when affected connections reduce the ability of memory circuits to use alternative pathways. Therefore, future studies should combine glial-state markers, synaptic biomarkers, spatial mapping, and brain-network measures to test this framework and guide treatments aimed at protecting memory function.

Keywords: Alzheimer's disease; microglia; synapse loss; complement; APOE ε4; TREM2; cognitive reserve; network redundancy

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia and is usually identified by extracellular amyloid-beta (Aβ) plaques and intracellular tau tangles (1). These pathologies remain central, but they do not fully explain how early cognitive impairment emerges. Some patients begin to lose memory and reasoning ability before large numbers of neurons have died. Although multiple pathological processes contribute to AD, they eventually lead to a final pathway, which is the damage to synapses. Classic

neuropathological and recent biomarker studies show that synapse loss is one of the strongest biological correlates of cognitive impairment in AD (2-6). A memory circuit can still contain many neurons, but weakened or removed synaptic connections can make the circuit unreliable.

Informational redundancy explains how damage to synapses can disrupt neural circuits, resulting in clinical issues. In a healthy brain, cognition does not depend on one synapse or one pathway. Circuits usually contain overlapping routes, which means that some damage can be tolerated. Studies of network redundancy and cognitive reserve support the idea that the way the brain is organized affects how much brain damage affects cognitive function (7,8). From their perspective, the effects of synapse loss does not depend only on how many synapses are lost. Loss of a small number of critical connections in the hippocampus or default-mode network can be more damaging than loss of a larger number of less central connections (7,8).

Recent AD research has increasingly looked beyond plaques and tangles to the cells that shape the local environment around neurons. Microglia are especially relevant because they survey tissue, clear debris, release inflammatory signals, and remodel synaptic material (9,13). Astrocytes are also part of the same system because they support synapses metabolically and structurally, regulate neurotransmitter balance, and respond to inflammatory signals from microglia (23,24). Astrocytes also influence microglial activation, so the glial response is two-way rather than a one-way pathway from microglia to astrocytes (23-25).

The framework developed here treats microglia and astrocytes as homeostatic cells whose usual functions can contribute to synaptic vulnerability during the progression of AD. Under healthy conditions, glial pruning and debris removal help maintain neural tissue (9,13,23,24). In AD, repeated amyloid stress, tau-related injury, metabolic weakness, and inflammatory signaling change the environment surrounding glial cells (9-13,29-33). Complement, APOE ε4, and TREM2 are important in this process because they influence synaptic tagging, lipid and immune responses, and stage-dependent microglial states (9-22). This pathway is not presented as a single cause of AD. It is one possible route by which molecular and cellular pathology can contribute to early circuit failure.

REVIEW APPROACH AND SCOPE

A literature review design was used rather than a systematic review or meta-analysis. Peer-reviewed studies published between 1990 and 2026 were used to cover synapse loss, microglial phagocytosis, complement signaling, APOE ε4, TREM2, astrocyte-microglia interactions, spatial transcriptomics, and network vulnerability in AD. This review focuses on studies that provided causal evidence from experimental models, human evidence from tissue or imaging, or concepts from network neuroscience.

Since AD biology is broad, this review prioritizes mechanisms that link cellular stress to early circuit dysfunction before widespread neuronal loss. The focus moves from molecular and cellular processes to regional brain vulnerability and then to systems-level predictions. Throughout the paper, microglia are treated as more than simply helpful or harmful. The purpose is to synthesize the previous studies, compare competing explanations, and present a testable explanation for early circuit failure.

SYNAPSE LOSS AS A NETWORK PROBLEM

In the experimental models, synapse loss can be quantified directly. On the other hand, in living humans, synaptic injury is tested indirectly through biomarkers, imaging, and brain network measures rather than direct counting of individual synapses. After consulting several methods, the location and role of the affected synapses are as important as the total amount of loss. Brain circuits are not composed of interchangeable parts. Some synapses support local communication, while others help connect larger networks involved in memory, attention, and executive function, meaning every synapses have different roles. Classic tissue studies showed that synapse loss is strongly associated with cognitive impairment in AD (2,3). Newer biomarker studies also support the clinical importance of synaptic damage, since synaptic dysfunction can appear early and track disease progression (4-6).

Network redundancy refers to the ability of brain circuits to maintain function through overlapping routes. Redundancy does not mean that the brain contains useless extra connections. It means that a function can continue when one route becomes disrupted. Network redundancy has been reported to change across early AD stages, which suggests that how the brain reorganizes to compensate for damage shifts before severe dementia develops (7). Work on cognitive reserve and resting-state networks also supports the broader idea that the way the brain networks are organized influences whether pathology produces symptoms (8).

The main claim is that synapse loss becomes clinically important when affected connections reduce the brain's ability to use alternative routes. Microglia are relevant to this model because they are not only inflammatory cells, but they also participate in removal and remodel of synapses (9,13). When local signals repeatedly mark stressed synapses for removal, network flexibility can decline faster than circuits can reorganize.

MICROGLIA AS SYNAPTIC HOMEOSTATIC CELLS

Microglia are important innate immune cells of the central nervous system (9,13). In the healthy brain, they survey the local environment, respond to injury, clear debris, and help remodel synaptic connections (9,13). None of these roles is automatically harmful. During development, microglial pruning helps refine circuits by removing weaker or unnecessary connections. In adults, microglia also support repair and homeostasis (9,13). Communication between microglia and neurons is therefore a normal part of brain maintenance, not just a response to damage.

Microglial synaptic pruning is a normal process that helps the brain maintain its function. Microglia help remove material that no longer supports tissue function, including debris and synapses marked for elimination. The challenge in AD is not that microglia exist or become active, but the challenge is that the local environment changes the signals that microglia receive. Persistent amyloid stress, tau-related neuronal injury, complement activation, inflammatory cytokines, and metabolic weakness influence how microglia respond (9-13,31,33).

The relevant biological question is how microglial state, disease stage, brain region, and nearby neuronal or astrocytic signals shape the outcome of microglial activity. Clearing debris near plaques can protect

tissue, while engulfment of still-functional synaptic material can reduce neural connectivity (9,13). The term 'microglial activation' is therefore too general unless the specific activation state, brain region, disease stage, and surrounding cellular substrate are defined.

COMPLEMENT SIGNALING AND SYNAPTIC TAGGING

Complement signaling provides one of the clearest links between innate immunity and synapse removal. Complement proteins such as C1q and C3 can mark cellular material for clearance, and microglia can recognize complement-tagged targets through receptors such as complement receptor 3 (9-12). During development, this type of tagging helps shape circuits. In AD, the same clearance pathway can be reactivated and can affect synapses in regions already stressed by amyloid, tau, or metabolic dysfunction (9-12).

Mouse-model studies have shown that complement and microglia mediate early synapse loss with C1q increasing at synapses before obvious plaque buildup (9). Additional mouse-model evidence indicates that astrocyte-microglia cross-talk through complement modifies amyloid pathology (10). Reviews of complement in AD emphasize that complement is not simply damaging, but it also supports clearance and tissue protection (11,12). The important question is whether local tagging removes material that is already harmful or removes synapses that still support circuit function.

From the perspective of network redundancy loss, complement tagging identifies synaptic material for glial attention. If complement marks synapses already disconnected from neural communication, clearance can be protective. If complement marks metabolically stressed but recoverable synapses, removal can reduce the brain’s ability to compensate for damage(9-12). The most clinically important pattern is therefore not random synapse removal, but removal concentrated in highly connected memory circuits, where relatively small losses can disrupt alternative routes for information flow.

APOεE4 AND PERSISTENCE OF GLIAL-METABOLIC STRESS

APOE ε4 is the most prominent genetic risk factor for late-onset AD, but its effects should not be reduced to amyloid deposition alone (14-18). APOE participates in lipid transport, metabolic support, and injury response (14-18). Human induced pluripotent stem cell-derived brain cell models show that APOE4 causes many molecular and cellular changes associated with AD (14). Primary mouse microglia also show changes in gene expression and function related to APOE4, supporting a direct relationship between APOE genotype and microglial state (15).

Together, these studies suggest that APOE ε4 is associated with persistent glial, lipid, and metabolic stress responses. Human imaging evidence links APOE ε4 with microglial activation independently of Aβ plaques and tau tangles (17). Brain-slice experiments also show that aging and APOE4 genotype impair microglial responses to injury and to Aβ through P2RY12-related mechanisms (18).

Persistence matters for network redundancy because short-lived inflammatory responses differ from long-lasting stress responses. A transient response allows tissue to recover. A prolonged response

repeatedly exposes nearby synapses to complement tagging, cytokines, altered lipid handling, and increased phagocytic activity (14-18). In this context, APOE ε4 can increase vulnerability not only through amyloid-related pathways but also by reducing the completeness of recovery after local stress.

TREM2 AND STAGE-DEPENDENT MICROGLIAL RESPONSES

TREM2 is a receptor expressed mainly by microglia and is linked to microglial survival, lipid sensing, plaque-associated responses, and disease-associated microglial states (19,20). Although TREM2 is often discussed as a protective factor because it supports plaque-associated microglial responses and debris clearance, this interpretation is incomplete. TREM2 changes how microglia respond to disease, and the effects depend on disease stage, genotype, and local tissue conditions (19-22).

APP/PS1 mouse evidence illustrates this stage dependence. Trem2 contributed to synaptic impairment at an early disease stage but limited amyloidosis later in disease (21). Genetic evidence adds another important fact. The AD-associated R47H TREM2 variant drives disease-enhancing microglial states through AKT hyperactivation (22). Together, these findings show that TREM2-related microglial responses can have different effects depending on disease stage and genetic context.

In a network redundancy-loss framework, TREM2 is important because it shapes the intensity and timing of microglial responses around vulnerable synapses. Around plaques, TREM2-associated activation can help contain damage (19,20). In early vulnerable circuits, stronger phagocytic activity can increase loss of stressed but still useful synapses (21,22). This stage dependence explains why TREM2-targeted treatments require careful timing and patient selection.

ASTROCYTES AND THE LOCAL TISSUE ENVIRONMENT

A microglia-centered model is still incomplete without astrocytes. Astrocytes regulate neurotransmitter clearance, metabolic support, water and ion balance, and synaptic structure (23,24). They also respond to inflammation. Activated microglia can push astrocytes into reactive states that may harm neurons and synapses, creating a cycle where both glial cell types amplify local injury (23). The reverse direction is also important. Activated or stressed astrocytes can release signals that sustain or modify microglial activation. The microglia-astrocyte relationship is therefore circular rather than one-sided (10,23-25).

Research on astrocyte-synapse structural plasticity shows that astrocytes actively reshape the synaptic environment rather than simply supporting neurons in the background (24). Human AD tissue also supports a role for both glial cell types in removing synaptic material. Astrocytes and microglia contain more synaptic protein in AD brain tissue than in non-disease tissues, suggesting increased ingestion of synaptic material in human disease (25). This observation does not show that every engulfed synapse was harmful to remove. It shows that glial handling of synaptic material occurs in human AD tissue and should be studied alongside neuronal and vascular mechanisms (25).

Astrocytes also connect synapse loss to metabolism and blood vessel function. Their endfeet contact blood vessels, and their processes surround synapses. Because of this position, astrocytes help link energy

supply, neurotransmitter balance, and immune signaling (23,24,32). If astrocytic support weakens or astrocytes amplify complement and cytokine signaling, microglia encounter more synapses in a stressed local environment (10,23-25).

HUMAN EVIDENCE, SPATIAL METHODS, AND REGIONAL VULNERABILITY

Evidence from human studies highlights the location and timing of glial-state changes. Instead, researchers focus on where immune-active glial states appear, when they appear, and how nearby synapses are affected. Microglial MHC-I induction with aging and AD is conserved in mouse models and humans, supporting the presence of specific immune-active microglial states rather than one general form of activation (26). Single-cell sequencing and spatial transcriptomics further show that disease-linked microglial and astrocytic states vary by brain region and local pathology (27).

Spatial methods are valuable because AD does not affect all brain areas equally. A spatially resolved hippocampal atlas identified region-specific molecular changes in human AD tissue (28). These findings support the conclusion that synaptic vulnerability is not uniformly distributed. Synapse loss is most likely to affect function when amyloid pathology, tau-related neuronal stress, inflammatory signaling, vulnerable glial states, and high network importance converge (26-28,31).

These studies help move the argument beyond the general idea that microglia become active in AD. They support a local environment in which genotype, cell state, and regional network structure shape whether microglial activation is helpful or harmful (26-28). Therefore, early circuit failure can result from local failure of classification, clearance, and compensation rather than only a global increase in inflammation.

COMPETING AND INTERACTING MECHANISMS

Although complement signaling, APOE ε4, and TREM2 provide a useful framework for understanding microglial contributions to synapse loss, this pathway cannot explain all early circuit failure in AD. AD is a heterogeneous disorder in which multiple mechanisms act in parallel or sequence. Tau pathology, metabolic stress, vascular dysfunction, mitochondrial impairment, astrocyte reactivity, and network hyperexcitability each increase synaptic vulnerability (29-33). Evaluating these mechanisms alongside the microglial model identifies contexts in which other pathways provide stronger explanations.

Tau pathology is one of the clearest reasons why early synapse loss cannot be explained by microglia alone. Tau is closely tied to neurodegeneration and cognitive decline, and it can move through connected brain regions (31). Tau-related stress can directly damage synapses and can also change the signals to which nearby glial cells respond (31). In a brain region where tau markers predict decline better than inflammatory markers, tau-related neuronal injury provides a stronger explanation for the observed damage.

Energy failure is another way synapses become vulnerable. Synapses need a constant energy supply to maintain ion gradients, recycle vesicles, release neurotransmitters, and support plasticity (33). When mitochondria or glucose metabolism fail, synapses become weaker even before inflammation becomes

obvious (33). Vascular injury and blood-brain barrier dysfunction worsen this process by changing blood flow, clearance, and immune regulation in the brain (32). These changes interact with glial signaling and also damage synapses independently.

Network hyperexcitability is another relevant pathway. Early AD is associated with abnormal activity in hippocampal and cortical circuits (29,30). Increased activity can reflect compensatory responses. Persistent hyperexcitability raises energy demand, disrupts synaptic balance, and helps dysfunction spread through connected regions (29,30).

These mechanisms should be treated as interacting factors rather than competing explanations for a single root cause. Complement, APOE ε4, TREM2, tau, energy stress, vascular injury, astrocyte reactivity, and abnormal network activity connect in complex ways (9-33). The practical goal is to identify which combination of mechanisms best explains vulnerability in a specific person, brain region, and disease stage, while recognizing that several pathways can contribute at the same time.

A NETWORK REDUNDANCY-LOSS FRAMEWORK OF EARLY CIRCUIT FAILURE

The network redundancy-loss framework can be summarized in three steps. First, early AD reduces compensatory capacity in memory-related and high-connectivity regions (7,8,28). Second, glial clearance contributes to vulnerability when synaptic remodeling occurs in an environment shaped by amyloid, tau, metabolic, vascular, and inflammatory stress (9-13,25,29-33). Third, complement provides local tagging, APOE ε4 influences lipid and stress-resolution pathways, and TREM2 shapes stage-dependent microglial responses (9-22).

The main idea is that disease becomes clinically serious when local synapse removal reduces the network's ability to compensate. This helps explain why similar amounts of plaque or tau pathology can produce different symptoms in different people (7,8). A person with stronger cognitive reserve or more flexible alternative routes can tolerate pathology for longer (7,8). A person who loses crucial memory connections earlier can decline more quickly, even if the total amount of visible pathology appears similar.

The framework has clear boundaries. It is intended to guide testable questions rather than explain every case of AD. Complement-mediated synaptic removal is not necessary in every AD. Context, and complement, APOE ε4, and TREM2 signaling are not sufficient by themselves to explain dementia. These boundaries are useful because they explain where other mechanisms, including tau, vascular dysfunction, metabolic failure, or hyperexcitability, provide stronger explanations. The model remains consistent with evidence showing that complement, APOE ε4, and TREM2 can have protective or harmful roles depending on context (9-22).

The following table summarizes how several mechanisms connect to early circuit failure.

Mechanistic route	**Representative evidence**	**Prediction from network redundancy-loss framework**	**Evidence that would weaken ~~it~~ this route**
Complement, APOE ε4, and TREM2	Complement-dependent synapse loss, APOE ε4-linked glial-state shifts, and TREM2 stage dependence (9-22).	Clinical effect should be greatest when complement-tagged synapses occur in hippocampal or memory-network regions with high connectivity.	Early synapse loss progresses without complement activation, glial ingestion of synaptic material, or measurable network vulnerability.
Tau-associated neuronal stress	Tau mechanisms and biomarkers are strongly linked to neurodegeneration and cognitive decline (31).	Tau-related decline should be strongest when tau overlaps with vulnerable hubs and local glial injury signals.	Cognition remains stable despite tau spread through important regions, or tau markers do not track synaptic vulnerability.
Metabolic or mitochondrial stress	Energy failure lowers synaptic resilience before neurons die (33).	FDG-PET or mitochondrial stress markers should identify synapses that later become vulnerable to glial clearance.	Severe synapse loss occurs while metabolism and mitochondrial function remain preserved.
Vascular or blood-brain barrier injury	BBB breakdown and vascular dysfunction alter clearance, perfusion, and inflammation (32).	Perfusion or BBB markers should explain regional asymmetry that amyloid or complement alone cannot explain.	Focal degeneration progresses despite normal perfusion and intact BBB markers.

Network hyperexcitability	Hyperexcitability is observed in AD models and human AD-related research (29,30).	EEG, MEG, or functional-connectivity changes should predict which circuits lose redundancy fastest.	Networks remain stable despite strong excitability markers.

Table 1: Mechanistic routes, predictions, and evidence that would weaken each route.

PREDICTIONS AND EXPERIMENTAL TESTS

The network redundancy-loss framework leads to several testable expectations.

First, the location of synapse loss should matter more than the total amount alone. Spatial transcriptomic studies, including a hippocampal atlas of human AD tissue, make it more possible to connect local gene expression and cell states with regional vulnerability (28). If the framework is correct, glial synapse-removal signatures should be most clinically meaningful when they appear in hippocampal regions or memory networks. Measuring complement or microglial activation without location is likely to be too broad (26-28).

Second, APOE ε4 should be tested as a factor associated with persistence of glial and metabolic stress. A longitudinal study could compare how quickly APOE ε4 carriers and non-carriers recover to normal after a stress event. If APOE ε4 mainly affects persistence, repeated measurements over time will be more informative than a single measurement (17,18).

Third, TREM2 effects should be expected to change with disease stage. Early in disease, stronger TREM2-linked phagocytic activity can be associated with synaptic damage. Later, the same activity can help contain plaques or clear debris (19-22). This pattern explains why TREM2-targeted therapies are unlikely to work equally at all disease stages.

Fourth, therapeutic success should be judged partly by preservation of network flexibility. A treatment can reduce inflammatory markers but still fail if important synapses continue to disappear. Conversely, a therapy that preserves connectivity and cognitive reserve can be valuable even if all pathology is not removed (4,7,8).

UNCERTAINTY, DEBATE, AND MODEL BOUNDARIES

The evidence reviewed here should be interpreted carefully because microglial effects are highly context-dependent. The same pathway can support debris clearance in one setting and synaptic injury in another, depending on disease stage, genotype, brain region, and experimental system (9-13,19-22). Studies of microglial phagocytosis and complement-microglia interactions support this context-dependent view (9-13).

The same caution applies to APOE ε4 and TREM2. APOE ε4 is associated with glial activation and altered microglial function, but not every APOE ε4-related effect is mediated through microglia (14-18). TREM2 helps microglia respond to pathology, yet its effects can be stage-dependent or variant-dependent (19-22). For that reason, the most accurate conclusion is that microglia contribute to early synapse loss in some AD contexts. They should not be described as the consistent cause of synapse loss at every stage or in every brain region.

Another limitation is the type of evidence available. The strongest evidence for complement-mediated microglial synapse loss comes from animal models, where genes and pathways can be directly manipulated (9,10,21,22). These models are valuable, but they do not reproduce every feature of human AD. Human evidence often comes from donated tissue, imaging, induced pluripotent stem cell models, or gene-expression maps (14,17,25-28). These approaches increase relevance to human disease, although they usually show association more clearly than direct causation.

Network redundancy is also difficult to measure as a direct biological way. The framework highlights its ability to connect molecular synapse loss, glial state, regional vulnerability, and functional connectivity. Existing studies of redundancy and cognitive reserve support the concept, but they do not yet prove a direct link between network measures and molecular synapse loss (7,8).

THERAPEUTIC IMPLICATIONS

If early AD involves a loss of network redundancy, then treatment should not simply try to shut down inflammation. Microglia and astrocytes can be harmful in some situations, but they also clear debris, support repair, and help keep tissue stable (11-13,23,24). Blocking glial activity too strongly might remove functions the brain still needs. A more practical goal is to preserve protective glial functions while reducing signals that cause recoverable synapses to be marked for removal. Complement-related treatments could be useful if they reduce harmful synaptic tagging while still allowing normal debris clearance (11,12).

The same careful approach is required for other pathways. APOE-related treatments may need to improve lipid handling, metabolic support, or recovery from prolonged inflammation (14-18). TREM2-targeted treatments may need to be used differently in early and later disease because the same pathway can have different effects at different stages (19-22). Astrocytes may also be important because they affect both synaptic support and inflammatory signaling (23-25). This implies that future treatments should aim to preserve circuit resilience rather than merely reducing inflammation.

The redundancy framework also changes the way treatment should be evaluated. Synaptic biomarkers, functional connectivity, EEG or MEG measures of hyperexcitability, and spatial markers of glial state can help show whether a therapy preserves circuit resilience (4,7,8,26-30). These measures can complement amyloid, tau, and general inflammatory markers, rather than replacing them.

CONCLUSION

AD should not be understood only as the accumulation of plaques and tangles. It is also a disease of circuit failure. Synaptic failure is one route through which many AD-related processes affect cognition. Microglia and astrocytes are adaptive cells that clear debris, regulate the local environment, and protect tissue. In AD, persistent amyloid stress, tau pathology, metabolic dysfunction, vascular injury, and inflammatory signaling can change the environment in which those glial cells act (9-33).

The evidence supports the idea that glial synaptic clearance contributes to early circuit failure under specific disease conditions. Complement signaling can tag synapses for removal, APOE ε4 is associated with persistent glial and metabolic stress, and TREM2 shapes stage-dependent microglial responses (9-22). Astrocytes, tau pathology, vascular dysfunction, metabolic stress, and hyperexcitability are not secondary details. They are interacting pathways that influence synaptic vulnerability (23-33).

The network redundancy-loss framework organizes these mechanisms by connecting synapse loss with reduced compensatory capacity in memory networks. Synapse loss matters not only because connections disappear, but because affected circuits lose backup routes for information flow. This perspective explains selective brain region vulnerability, cognitive reserve, regional progression, and the mismatch sometimes seen between pathology burden and symptoms (7,8,28). The framework does not provide a complete explanation for AD, but it provides testable questions about when, where, and why synapse removal becomes clinically damaging.

CONFLICT OF INTEREST STATEMENT

The author declares no competing interests.

ETHICAL APPROVAL

Ethical approval was not required because the work is a literature review and did not involve human participants, animal experiments, or new data collection.

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